AO 120 (Rev. 08/10)

TO:	**Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313–1450**	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the **U.S. District Court for the District of New Jersey** on the following:
____ Trademarks or **X** Patents. (____ the patent action involves 35 U.S.C. § 292.)

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
3:13–cv–04022–JAP–DEA	6/28/2013	TRENTON, NJ

PLAINTIFF	DEFENDANT
ASTRAZENECA AB	MYLAN PHARMACEUTICALS

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 US 6,926,907 B2	8/9/2005	POZEN INC.
2 5,948,789	9/7/1999	ASTRA AKTIEBOLAG
3		
4		
5		

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ___ Amendment ___ Answer ___ Cross Bill ___ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
William T. Walsh	s/ JAWEIA CAMPBELL	6/28/2013

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

AO 120 (Rev. 08/10)

TO:	**Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313–1450**	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the **U.S. District Court for the District of New Jersey** on the following:
____ Trademarks or **X** Patents. (____ the patent action involves 35 U.S.C. § 292.)

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
3:13–cv–00091–JAP–TJB	1/7/2013	TRENTON, NJ

PLAINTIFF	DEFENDANT
ASTRAZENECA AB	DR. REDDY'S LABORATORIES, INC.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 6,926,907 B2	8/9/2005	POZEN, INC.
2 5,714,504	2/3/98	ASTRA AKTIEBOLAG
3 7,745,466 B2	6/29/2010	ASTRAZENECA AB
4 7,411,070 B2	8/12/2008	ASTRAZENECA AB
5 6,369,085	4/9/2002	ASTRAZENECA AB

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ___ Amendment ___ Answer ___ Cross Bill ___ Other Pleading

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
William T. Walsh	s/ KIM STILLMAN	1/7/2013

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

AO 120 (Rev. 08/10)

TO:	**Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313–1450**	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the **U.S. District Court for the District of New Jersey** on the following:
____ Trademarks or **X** Patents. (____ the patent action involves 35 U.S.C. § 292.)

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
3:11–cv–06348–JAP–DEA	10/31/2011	TRENTON, NJ

PLAINTIFF	DEFENDANT
ASTRAZENECA AB	ANCHEN PHARMACEUTICALS, INC.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 6,926,907 B2	8/9/2005	POZEN INC.
2 6,369,085 B1	4/9/2002	ASTRAZENECA AB
3 7,411,070 B2	9/12/2008	
4 7,745,466 B2	6/29/2010	ASTRAZENECA AB
5		

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ___ Amendment ___ Answer ___ Cross Bill ___ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
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4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
William T. Walsh	s/ JAWEIA CAMPBELL	10/31/2011

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

AO 120 (Rev. 08/10)

TO:	**Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313–1450**	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

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____ Trademarks or **X** Patents. (____ the patent action involves 35 U.S.C. § 292.)

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
3:11–cv–04275–JAP –DEA	7/25/2011	TRENTON, NJ

PLAINTIFF	DEFENDANT
ASTRAZENECA AB	LUPIN LTD.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 5,714,504	02/03/1998	ASTRA AKTIEBOLAG
2 6,875,872	04/05/2005	ASTRAZENECA
3 6,369,085	04/09/2002	
4 7,411,070	08/12/2008	ASTRAZENECA AB
5 7,745,466	06/29/2010	ASTRAZENECA AB

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ___ Amendment ___ Answer ___ Cross Bill ___ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
William T. Walsh	s/ MURTUZA AKBARI	7/25/2011

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	PATENT NUMBER	GROUP ART UNIT	FILE WRAPPER LOCATION
10/158,216	6926907	1615	7581

OC000000056242043

Correspondence Address/Fee Address Change

The following fields have been set to Customer Number 108197 on 08/28/2012

- **Correspondence Address**
- **Maintenance Fee Address**

The address of record for Customer Number 108197 is:

108197
Parker Highlander PLLC
1120 South Capital of Texas Highway
Bldg. 1, Suite 200
Austin, TX 78746

PTO/SB/80 (11-08)
Approved for use through 11/30/2011. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(b).

I hereby appoint:

☑ Practitioners associated with the Customer Number: 108197

OR

☐ Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

as attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 3.73(b).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(b) to:

☑ The address associated with Customer Number: 108197

OR

☐ Firm or Individual Name			
Address			
City		State	Zip
Country			
Telephone		Email	

Assignee Name and Address:

POZEN Inc.
1414 Raleigh Road, Suite 400
Chapel Hill, North Carolina 27517

A copy of this form, together with a statement under 37 CFR 3.73(b) (Form PTO/SB/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(b) may be completed by one of the practitioners appointed in this form if the appointed practitioner is authorized to act on behalf of the assignee, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature	Gilda Thomas	Date	8/8/12
Name	Gilda Thomas	Telephone	
Title	Senior Vice President, General Counsel		

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Electronic Acknowledgement Receipt	
EFS ID:	13514576
Application Number:	10158216
International Application Number:	
Confirmation Number:	5014
Title of Invention:	PHARMACEUTICAL COMPOSITIONS FOR THE COORDINATED DELIVERY OF NSAIDS
First Named Inventor/Applicant Name:	John R. Plachetka
Customer Number:	32425
Filer:	Steven Lee Highlander/Tressie Bates
Filer Authorized By:	Steven Lee Highlander
Attorney Docket Number:	POZN.P0004US
Receipt Date:	16-AUG-2012
Filing Date:	31-MAY-2002
Time Stamp:	15:27:40
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		POZNP0004US.pdf	851772 5dc6c0e8f26533277e651f23f7742237acbf3288	yes	2

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Assignee showing of ownership per 37 CFR 3.73(b).	1	1
	Power of Attorney	2	2
Warnings:			
Information:			
	Total Files Size (in bytes):	851772	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/96 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: John R. Plachetka

Application No./Patent No.: 10/158,216 / 6,926,907 Filed/Issue Date: May 31, 2002 / August 9, 2005

Titled: PHARMACEUTICAL COMPOSITIONS FOR THE COORDINATED DELIVERY OF NSAIDS

POZEN, INC. , a corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. [X] the assignee of the entire right, title, and interest in;

2. [ ] an assignee of less than the entire right, title, and interest in (The extent (by percentage) of its ownership interest is _____ %); or

3. [ ] the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. [X] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 013256, Frame 0958, or for which a copy therefore is attached.

OR

B. [ ] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

[ ] Additional documents in the chain of title are listed on a supplemental sheet(s).

[X] As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Signature	August 10, 2012 Date
Steven L. Highlander; Reg. No. 37,642 Printed or Typed Name	Attorney Title

This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/158,216	05/31/2002	John R. Plachetka	7569/73281

CONFIRMATION NO. 5014

POWER OF ATTORNEY NOTICE

66991
LAW OFFICE OF MICHAEL A. SANZO, LLC
15400 CALHOUN DR.
SUITE 125
ROCKVILLE, MD 20855

OC000000049123872

Date Mailed: 08/08/2011

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 07/29/2011.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

/hchristian/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/158,216	05/31/2002	John R. Plachetka	POZN.P0004US

CONFIRMATION NO. 5014

POA ACCEPTANCE LETTER

32425
FULBRIGHT & JAWORSKI L.L.P.
98 SAN JACINTO BOULEVARD
SUITE 1100
AUSTIN, TX 78701-4255

OC000000049123889

Date Mailed: 08/08/2011

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 07/29/2011.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/hchristian/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

Patent Owner Ex. 2005
IPR2015-01344
Page 11 of 613

PTO/SB/81 (01-06) MODIFIED

POWER OF ATTORNEY AND CORRESPONDENCE ADDRESS INDICATION FORM		
	Patent Number:	6,926,907
	Issue Date:	August 9, 2005
	Application Number:	10/158,216
	Filing Date:	May 31, 2002
	First Named Inventor:	John R. PLACHETKA
	Attorney Docket Number:	POZN.P0004US

I hereby revoke all previous powers of attorney given in the above-identified application.

☐ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint the practitioners associated with the Customer Number: 32425

as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.

Please recognize or change the correspondence address for the above-identified application to:

☒ The address associated with Customer Number: 32425

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the:

☐ Applicant/Inventor.

☒ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

SIGNATURE OF APPLICANT OR ASSIGNEE OF RECORD

Signature	Gilda Thomas		
Name	Gilda Thomas		
Title and Company	Senior Vice President, General Counsel POZEN Inc.	Telephone	
Date	7/7/11		

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☒ *Total of 1 form is submitted.

95053175.1

Electronic Acknowledgement Receipt

EFS ID:	10631199
Application Number:	10158216
International Application Number:	
Confirmation Number:	5014
Title of Invention:	PHARMACEUTICAL COMPOSITIONS FOR THE COORDINATED DELIVERY OF NSAIDS
First Named Inventor/Applicant Name:	John R. Plachetka
Customer Number:	66991
Filer:	Steven Lee Highlander/Tressie Bates
Filer Authorized By:	Steven Lee Highlander
Attorney Docket Number:	7569/73281
Receipt Date:	29-JUL-2011
Filing Date:	31-MAY-2002
Time Stamp:	16:17:40
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		POZNP0004US-POA.pdf	702300 bbcd22ae3cc7edbcda41fb25cfd36138c9de292f	yes	2

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Assignee showing of ownership per 37 CFR 3.73(b).	1	1
	Power of Attorney	2	2
Warnings:			
Information:			
	Total Files Size (in bytes):	702300	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/96 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: John R. PLACHETKA

Application No./Patent No.: 6,926,907 Filed/Issue Date: August 9, 2005

Titled:
PHARMACEUTICAL COMPOSITIONS FOR THE COORDINATED DELIVERY OF NSAIDS

POZEN INC. , a corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. [X] the assignee of the entire right, title, and interest in;

2. [ ] an assignee of less than the entire right, title, and interest in
(The extent (by percentage) of its ownership interest is _____ %); or

3. [ ] the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. [X] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 013256, Frame 0958, or for which a copy therefore is attached.

OR

B. [ ] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

3. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

[ ] Additional documents in the chain of title are listed on a supplemental sheet(s).

[ ] As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

_____ July 29, 2011
Signature Date

Steven L. Highlander, Reg. No. 37,642 Attorney
Printed or Typed Name Title

This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,926,907 B2
APPLICATION NO. : 10/158216
DATED : August 9, 2005
INVENTOR(S) : John Plachetka

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the first line of claim 1 line 1 in the issued patent, the word "dose" should be --dosage.-- Thus, the correct claim should read as follows:

Col. 20, Claim

1. A pharmaceutical composition in unit dosage form suitable for oral administration to a patient, comprising: (a) an acid inhibitor present in an amount effective to raise the gastric pH of said patient to at least 3.5 upon the administration of one or more of said unit dosage forms; (b) a non-steroidal anti-inflammatory drug (NSAID) in an amount effective to reduce or eliminate pain or inflammation in said patient upon administration of one or more of said unit dosage forms;

and wherein said unit dosage form provides for coordinated release such that: i) said NSAID is surrounded by a coating that, upon ingestion of said unit dosage form by said patient, prevents the release of essentially any NSAID from said dosage form unless the pH of the surrounding medium is 3.5 or higher; ii) at least a portion of said acid inhibitor is not surrounded by an enteric coating and, upon ingestion of said unit dosage form by said patient, is released regardless of whether the pH of the surrounding medium is below 3.5 or above 3.5.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,926,907 B2
APPLICATION NO. : 10/158216
DATED : August 9, 2005
INVENTOR(S) : John Plachetka

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Col. 21, Line 1 of claim 16 and 17 should refer to "any one of claims 12-14" and not to "claim 15." In addition, the phrase --wherein said acid inhibitor is a proton pump inhibitor-- should be included in 16 and 17. Thus, the claims should read as follows:

Col. 21

16. The pharmaceutical composition of any one of claims 12-14, wherein said acid inhibitor is a proton pump inhibitor and wherein said coating surrounding said core does not dissolve unless the pH of the surrounding medium is 4 or greater.

17. The pharmaceutical composition of any one of claims 12-14, wherein said acid inhibitor is a proton pump inhibitor and wherein said coating surrounding said core does not dissolve unless the pH of the surrounding medium is 5 or greater.

Col. 21, Line 1 of claims 19 and 20 should refer to "any one of claims 12-14" and not to "claim 18." In addition, the phrase --wherein said acid inhibitor is an H2 blocker-- should be included in 19 and 20. Thus, the claims should read as follows:

Col. 21

19. The pharmaceutical composition of any one of claims 12-14, wherein said acid inhibitor is an H2 blocker and wherein said tablet has an inner core of said NSAID surrounded by a barrier coating that dissolves at a rate such that said NSAID is not released until the pH of the surrounding medium is 4 or greater.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,926,907 B2
APPLICATION NO. : 10/158216
DATED : August 9, 2005
INVENTOR(S) : John Plachetka

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Col. 21

20. The pharmaceutical composition of any one of claims 12-14, wherein said acid inhibitor is an H2 blocker and wherein said tablet has an inner core of said NSAID surrounded by a barrier coating that dissolves at a rate such that said NSAID is not released until the pH of the surrounding medium is 5 or greater.

Signed and Sealed this

Twenty-fifth Day of December, 2007

JON W. DUDAS
Director of the United States Patent and Trademark Office

PUBS Routing Sheet

Application # 10/158216 Doc Code Date _____

Date of Request 4-24-07 Doc Code _____ (if not listed)

☐ 892 List of References cited by Examiner	☐ ISSUE.WD.NTC Notice of Withdrawal from Issue	☐ PETDEC Petition Decision
☐ 1449 List of References cited by Applicant	☐ IIFW Issue Information	☐ PGEA.D PreGrant Publication Express Abandonment-Dismissed
☐ ABN Abandonment	☐ IMIS Internal Miscellaneous Paper	☐ PGEA.G PreGrant Publication Express Abandonment - Granted
☐ BIB Bibliographic Data Sheet	☐ LET. Miscellaneous Incoming Letter	☐ PGREF Request for Refund of Publication Fee Paid
☐ CDEN Request for Certificate of Correction Denied	☐ M327 Miscellaneous Communication to Applicant	☐ RUSH Printer Query Form
☒ CLM Claims	☐ M903 Notice of DO/MO Acceptance Mailed	☐ SPEC Specification
☐ COCIN Request for Certificate of Correction	☐ N271 Response to Amendment under Rule 312	☐ STAT.DISCLMR Statutory Disclaimers
☐ COCOUT Certificate of Correction	☐ N417 Status Letter Mailed to Applicant	☐ W/AC Withdrawal of previous action
☐ COCX SPE Response to Request for Certificate of Correction	☐ N427 Post Allowance Communication Transaction	☐ XRUSH Internal Response to Printer Query
☐ CTMS Miscellaneous Office Action	☐ N570 Accepted Change to Power of Attorney	
☐ IFEE issue Fee Payment Record	☐ PET.DEC.PUBS Petition decision routed to Publications	

SPE RESPONSE FOR CERTIFICATE OF CORRECTION

DATE : 4-24-07 **Paper No.**: _____

TO SPE OF : ART UNIT 1615

SUBJECT : Request for Certificate of Correction on Patent No.: 6926907 B2 (10/158216

A response is requested with respect to the accompanying request for a certificate of correction.

Please complete this form and return with file, within **7** days to:
Palm location **7580, Certificates of Correction Branch – South Tower – 9A22**
If response is for an IFW, **return to employee (named below) via PUBSCofC Team in MADRAS.**
With respect to the change(s) requested, correcting Office and/or Applicant's errors, should the patent read as shown in the certificate of correction (COCIN)? No new matter should be introduced, nor should the scope or meaning of the claims be changed.

Eva James

Should claims be entered as requested

Thank You For Your Assistance

Certificates of Correction Branch
Tel. No. 703-305-8309

Thanks

The request for issuing the above-identified correction(s) is hereby:
Note your decision on the appropriate box.

- ☐ **Approved** — **All** changes apply.
- ☐ **Approved in Part** — Specify below which changes **do not** apply.
- ☐ **Denied** — State the reasons for denial below.

Comments:

_____

_____

_____

_____

_____

_____ _____
SPE Art Unit

PTOL-306 (REV. 7/03) U.S. DEPARTMENT OF COMMERCE Patent and Trademark Office

OIPE
APR 05 2007
PATENT & TRADEMARK OFFICE

Law Office of Michael A. Sanzo, LLC

Practice Limited to Patent Law

OIPE
APR 05 2007
PATENT & TRADEMARK OFFICE

April 5, 2007

Commissioner of Patents
U.S. Patent and Trademark Office
Attn: Certificate of Correction Branch
Customer Service Window,
Randolph Building
401 Dulany Street
Alexandria, VA 22314

Certificate
APR 10 2007
of Correction

Re: Request for Certificate of Correction

Pat No.	6,926,907
Appl. No.:	10/158,216
Filed:	May 31, 2002
Title:	**Pharmaceutical Compositions for the Coordinated Delivery of NSAIDs**
Inventor(s):	Plachetka, John R.
Atty. Dkt.:	7569/73281

Dear Sir:

The following documents are being forwarded for appropriate action by the U.S. Patent and Trademark Office:

1. Request for Certificate of Correction Under 37 C.F.R. § 1.323;
2. Two copies of Certificate of Correction;
3. Our check in the amount of $100 to cover the fee for a Certificate of Correction; and
4. One return postcard.

Applicant believes that the fee for the filing of the present documents under 37 CFR §1.20(a) is $100 and this is provided for in the enclosed check. The Director is hereby authorized to charge any fee deficiency with respect to this filing or credit any overpayment to our Deposit Account No. 50-4056 under Order No. 7569/73281.

APR 10 2007

15400 Calhoun Drive • Suite 125 • Rockville, Md. 20855
Member Patent Bar and DC Bar Only
Phone: (240)864-0915 • Fax: (240)597-1153 • E-mail: mike@msanzolaw.com

It is respectfully requested that the enclosed postcard be stamped with the date that the enclosed documents are received by the PTO and that they be returned by courier.

Very truly yours,
LAW OFFICE OF MICHAEL A. SANZO, LLC

Michael A. Sanzo

Michael A. Sanzo
Reg. No. 36,912
Attorney for Applicants

APR 10 2007

OIPE 1A759
APR 05 2007
PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent of:	
PLACHETKA, John	Patent No. 6,926,907
Appl. No. 10/158,216	Art Unit: 1624
Filed: May 31, 2002	Examiner: James M. Spear
Issued: August 9, 2005	Atty. Dkt. 7569/73281
For: **Pharmaceutical Compositions for the Coordinated Delivery of NSAIDs**	

Request for Certificate of Correction Under 37 C.F.R. § 1.323

Commissioner of Patents
U.S. Patent and Trademark Office
Customer Service Window
Randolph Building
401 Dulany Street
Alexandria, VA 22314

Attention: Certificate of Correction Branch

Sir:

It is respectfully requested that a Certificate of Correction be issued in the above-captioned patent. The corrections requested are set forth below and on the accompanying form. The corrections concern a grammatical error in claim 1 and errors with respect to dependency in claims 16, 17, 19 and 20. The errors were the fault of Applicants, but were mistakes that occurred in good faith and are of a minor character. The corrections do not broaden the scope of the claims in the issued in the patent. Included herewith are two properly completed Certificate of Correction Forms. It is respectfully requested that one of these forms be entered and that the other be returned to the undersigned attorney. The exact errors are shown below with words being omitted struck through, and words being added underlined. An explanation of the errors may be found on pages 4 and 5 of the present document.

04/06/2007 IADDO1 00000071 6926907
01 FC:1811 100.00 OP

APR 10 2007

Corrected Claims

1. A pharmaceutical composition in unit ~~dose~~ dosage form suitable for oral administration to a patient, comprising: (a) an acid inhibitor present in an amount effective to raise the gastric pH of said patient to at least 3.5 upon the administration of one or more of said unit dosage forms; (b) a non-steroidal anti-inflammatory drug (NSAID) in an amount effective to reduce or eliminate pain or inflammation in said patient upon administration of one or more of said unit dosage forms;
and wherein said unit dosage form provides for coordinated release such that: i) said NSAID is surrounded by a coating that, upon ingestion of said unit dosage form by said patient, prevents the release of essentially any NSAID from said dosage form unless the pH of the surrounding medium is 3.5 or higher; ii) at least a portion of said acid inhibitor is not surrounded by an enteric coating and, upon ingestion of said unit dosage form by said patient, is released regardless of whether the pH of the surrounding medium is below 3.5 or above 3.5.

16. The pharmaceutical composition of ~~claim 15~~ any one of claims 12-14, wherein said acid inhibitor is a proton pump inhibitor and wherein said coating surrounding said core does not dissolve unless the pH of the surrounding medium is 4 or greater.

17. The pharmaceutical composition of ~~claim 15~~ any one of claims 12-14, wherein said acid inhibitor is a proton pump inhibitor and wherein said coating surrounding said core does not dissolve unless the pH of the surrounding medium is 5 or greater.

19. The pharmaceutical composition of ~~claim 18~~ any one of claims 12-14, wherein said acid inhibitor is an H2 blocker and wherein said tablet has an inner core of said NSAID surrounded by a barrier coating that dissolves at a rate such that said NSAID is not released until the pH of the surrounding medium is 4 or greater.

APR 1 0 2002

20. The pharmaceutical composition of ~~claim 18~~ any one of claims 12-14, wherein said acid inhibitor is an H2 blocker and wherein said tablet has an inner core of said NSAID surrounded by a barrier coating that dissolves at a rate such that said NSAID is not released until the pH of the surrounding medium is 5 or greater.

APR 1 0 2007

Remarks

Claim 1 was amended in line 1 to change the word "dose" to "dosage," the term used in the rest of the claim and in the specification (see, *e.g.*, col. 3, line 60- col.4, line 5). This change has no affect on claim scope and merely serves to make terms consistent throughout the claim and specification.

Claims 16 and 17 were amended to correct an error in dependency. In the patent as issued, these claims depend from claim 15 which, in turn, depends from claims 1 and 7-14. As issued, claims 16 and 17 recite "said core." The problem is that, although claims 12-14 recite a core, claims 1 or 7-11 do not recite a core. The dependency of claim 16 to claims 1 or 7-11 resulted from a mistake made during prosecution changing the dependency of claims 16 and 17 (which had originally been to claims 12-14) to claim 15. The amendments herein reinstate the original dependency. Thus, the amended claims are the same as the claims that issued with respect to claims 12-14 but dependency on claims 1 and 7-11 has been eliminated. All dependent claims now refer to claims that recite a core.

Very similar considerations apply with respect to claims 19 and 20. These claims depend from claim 18, which depends from claims 7-14. Both 19 and 20 recite "said tablet." and although claims 12-14 recite a tablet, claims 7-11 do not recite a tablet. As with the error discussed above, the error with respect to claims 19 and 20 was due to a mistake during prosecution in which dependency was changed from 12-14 to claim 18. The amendments herein reinstate the original dependency of claims 19 and 20. Thus the amended claims are the same as the claims that issued with respect to claims 12-14 but dependency on claims 7-11 has been eliminated.

It is submitted that all of the corrections made are clearly supported by the claims and specification of the issued patent. The corrections do not require that there be additional examination and their entry is respectfully requested.

APR 1 0 2007

A check is provided herein to cover the fee required for providing a Certificate of Correction as set forth in 37 C.F.R. § 1.20(a). The Director is also hereby authorized to charge any additional fees that may be required to our Deposit Account No. 50-4056 under order number 7569/73281.

Respectfully submitted,

LAW OFFICE OF MICHAEL A. SANZO, LLC

Michael A. Sanzo

By:_____

Michael A. Sanzo
Reg. No. 36,912
Attorney for Applicants

Date: April 5, 2007
14500 Calhoun Drive, Suite 125
Rockville, Md. 20855
Telephone: (240)864-0915

APR 10 2007

Staple Here Only Printer's Trim Line →

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO.	: 6,926,907
DATED	: August 9, 2005
INVENTOR(S)	: PLACHETKA, John

It is certified that an error or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the first line of claim 1in the issued patent, the word "dose" should be "dosage." Thus, the correct claim should read as follows:

1. A pharmaceutical composition in unit dosage form suitable for oral administration to a patient, comprising: (a) an acid inhibitor present in an amount effective to raise the gastric pH of said patient to at least 3.5 upon the administration of one or more of said unit dosage forms; (b) a non-steroidal anti-inflammatory drug (NSAID) in an amount effective to reduce or eliminate pain or inflammation in said patient upon administration of one or more of said unit dosage forms;
and wherein said unit dosage form provides for coordinated release such that: i) said NSAID is surrounded by a coating that, upon ingestion of said unit dosage form by said patient, prevents the release of essentially any NSAID from said dosage form unless the pH of the surrounding medium is 3.5 or higher; ii) at least a portion of said acid inhibitor is not surrounded by an enteric coating and, upon ingestion of said unit dosage form by said patient, is released regardless of whether the pH of the surrounding medium is below 3.5 or above 3.5.

MAILING ADDRESS OF SENDER
Law Office of Michael A. Sanzo, LLC
14500 Calhoun Drive, Suite 125
Rockville, Md. 20885

PATENT NO. 6, 926,907

APR 1 0 2007

SUBSTITUTE FORM PTO 1050

Pat-1050 2/00

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO.	: 6,926,907
DATED	: August 9, 2005
INVENTOR(S)	: PLACHETKA, John

Line 1 of claim 16 and 17 should refer to "any one of claims 12-14" and not to "claim 15." In addition, the phrase "wherein said acid inhibitor is a proton pump inhibitor" should be included in 16 and 17. Thus, the claims should read as follows:

16. The pharmaceutical composition of any one of claims 12-14, wherein said acid inhibitor is a proton pump inhibitor and wherein said coating surrounding said core does not dissolve unless the pH of the surrounding medium is 4 or greater.

17. The pharmaceutical composition of any one of claims 12-14, wherein said acid inhibitor is a proton pump inhibitor and wherein said coating surrounding said core does not dissolve unless the pH of the surrounding medium is 5 or greater.

Line 1 of claims 19 and 20 should refer to "any one of claims 12-14" and not to "claim 18." In addition, the phrase "wherein said acid inhibitor is an H2 blocker" should be included in 19 and 20. Thus, the claims should read as follows:

19. The pharmaceutical composition of any one of claims 12-14, wherein said acid inhibitor is an H2 blocker and wherein said tablet has an inner core of said NSAID surrounded by a barrier coating that dissolves at a rate such that said NSAID is not released until the pH of the surrounding medium is 4 or greater.

MAILING ADDRESS OF SENDER
Law Office of Michael A. Sanzo, LLC
14500 Calhoun Drive, Suite 125
Rockville, Md. 20885

PATENT NO. 6, 926,907

APR 1 0 2007

SUBSTITUTE FORM PTO 1050

Pat-1050 2/00

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO.	: 6,926,907
DATED	: August 9, 2005
INVENTOR(S)	: PLACHETKA, John

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MAILING ADDRESS OF SENDER
Law Office of Michael A. Sanzo, LLC
14500 Calhoun Drive, Suite 125
Rockville, Md. 20885

PATENT NO. 6, 926,907

SUBSTITUTE FORM PTO 1050

APR 1 0 2007

Pat-1050 2/00

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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.	: 6,926,907
DATED	: August 9, 2005
INVENTOR(S)	: PLACHETKA, John

It is certified that an error or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the first line of claim 1in the issued patent, the word "dose" should be "dosage." Thus, the correct claim should read as follows:

1. A pharmaceutical composition in unit dosage form suitable for oral administration to a patient, comprising: (a) an acid inhibitor present in an amount effective to raise the gastric pH of said patient to at least 3.5 upon the administration of one or more of said unit dosage forms; (b) a non-steroidal anti-inflammatory drug (NSAID) in an amount effective to reduce or eliminate pain or inflammation in said patient upon administration of one or more of said unit dosage forms;
and wherein said unit dosage form provides for coordinated release such that: i) said NSAID is surrounded by a coating that, upon ingestion of said unit dosage form by said patient, prevents the release of essentially any NSAID from said dosage form unless the pH of the surrounding medium is 3.5 or higher; ii) at least a portion of said acid inhibitor is not surrounded by an enteric coating and, upon ingestion of said unit dosage form by said patient, is released regardless of whether the pH of the surrounding medium is below 3.5 or above 3.5.

MAILING ADDRESS OF SENDER
Law Office of Michael A. Sanzo, LLC
14500 Calhoun Drive, Suite 125
Rockville, Md. 20885

PATENT NO. 6, 926,907

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO.	: 6,926,907
DATED	: August 9, 2005
INVENTOR(s)	: PLACHETKA, John

Line 1 of claim 16 and 17 should refer to "any one of claims 12-14" and not to "claim 15." In addition, the phrase "wherein said acid inhibitor is a proton pump inhibitor" should be included in 16 and 17. Thus, the claims should read as follows:

16. The pharmaceutical composition of any one of claims 12-14, wherein said acid inhibitor is a proton pump inhibitor and wherein said coating surrounding said core does not dissolve unless the pH of the surrounding medium is 4 or greater.

17. The pharmaceutical composition of any one of claims 12-14, wherein said acid inhibitor is a proton pump inhibitor and wherein said coating surrounding said core does not dissolve unless the pH of the surrounding medium is 5 or greater.

Line 1 of claims 19 and 20 should refer to "any one of claims 12-14" and not to "claim 18." In addition, the phrase "wherein said acid inhibitor is an H2 blocker" should be included in 19 and 20. Thus, the claims should read as follows:

19. The pharmaceutical composition of any one of claims 12-14, wherein said acid inhibitor is an H2 blocker and wherein said tablet has an inner core of said NSAID surrounded by a barrier coating that dissolves at a rate such that said NSAID is not released until the pH of the surrounding medium is 4 or greater.

MAILING ADDRESS OF SENDER
Law Office of Michael A. Sanzo, LLC
14500 Calhoun Drive, Suite 125
Rockville, Md. 20885

PATENT NO. 6, 926,907

APR 1 0 2007

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Pat-1050 2/00

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO.	: 6,926,907
DATED	: August 9, 2005
INVENTOR(S)	: PLACHETKA, John

20. The pharmaceutical composition of any one of claims 12-14, wherein said acid inhibitor is an H2 blocker and wherein said tablet has an inner core of said NSAID surrounded by a barrier coating that dissolves at a rate such that said NSAID is not released until the pH of the surrounding medium is 5 or greater.

MAILING ADDRESS OF SENDER
Law Office of Michael A. Sanzo, LLC
14500 Calhoun Drive, Suite 125
Rockville, Md. 20885

PATENT NO. 6, 926,907

APR 1 0 2007

SUBSTITUTE FORM PTO 1050

Pat-1050 2/00

10/158,216

IFW



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of:

PLACHETKA, John R.

Pat No.: 6,926,907

Issued: August 9, 2005

For: **Pharmaceutical Compositions for the Coordinated Delivery of NSAIDS**

Atty. Dkt.: 7569/73281

Change of Correspondence Address

Please recognize the correspondence address for the above-captioned application as the address associated with the following customer number:

66991.

Respectfully submitted,

Law Office of Michael A. Sanzo, LLC.

By_____
Michael A. Sanzo
Reg. No. 36,912
Attorney for Applicant

Date: February 22, 2007
15400 Calhoun Drive, Suite 125
Rockville, Md. 20855
Phone: (240) 864-0915

OIPE IAP97 FEB 22 2007 PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of:

PLACHETKA, John R.

Atty. Dkt.: 7569/73281

Pat No.: 6,926,907

Issued: August 9, 2005

For: **Pharmaceutical Compositions for the Coordinated Delivery of NSAIDS**

Change of Fee Address

Please recognize the fee address under 37 C.F.R. § 1.363 for the above-captioned application as the address associated with the following customer number:

66991.

Respectfully submitted,

Law Office of Michael A. Sanzo, LLC.

By_____
Michael A. Sanzo
Reg. No. 36,912
Attorney for Applicant

Date: February 22, 2007
15400 Calhoun Drive, Suite 125
Rockville, Md. 20855
Phone: (240) 864-0915

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

Bib Data Sheet

CONFIRMATION NO. 5014

SERIAL NUMBER	FILING OR 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
10/158,216	05/31/2002 RULE	424	1615	7569/73281

APPLICANTS

John R. Plachetka, Chapel Hill, NC;

**** CONTINUING DATA ***************************

This appln claims benefit of 60/294,588 06/01/2001

**** FOREIGN APPLICATIONS ********************

IF REQUIRED, FOREIGN FILING LICENSE GRANTED
** 07/02/2002

Foreign Priority claimed	STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
☐ yes ☐ no 35 USC 119 (a-d) conditions met ☐ yes ☐ no ☐ Met after Allowance Verified and Acknowledged _____ Examiner's Signature Initials	NC	2	50	3

ADDRESS

42798

TITLE

PHARMACEUTICAL COMPOSITIONS FOR THE COORDINATED DELIVERY OF NSAIDS

FILING FEE RECEIVED		
2189	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (703) 746-4000

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

7590 03/29/2005

Michael A Sanzo
Fitch Even Tabin & Flannery
1801 K Street NW Suite 4011
Washinton, DC 20006-1201



Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (703) 746-4000, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/158,216	05/31/2002	John R. Plachetka	7569/73281	5014

TITLE OF INVENTION: PHARMACEUTICAL COMPOSITIONS FOR THE COORDINATED DELIVERY OF NSAIDS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	~~$700~~ $1,400	$300	~~$1000~~ $1,700	06/29/2005

EXAMINER	ART UNIT	CLASS-SUBCLASS
SPEAR, JAMES M	1615	424-472000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☒ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Michael A. Sanzo
2 Fitch, Even, Tabin & Flannery
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: POZEN Inc.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Chapel Hill, North Carolina

04/19/2005 SZEWDIE2 00000154 061135 10158216
01 FC:1501 1400.00 DA
02 FC:1504 300.00 DA
03 FC:8001 30.00 DA

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are enclosed:
- ☒ Issue Fee
- ☒ Publication Fee (No small entity discount permitted)
- ☒ Advance Order - # of Copies 10

4b. Payment of Fee(s):
- ☐ A check in the amount of the fee(s) is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☒ The Director is hereby authorized by charge the required fee(s), or credit any overpayment, to Deposit Account Number 06-1135 (enclose an extra copy of this form).

Under Order No. 7569/73281

5. **Change in Entity Status** (from status indicated above)
- ☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
- ☒ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

The Director of the USPTO is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.
NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature Michael A. Sanzo Date April 15, 2005
Typed or printed name Michael A. Sanzo Registration No. 36,912

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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Patent Owner Ex. 2005
IPR2015-01344
Page 37 of 613

OIPE JC85
APR 18 2005
PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of:

Plachetka, John R.	**Confirmation No.: 5014**
Appl. No.: 10/158,216	Art Unit: 1615
Filed: May 31, 2002	Examiner: J. Spear
For: **Pharmaceutical Compositions for the Coordinated Delivery of NSAIDs**	Atty. Dkt.: 7569/73281

CHANGE OF FEE ADDRESS

Please recognize the fee address under 37 C.F.R. § 1.363 for the above-captioned application as the address associated with the following customer number:

42798.

Respectfully submitted,

FITCH, EVEN, TABIN & FLANNERY

By Michael A. Sanzo

Michael A. Sanzo
Reg. No. 36,912
Attorney for Applicant

Date April 15, 2005
1801 K Street, N.W., Suite 401L
Washington, DC 20006-1201
Phone: (202) 419-7013

OIPE JC#5
APR 18 2005
PATENT & TRADEMARK OFFICE

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LISA M. SOMMER
GEORGE H. SPENCER, P.C.*

TECHNICAL ADVISOR
JOHN M. BRONK, PH.D.

*ADMITTED TO D.C. BAR
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LIMITED TO FEDERAL COURTS
AND AGENCIES

April 18, 2005

Commissioner of Patents
U.S. Patent and Trademark Office
Customer Service Window, **MS Issue Fee**
Randolph Building
401 Dulany Street
Alexandria, VA 22314

Re: Payment of Issue and Publication Fees
Appl. No.: 10/158,216
Filed: May 31, 2002
Title: **Pharmaceutical Compositions for the Coordinated Delivery of NSAIDs**
Inventor(s): Plachetka, John R.
Atty. Dkt.: 7569/73281

Dear Sir:

The following documents are being forwarded herewith for appropriate action by the U.S. Patent and Trademark Office:

1. Part B - Fee(s) Transmittal;
2. Change of Fee Address; and
3. Return postcard.

The Director is hereby authorized to charge the following fees to our Deposit Account No. 06-1135 under Order No. 7569/73218:

Issue Fee	**$ 1,400.00**
Publication Fee	**300.00**
10 Copies of Patent	**30.00**
	$ 1,730.00

The Director is also authorized to charge any fee deficiency with respect to this filing and any other fee required in connection with the present case, or credit any overpayment, to our Deposit Account No. 06-1135 under Order No. 7569/73218.

It is respectfully requested that the enclosed postcard be stamped with the date the enclosed documents are received by the PTO and that it be returned as soon as possible.

Very truly yours,

FITCH, EVEN, TABIN & FLANNERY

Michael A. Sanzo
Reg. No. 36,912
Attorney for Applicant

MAS:ct
Enclosures

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

7590 03/29/2005

Michael A Sanzo
Fitch Even Tabin & Flannery
1801 K Street NW Suite 4011
Washinton, DC 20006-1201

EXAMINER	
SPEAR, JAMES M	
ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 03/29/2005

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/158,216	05/31/2002	John R. Plachetka	7569/73281	5014

TITLE OF INVENTION: PHARMACEUTICAL COMPOSITIONS FOR THE COORDINATED DELIVERY OF NSAIDS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	$700	$300	$1000	06/29/2005

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE REFLECTS A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE APPLIED IN THIS APPLICATION. THE PTOL-85B (OR AN EQUIVALENT) MUST BE RETURNED WITHIN THIS PERIOD EVEN IF NO FEE IS DUE OR THE APPLICATION WILL BE REGARDED AS ABANDONED.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL should be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). Even if the fee(s) have already been paid, Part B - Fee(s) Transmittal should be completed and returned. If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (Rev. 12/04) Approved for use through 04/30/2007.

Patent Owner Ex. 2005
IPR2015-01344
Page 41 of 613

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (703) 746-4000

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

7590 03/29/2005

Michael A Sanzo
Fitch Even Tabin & Flannery
1801 K Street NW Suite 4011
Washinton, DC 20006-1201

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (703) 746-4000, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/158,216	05/31/2002	John R. Plachetka	7569/73281	5014

TITLE OF INVENTION: PHARMACEUTICAL COMPOSITIONS FOR THE COORDINATED DELIVERY OF NSAIDS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	$700	$300	$1000	06/29/2005

EXAMINER	ART UNIT	CLASS-SUBCLASS
SPEAR, JAMES M	1615	424-472000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are enclosed:
- ☐ Issue Fee
- ☐ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies _____

4b. Payment of Fee(s):
- ☐ A check in the amount of the fee(s) is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☐ The Director is hereby authorized by charge the required fee(s), or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
- ☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

The Director of the USPTO is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above. NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Patent Owner Ex. 2005
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Page 42 of 613

UNITED STATES PATENT AND TRADEMARK OFFICE

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P.O. Box 1450
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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/158,216	05/31/2002	John R. Plachetka	7569/73281	5014

7590 03/29/2005

Michael A Sanzo
Fitch Even Tabin & Flannery
1801 K Street NW Suite 4011
Washinton, DC 20006-1201

EXAMINER	
SPEAR, JAMES M	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 03/29/2005

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 273 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 273 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571) 272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at (703) 305-8283.

PTOL-85 (Rev. 12/04) Approved for use through 04/30/2007.

Patent Owner Ex. 2005
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Notice of Allowability	Application No.	Applicant(s)	
	10/158,216	PLACHETKA, JOHN R.	
	Examiner	Art Unit	
	James M. Spear	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *The Request for Continued Examination and Amendment filed 11/22/2004*.

2. ☒ The allowed claim(s) is/are *1-50 and 53-57*.

3. ☒ The drawings filed on *31 May 2002* are accepted by the Examiner.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).
   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☐ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

James M. Spear

JAMES M. SPEAR
PRIMARY EXAMINER

AU 1615

Patent Owner Ex. 2005
IPR2015-01344
Page 44 of 613

1. The following is an examiner's statement of reasons for allowance:

2. Applicant shows a unit dose form of an acid inhibitor and a non-steroidal anti-inflammatory drug (NSAID) formulated to provide coordinated release of said drugs. Combinations of such drugs are known. Goldman et al US 5,204,118 and Depui et al US 6,613,354 B2, considered the closest prior art of record show combinations of such drugs. The prior art does not show nor fairly suggest the particular combination wherein said NSAID is incorporated in the dosage form such that it is surrounded by a coating that upon ingestion of said unit dosage form by a patient prevents the release of essentially any NSAID from said dosage form unless the ph of the surrounding medium is 3.5 or higher and at least a portion of said acid inhibitor is not surrounded by an enteric coating and upon ingestion of said unit dosage form by a patient is released regardless of whether the ph of the surrounding medium is below 3.5 or above 3.5. This relationship between ph and drug delivery enables more safe delivery of the active agents than previous dosage forms.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays,

should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Claims 1-50 and 53-57 are allowed.

Claims 51 and 52 have been canceled.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James M Spear whose telephone number is 571 272 0605. The examiner can normally be reached on Monday thru Friday from 6:30 AM to 3 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page, can be reached on 571 272 0602. The fax phone number for the organization where this application or proceeding is assigned is 571 273 8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

James M. Spear

James M Spear
Primary Examiner
Art Unit 1615

March 20, 2005

Issue Classification	Application/Control No.	Applicant(s)/Patent under Reexamination
	10/158,216	PLACHETKA, JOHN R.
	Examiner	Art Unit
	James M. Spear	1615

ISSUE CLASSIFICATION

ORIGINAL CLASS	ORIGINAL SUBCLASS	CROSS REFERENCE(S) CLASS	CROSS REFERENCE(S) SUBCLASS (ONE SUBCLASS PER BLOCK)
424	472	424	457 463 468 474 480 482

INTERNATIONAL CLASSIFICATION

A61	K	9/22	
A61	K	9/24	
A61	K	9/32	
A61	K	9/52	

(Assistant Examiner) (Date)

(Legal Instruments Examiner) 3/28/05 (Date)

JAMES M. SPEAR
PRIMARY EXAMINER

James M. Spear
(Primary Examiner) (Date)
3-20-2005

Total Claims Allowed: 55

O.G. Print Claim(s)	O.G. Print Fig.
1	1

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1	31	31		61		91		121		151		181
2	2	32	32		62		92		122		152		182
3	3	33	33		63		93		123		153		183
4	4	34	34		64		94		124		154		184
5	5	35	35		65		95		125		155		185
6	6	36	36		66		96		126		156		186
7	7	37	37		67		97		127		157		187
8	8	38	38		68		98		128		158		188
9	9	39	39		69		99		129		159		189
10	10	40	40		70		100		130		160		190
11	11	41	41		71		101		131		161		191
12	12	42	42		72		102		132		162		192
13	13	43	43		73		103		133		163		193
14	14	44	44		74		104		134		164		194
15	15	45	45		75		105		135		165		195
16	16	46	46		76		106		136		166		196
17	17	47	47		77		107		137		167		197
18	18	48	48		78		108		138		168		198
19	19	49	49		79		109		139		169		199
20	20	50	50		80		110		140		170		200
21	21		~~51~~		81		111		141		171		201
22	22		~~52~~		82		112		142		172		202
23	23	51	53		83		113		143		173		203
24	24	52	54		84		114		144		174		204
25	25	53	55		85		115		145		175		205
26	26	54	56		86		116		146		176		206
27	27	55	57		87		117		147		177		207
28	28		58		88		118		148		178		208
29	29		59		89		119		149		179		209
30	30		60		90		120		150		180		210

Search Notes

Application/Control No.	Applicant(s)/Patent under Reexamination	
10/158,216	PLACHETKA, JOHN R.	
Examiner	**Art Unit**	
James M. Spear	1615	

SEARCHED			
Class	Subclass	Date	Examiner
424	457	3-20-05	JSpear
	463		
	468		
	472		
	474		
	480		
	482		

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner
424	457	3-20-05	JSpear
	463		
	468		
	472		
	474		
	480		
	482		

SEARCH NOTES (INCLUDING SEARCH STRATEGY)	DATE	EXMR
WEST update Inventor search, searched for combination dosage forms of NSAID and acid inhibitor with a relationship to Ph.	3-20-05	JSpear

U.S. Patent and Trademark Office

Part of Paper No. 03202005

WEST Search History

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	DB=PGPB,USPT,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=AND		
☐	L9	L8 and 424/$.ccls.	285
☐	L8	L7 and (ph same coat$)	483
☐	L7	(cimetidine or ranitidine or ebrotidine or pabutidine or lafutidine or loxtidine or famotidine) and (aspirin or acetaminophen or ibuprofen or flurbiprofen or ketoprofen or lornoxicam or naproxen or oxaprozin or etodolac or indomethacin or ketorolac or nabumetone)	2738
☐	L6	L5 and (cimetidine or ranitidine or ebrotidine or pabutidine or lafutidine or loxtidine or famotidine)	11
☐	L5	L4 and coat$	46
☐	L4	L3 and ph	104
☐	L3	(antiinflammatory) same (acid near2 inhibitor)	150
☐	L2	L1 and ph	8
☐	L1	(plachetka near2 john).in.	17

END OF SEARCH HISTORY

Patent Owner Ex. 2005
IPR2015-01344
Page 50 of 613

OIPE JC56
NOV 22 2004
PATENT & TRADEMARK OFFICE

IAW RCE/ 1615

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of:	
Plachetka, John R.	Art Unit: 1615
Appl. No.: 10/158,216	Examiner: Spear, J.
Filed: May 31, 2002	Atty. Dkt.: 7569/73281
For: **Pharmaceutical Compositions for the Coordinated Delivery of NSAIDs**	

Request for Continued Examination

Commissioner of Patents
U.S. Patent and Trademark Office
220 20th Street South
Customer Window, **MS RCE**
Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

This is a request for Continued Examination (RCE) of the above-identified application under 37 C.F.R. §1.114.

1. Submission required under 37 C.F.R. §1.114:

   a. Previously submitted:

   ☐ Consider the amendment(s)/reply under 37 C.F.R. §1.116 previously filed on [1.116 Amendment filed].

   ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on [Appeal Brief filed].

   ☐ Other:

   b. Enclosed:

   ☒ Amendment and Response Under 37 C.F.R. § 1.116

   ☐ Affidavit(s)/Declaration(s)

   ☐ Information Disclosure Statement (IDS)

   ☐ Other:

11/24/2004 AWONDAF1 00000079 061135 10158216
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2. Additional Items:

☐ Suspension of action on the above-identified application is requested under 37 C.F.R. §1.103(c) for a period of [No. of Months Suspension 1.103(c)] months. *(Period of suspension shall not exceed three months; fee under 37 C.F.R. §1.17(i) required.)*

☐ A petition for extension of time is enclosed.

☒ A return postcard is enclosed.

☐ Other: Change of Address Notice

☐ Applicant(s) assert entitlement to Small Entity Status.

☐ RCE Fee required under 37 C.F.R. § 1.17(e) without a claim of small entity status is: $790.00.

☒ RCE Fee required under 37 C.F.R. § 1.17(e) by an entity claiming small entity status is: $395.00.

☐ A check in the amount of $[Check Amount enclosed] is enclosed.

☒ Charge $$395.00 to Deposit Account No. 06-1135 under Order No. 7569/73281.

☒ The Director is hereby authorized to charge any additional fees which may be required in this application under 37 C.F.R. §§1.16-1.17 during its entire pendency, or credit any overpayment, to Deposit Account No. 06-1135. Should no proper payment be enclosed herewith, the Director is authorized to charge the unpaid amount to Deposit Account No. 06-1135. This sheet is filed in duplicate.

Respectfully submitted,

FITCH, EVEN, TABIN & FLANNERY

By Michael A. Sanzo

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Date November 19, 2004
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OIPE JC56
NOV 22 2004
PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of:

Plachetka, John R.

Appl. No.: 10/158,216

Filed: May 31, 2002

For: **Pharmaceutical Compositions for the Coordinated Delivery of NSAIDs**

Group Art Unit: 1615

Examiner: Spear, J.

Atty. Dkt.: 7569/73281

Amendment and Response Under 37 C.F.R. § 1.116

Commissioner for Patents
U.S. Patent and Trademark Office
220 20th Street South
Customer Window, **MS RCE**
Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

Sir:

In response to the Office Action dated October 20, 2004, Applicant respectfully requests reconsideration of the above-captioned application in view of the following amendments and remarks.

Amendments to the Claims begin on page 2 of the present document.

Remarks begin on page 10 of the present document.

Amendments to the Claims

Please cancel claims 51 and 52 without prejudice. Please add new claims 55-57 and amend the remaining claims as indicated below in the "List of Claims."

List of Claims

1. (Currently amended) A pharmaceutical composition in unit dose form suitable for oral administration to a patient, comprising:

   (a) an acid inhibitor present in an amount effective to raise the gastric pH of said patient to at least 3.5 upon the administration of one or more of said unit dosage forms;

   (b) a non-steroidal anti-inflammatory drug (NSAID) in an amount effective to reduce or eliminate pain or inflammation in said patient upon administration of one or more of said unit dosage forms;

   and wherein said unit dosage form provides for coordinated release such that: ~~said acid inhibitor is released first and said NSAID is not released until the gastric pH of said patient is 3.5 or higher~~

   i) said NSAID is surrounded by a coating that, upon ingestion of said unit dosage form by said patient, prevents the release of essentially any NSAID from said dosage form unless the pH of the surrounding medium is 3.5 or higher;

   ii) at least a portion of said acid inhibitor is not surrounded by an enteric coating and, upon ingestion of said unit dosage form by said patient, is released regardless of whether the pH of the surrounding medium is below 3.5 or above 3.5.

2. (Currently amended) The pharmaceutical composition of claim 1, wherein said acid inhibitor is ~~selected from: a proton pump inhibitor and~~ an H2 blocker.

3. (Currently amended) The pharmaceutical composition of claim 2, wherein said ~~acid inhibitor is an~~ H2 blocker is selected from the group consisting of: cimetidine; ranitidine; ebrotidine; pabutidine; lafutidine; loxtidine and famotidine.

4. (Original) The pharmaceutical composition of claim 3, wherein said H2 blocker is famotidine, present in said unit dosage form in an amount of between 5 mg and 100 mg.

5. (Original) The pharmaceutical composition of claim 1, wherein said acid inhibitor is a proton pump inhibitor selected from the group consisting of: omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole.

6. (Original) The pharmaceutical composition of claim 5, wherein said proton pump inhibitor is pantoprazole, present in said unit dosage form in an amount of between 10 mg and 200 mg.

7. (Original) The pharmaceutical composition of claim 1, wherein said NSAID is a cyclooxygenese-2 (COX-2) inhibitor.

8. (Original) The pharmaceutical composition of claim 7, wherein said COX-2 inhibitor is selected from the group consisting of celecoxib; rofecoxib; meloxicam; piroxicam; valdecoxib, parecoxib, etoricoxib, CS-502, JTE-522; L-745,337; and NS398.

9. (Original) The pharmaceutical composition of claim 1, wherein said NSAID is selected from the group consisting of: aspirin; acetaminophen; ibuprofen; flurbiprofen; ketoprofen; lornoxicam; naproxen; oxaprozin; etodolac; indomethacin; ketorolac; and nabumetone.

10. (Original) The pharmaceutical composition of claim 9, wherein said NSAID is naproxen present in an amount of between 50 mg and 1500 mg.

11. (Original) The pharmaceutical composition of claim 10, wherein said naproxen is present in an amount of between 200 mg and 600 mg.

12. (Currently amended) The pharmaceutical composition of claim 1 wherein said unit dosage form is a multilayer tablet comprising a single core and one or more layers outside of said single core, wherein:

i) said NSAID is present in said core;

ii) said coating that does not release said NSAID unless the pH of the surrounding medium is 3.5 or higher surrounds said core; and

iii) said acid inhibitor is in said one more layers outside said core.

13. (Currently amended) The pharmaceutical composition of claim 12, wherein ~~said unit dosage form is a trilayer tablet having an outer layer of said acid inhibitor and an inner core of said NSAID~~ said one or more layers outside of said core do not contain NSAID and are not surrounded by an enteric coating.

14. (Currently amended) The pharmaceutical composition of claim ~~12~~ 13, wherein said unit dosage form is a bilayer tablet having an outer layer of said acid inhibitor and an inner core of said NSAID and wherein said outer layer of said tablet is surrounded by a non-enteric film coating that releases said acid inhibitor upon ingestion by a patient.

15. (Currently amended) The pharmaceutical composition of any one of claims ~~12-14~~ 1 or 7-14, wherein said ~~tablet has an inner core of said NSAID surrounded by a barrier coating that does not dissolve unless the pH of the surrounding medium is 3.5 or greater~~ acid inhibitor is a proton pump inhibitor.

16. (Currently amended) The pharmaceutical composition of ~~any one of claims 12-14~~ claim 15, wherein said ~~tablet has an inner core of said NSAID surrounded by a barrier~~ coating ~~that~~ surrounding said core does not dissolve unless the pH of the surrounding medium is 4 or greater.

17. (Currently amended) The pharmaceutical composition of ~~any one of claims 12-14~~ claim 15, wherein said ~~tablet has an inner core of said NSAID surrounded by a barrier~~ coating

~~that~~ surrounding said core does not dissolve unless the pH of the surrounding medium is 5 or greater.

18. (Currently amended) The pharmaceutical composition of any one of ~~claims 12-14~~ claims 7-14, wherein ~~said tablet has an inner core of said NSAID surrounded by a barrier coating that dissolves at a rate such that said NSAID is not released until the pH of the surrounding medium is 3.5 or greater~~ said acid inhibitor is an H2 blocker.

19. (Currently amended) The pharmaceutical composition of ~~any one of claims 12-14~~ claim 18, wherein said tablet has an inner core of said NSAID surrounded by a barrier coating that dissolves at a rate such that said NSAID is not released until the pH of the surrounding medium is 4 or greater.

20. (Currently amended) The pharmaceutical composition of ~~any one of claims 12-14~~ claim 18, wherein said tablet has an inner core of said NSAID surrounded by a barrier coating that dissolves at a rate such that said NSAID is not released until the pH of the surrounding medium is 5 or greater.

21. (Original) The pharmaceutical composition of claim 1, wherein said unit dosage form is a capsule.

22. (Original) A method of treating a patient for pain or inflammation, comprising administering to said patient the pharmaceutical composition of any one of claims 1-14.

23. (Previously presented) The method of claim 22, wherein said pain or inflammation is due to either osteoarthritis or rheumatoid arthritis.

24. (Original) A method of treating a patient for pain or inflammation, comprising:

(a) orally administering to said patient an acid inhibitor at a dose effective to raise the gastric pH of said patient to at least 3.5; and

(b) orally administering to said patient an NSAID that is coated in a polymer that only dissolves at a pH of 3.5 or greater.

25. (Original) The method of claim 24, wherein said acid inhibitor is an H2 blocker.

26. (Original) The method of claim 25, wherein said H-2 blocker is selected from the group consisting of: cimetidine; ranitidine; ebrotidine; pabutidine; lafutidine; loxtidine and famotidine.

27. (Original) The method of claim 26, wherein said H2 blocker is famotidine administered at a dose of between 5 mg and 100 mg.

28. (Original) The method of claim 24, wherein said acid inhibitor is a proton pump inhibitor.

29. (Original) The method of claim 28, wherein said proton pump inhibitor is selected from the group consisting of: omeprazole, esomeprazole, lansoprazole, rabeprazole and pantoprazole.

30. (Original) The method of claim 29, wherein said proton pump inhibitor is pantoprazole administered at a dose of between 10 mg and 200 mg.

31. (Original) The method of any one of claims 24 - 30, wherein said NSAID is a COX-2 inhibitor selected from the group consisting of: celecoxib; rofecoxib; meloxicam; piroxicam; valdecoxib, parecoxib, etoricoxib, CS-502, JTE-522; L-745,337; and NS398.

32. (Original) The method of any one of claims 24 – 30, wherein said NSAID is selected from the group consisting of: aspirin; acetaminophen; ibuprofen; flurbiprofen; ketoprofen; lornoxicam; naproxen; oxaprozin; etodolac; indomethacin; ketorolac; and nabumetone.

33. (Original) The method of claim 32, wherein said NSAID is naproxen administered at a dose of between 50 mg and 1500 mg.

34. (Original) The method of claim 33, wherein said naproxen is administered at a dose of between 200 mg and 600 mg.

35. (Original) The method of claim 24, wherein said acid inhibitor and said NSAID are delivered as part of a single dosage form providing for the coordinated release of therapeutic agents.

36. (Original) The method of claim 35, wherein said single dosage form is a bilayer tablet with an outer layer comprising an H2 blocker and an inner core comprising an NSAID.

37. (Original) A method of treating a patient for pain or inflammation, comprising:

(a) orally administering to said patient an acid inhibitor at a dose effective to raise the gastric pH of said patient to at least 3.5; and

(b) concurrently administering to said patient an NSAID that is coated in a polymer that dissolves at a rate such that said NSAID is not released until said gastric pH is at 3.5 or higher.

38. (Original) The method of claim 37, wherein said acid inhibitor is an H2 blocker.

39. (Original) The method of claim 38, wherein said H-2 blocker is selected from the group consisting of: cimetidine; ranitidine; ebrotidine; pabutidine; lafutidine; loxtidine and famotidine.

40. (Original) The method of claim 39, wherein said H2 blocker is famotidine administered at a dose of between 5 mg and 100 mg.

41. (Original) The method of claim 37, wherein said acid inhibitor is a proton pump inhibitor.

42. (Original) The method of claim 41, wherein said proton pump inhibitor is selected from the group consisting of: omeprazole, esomeprazole, lansoprazole, rabeprazole and pantoprazole.

43. (Original) The method of claim 42, wherein said proton pump inhibitor is pantoprazole administered at a dose of between 10 mg and 200 mg.

44. (Original) The method of any one of claims 37 - 43, wherein said NSAID is a COX-2 inhibitor selected from the group consisting of: celecoxib; rofecoxib; meloxicam; piroxicam; valdecoxib, parecoxib, etoricoxib, CS-502, JTE-522; L-745,337; and NS398.

45. (Original) The method of any one of claims 37 – 43, wherein said NSAID is selected from the group consisting of: aspirin; acetaminophen; ibuprofen; flurbiprofen; ketoprofen; lornoxicam; naproxen; oxaprozin; etodolac; indomethacin; ketorolac; and nabumetone.

46. (Original) The method of claim 45, wherein said NSAID is naproxen administered at a dose of between 50 mg and 1500 mg.

47. (Original) The method of claim 46, wherein said naproxen is administered at a dose of between 200 mg and 600 mg.

48. (Original) The method of claim 47, wherein said acid inhibitor and said NSAID are delivered as part of a single dosage form providing for the coordinated release of therapeutic agents.

49. (Original) The method of claim 48, wherein said single dosage form is a bilayer tablet with an outer layer comprising an H2 blocker and an inner core comprising an NSAID.

50. (Original) A method of improving compliance in patients requiring frequent daily dosages of an acid inhibitor and an NSAID comprising administering said dosages in a coordinated unit dosage form in accordance with claim 1.

51-52. Cancelled

53. (Currently amended) A method of treating a patient for pain or inflammation, comprising administering to said patient the pharmaceutical composition of ~~claim 51~~ claim15.

54. (Previously presented) The method of claim 53, wherein said pain or inflammation is due to either osteoarthritis or rheumatoid arthritis.

55. (New) The pharmaceutical composition of any one of claims 5-11 wherein said unit dosage form is a multilayer tablet comprising a single core and one or more layers outside of said single core, wherein:

i) said NSAID is present in said core;

ii) said coating that does not release said NSAID unless the pH of the surrounding medium is 3.5 or higher surrounds said core; and

iii) said acid inhibitor is in said one more layers outside said core.

56. (New) The pharmaceutical composition of claim 55, wherein said one or more layers outside of said core do not contain NSAID and are not surrounded by an enteric coating.

57. (New) The pharmaceutical composition of claim 56, wherein said unit dosage form is a bilayer tablet having an outer layer of said acid inhibitor and an inner core of said NSAID and wherein said outer layer of said tablet is surrounded by a non-enteric film coating that, upon ingestion by a patient, releases said acid inhibitor into the stomach of said patient.

Remarks

I. Status of the Application and Claims

As originally filed, the present application had a total of 50 claims. Applicant added claims 51-54 in a previous submission to the PTO. Claims 51 and 52 have been cancelled herein and new claims 55-57 have been added. Thus, the claims pending in the application after the entry of the present amendments will be claims 1-50, 53-57.

II. The Amendments

Claims to pharmaceutical compositions were amended both to comply with suggestions in the Office Action and to emphasize characteristics that Applicants believe are central to their invention. Amended claims require that NSAID be surrounded by a coating that prevents its release from the dosage form unless the pH of the surrounding medium is 3.5 or higher, and that at least a portion of the acid inhibitor in compositions is not surrounded by an enteric coating and is released regardless of whether the pH is above 3.5 or below 3.5. Amendments were introduced into claims 12-14 to indicate that that the recited tablet dosage forms contain a single core with NSAID that is surrounded by the coating that prevents drug release and that acid inhibitor is in separate outer layers that are not enterically coated (claim 12). Other amendments indicate that the outer layers of the tablets do not contain NSAID (claim 13) and may be surrounded by a non-enteric film that allows for the release of acid inbitor into a patient's stomach (claim 14). New claims 55-57 introduce these same requirements but refer back to claims 5-11 rather than to claim 1. The dependency of other claims was changed and an attempt was made to restrict certain claims to either dosage forms containing H2 blockers or proton pump inhibitors.

These amendments do not add new matter to the application and their entry is therefore respectfully requested.

The Rejections

I. Rejection of Claims Under 35 USC § 102(b)

On pages 2 and 3 of the Office Action, the Examiner rejects claims under 35 USC §102(b) based upon Goldman *et al.* (US 5,204,118). However, Applicant has amended

pharmaceutical composition claims so that they now require that NSAID be surrounded by a coating that does not release the NSAID until the pH of the surrounding medium is at least 3.5. Based upon statements made in the Office Action, Applicant believes that this should be sufficient to obviate the rejection.

II. Rejection of Claims Under 35 USC § 102(e)

On page 3 of the Office Action, claims 1, 2, 5, 6, 9-12, 21 and 23 are rejected under 35 USC §102(e) based upon Depui, *et al.* (US 6,613,354). The arguments made by the Examiner are a little confusing. In one part, it appears that the Examiner seems to say that Applicant's previous arguments are not persuasive because the claims failed to include a requirement that NSAID be coated to prevent it from being released until the pH of the surrounding medium rises. If this is the case, then Applicant submits that the rejection has been overcome by the amendments made herein.

However, at the very end of page 3, the Examiner seems to imply that Depui would serve as an inherent anticipation of Applicant's composition claims even if a limitation concerning the coating of NSAID is included. If this is the case, then Applicant respectfully traverses the rejection.

An inherent anticipation occurs in cases where a reference fails to literally disclose an element required by a claim but it can be shown that the missing element is *necessarily* present based upon the other teachings in the reference. The fact that the missing element *might* be present is insufficient. For example, all of the physical properties of a compound are inherent in its chemical structure but the amount of the compound added to a chemical reaction is not. In the present case, the disclosure of a drug composition containing an NSAID and acid inhibitor in which the acid inhibitor is coated (Depui) certainly does not inherently anticipate a claim to a composition containing these drugs in which the NSAID is coated and acid inhibitor is not (Applicant's claims). The coating of one component does not mean that the other component must necessarily also be coated. It should also be recognized that Depui's compositions would act in a very different way than those claimed by Applicant. Specifically, release of acid inhibitor in Depui's compositions would be delayed whereas acid inhibitor release from

Applicant's compositions is immediate and only the release of NSAID is delayed. The basic concept of coating NSAIDs in a way that will prevent them from being released until the surrounding pH rises to at least 3.5 is entirely missing from the Depui reference. Applicant therefore submits that that the reference cannot be validly used to reject the presently pending claims as inherently anticipated.

III. Claim Objections

On page 4 of the Office Action, the Examiner objects to claims 7, 8, 13-20 and 51-54 as being dependent on a rejected base claim but indicates that they would be allowable if rewritten in independent form. Since Applicant believes that the base claims should now be allowable, it is respectfully submitted that the Examiner's objection has been overcome.

Conclusion

In light of the amendments and discussion above, Applicant believes that all of the rejections and objections in the present Office Action have been overcome and that the claims are now in condition for allowance. Early notice to this effect is earnestly solicited.

If, in the opinion of the Examiner, a phone call may help to expedite the prosecution of this application, the Examiner is invited to call Applicant's undersigned attorney at (202) 419-7013.

Respectfully submitted,

FITCH, EVEN, TABIN & FLANNERY

By: Michael A. Sanzo

Michael A. Sanzo
Reg. No. 36,912
Attorney for Applicant

Date: November 19, 2004
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OIPE JC66 NOV 22 2004 PATENT & TRADEMARK OFFICE

November 19, 2004

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220 20th Street South
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Crystal Plaza Two, Lobby, Room 1B03
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Re: Request for Continued Examination and Amendment and Response

Appl. No.:	10/158,216
Filed:	May 31, 2002
Title:	**Pharmaceutical Compositions for the Coordinated Delivery of NSAIDs**
Inventor(s):	Plachetka, John R.
Atty. Dkt.:	7569/73281

Dear Sir:

The following documents are being forwarded herewith for appropriate action by the U.S. Patent and Trademark Office:

1. Request for Continued Examination;

2. Amendment and Response Under 37 C.F.R. § 1.116; and

3 Return postcard.

The Director is hereby authorized to charge the fee in the amount of $395 (small entity status is claimed) for the filing of a Request for Continued Examination to our Deposit Account No. 06-1135 under Order No. 7569/73281. The Director is also authorized to charge any fee deficiency with respect to this filing and any other fee required in connection with the present case, or credit any overpayment, to our Deposit Account No. 06-1135 under Order No. 7569/73281.

It is respectfully requested that the enclosed postcard be stamped with the date the enclosed documents are received by the PTO and that it be returned as soon as possible.

Very truly yours,

FITCH, EVEN, TABIN & FLANNERY

Michael A. Sanzo
Reg. No. 36,912
Attorney for Applicant

MAS:ct
Enclosures

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OIPE JC66 NOV 22 2004 PATENT & TRADEMARK OFFICE

November 19, 2004

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Re: Request for Continued Examination and Amendment and Response

Appl. No.:	10/158,216
Filed:	May 31, 2002
Title:	**Pharmaceutical Compositions for the Coordinated Delivery of NSAIDs**
Inventor(s):	Plachetka, John R.
Atty. Dkt.:	7569/73281

Dear Sir:

The following documents are being forwarded herewith for appropriate action by the U.S. Patent and Trademark Office:

1. Request for Continued Examination;

2. Amendment and Response Under 37 C.F.R. § 1.116; and

3 Return postcard.

The Director is hereby authorized to charge the fee in the amount of $395 (small entity status is claimed) for the filing of a Request for Continued Examination to our Deposit Account No. 06-1135 under Order No. 7569/73281. The Director is also authorized to charge any fee deficiency with respect to this filing and any other fee required in connection with the present case, or credit any overpayment, to our Deposit Account No. 06-1135 under Order No. 7569/73281.

It is respectfully requested that the enclosed postcard be stamped with the date the enclosed documents are received by the PTO and that it be returned as soon as possible.

Very truly yours,

FITCH, EVEN, TABIN & FLANNERY

Michael A. Sanzo
Reg. No. 36,912
Attorney for Applicant

MAS:ct
Enclosures

PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 1, 2001

Application or Docket Number: 10158214

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS	50	
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	12.2 was 20=	* 92
INDEPENDENT CLAIMS	3 minus 3 =	*
MULTIPLE DEPENDENT CLAIM PRESENT		☒

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐		OR	OTHER THAN SMALL ENTITY	
RATE	FEE		RATE	FEE
BASIC FEE	370.00	OR	BASIC FEE	740.00
X$ 9=		OR	X$18=	1656.00
X42=		OR	X84=	
+140=		OR	+280=	280
TOTAL		OR	TOTAL	2676.00

CLAIMS AS AMENDED - PART II

7/12/04

AMENDMENT A	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 171	Minus	**	*
Independent	1	Minus	***	*
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

11/22/04

AMENDMENT B	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 201	Minus	** 122	* 79
Independent	* 3	Minus	*** 3	*
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=	711	OR	X$18=	
X42=	—	OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE	711	OR	TOTAL ADDIT. FEE	

AMENDMENT C	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	*
Independent	*	Minus	***	*
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

FORM PTO-875 (Rev. 8/01) — U.S. Government Printing Office: 2001 — Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

10/158216

CLAIMS ONLY

11/22/04

SERIAL NO. 10/158216 | FILING DATE

APPLICANT(S)

CLAIMS

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT		*		*		*	
	IND.	DEP.	IND.	DEP.	IND.	DEP.	IND.	DEP.	IND.	DEP.	IND.	DEP.
1	1		1				51					
2		1		1			52					
3		3		3			53			3		
4		3		3			54			3		
5		3		3			55			7		
6		3		8			56			7		
7		3		8			57			7		
8		3		8			58					
9		3		1			59					
10		3		1			60					
11		3		1			61					
12		3		1			62					
13		3		1			63					
14		3		1			64					
15		3		3			65					
16		3		3			66					
17		3		3			67					
18		3		8			68					
19		3		8			69					
20		3		8			70					
21		3		1			71					
22		0		14			72					
23		0		14			73					
24	1		1				74					
25		1		1			75					
26		1		1			76					
27		1		1			77					
28		1		1			78					
29		1		1			79					
30		1		1			80					
31		1		7			81					
32		7		7			82					
33		7		7			83					
34		7		7			84					
35		1		7			85					
36		1		1			86					
37	1		1				87					
38		1		1			88					
39		1		1			89					
40		1		1			90					
41		1		1			91					
42		1		1			92					
43		1		1			93					
44		7		7			94					
45		7		7			95					
46		7		7			96					
47		7		7			97					
48		7		7			98					
49		7		7			99					
50		7		7			100					
TOTAL IND.	3	-1	3	-1		-1	TOTAL IND.		-1	0	-1	-1
TOTAL DEP.	119		103				TOTAL DEP.			27		
TOTAL CLAIMS	122		174				TOTAL CLAIMS			27		

* MAY BE USED FOR ADDITIONAL CLAIMS OR AMENDMENTS

FORM PTO-2032 (1-96)

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

*U.S. GOVERNMENT PRINTING OFFICE: 1996 • 420-214/70332

BS

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/158,216	05/31/2002	John R. Plachetka	7569/73281	5014

7590 10/20/2004

Michael A Sanzo
Fitch Even Tabin & Flannery
1801 K Street NW Suite 4011
Washinton, DC 20006-1201

EXAMINER	
SPEAR, JAMES M	
ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 10/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

Office Action Summary	Application No.	Applicant(s)	
	10/158,216	PLACHETKA, JOHN R.	
	Examiner	Art Unit	
	James M Spear	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *24-49* is/are allowed.

6)☒ Claim(s) *1-6,9-12,21-23 and 50* is/are rejected.

7)☒ Claim(s) *7,8,13-20 and 51-54* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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The response and Information Disclosure Statement filed July 22, 2004 have been entered. Claims 1-54 are pending in the application as set forth in the Preliminary Amendment filed October 17, 2003. A complete copy of the IDS filed April 24, 2003 is enclosed and has been considered.

a. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 1-5, 9, 10, 11, 21, 22 and 50 are rejected under 35 U.S.C. 102(b) as being anticipated by Goldman et al US 5,204,118. The claims remain rejected for the reasons set forth in the Office Action mailed April 22, 2004.

3. Applicant's arguments filed July 22, 2004 have been fully considered but they are not persuasive. Applicants state that "all of applicant's claims have requirements not only with respect to the type of active ingredients present in compositions or methods, but also with respect to the way in which active ingredients are delivered in relation to one another". "Specifically claim 1 requires that there be a single unit dosage form containing both an acid inhibitor and an NSAID and that, upon administration to a patient, the dosage form deliver these drugs in a coordinated fashion such that the acid inhibitor is released first and the NSAID is not released until after the gastric ph of the patient is 3.5 or higher. Applicant submits that these characteristics are not disclosed in Goldman." Applicants further state that, "by preventing NSAID from being released until

the surrounding environment becomes more basic, the pharmaceutical composition defined in claim 1 provides for safer delivery." However claim 1 is a product claim. Applicant's arguments directed to release are more suited for process limitations while claim 1 is a composition. There is nothing in claim 1 that enables the release applicant is referring to. The Goldman reference shows the same components as applicants and the composition would therefore inherently function the same as applicant's. Amending claim 1 to incorporate a polymer coating as set forth in claims 24 and 51-54 would be given favorable consideration in overcoming the prior art rejection.

4. Claims 1, 2, 5, 6, 9-12, 21 and 23 are rejected under 35 U.S.C. 102(e) as being anticipated by Depui et al US 6,613,354 B2. The claims remain rejected for the reasons set forth in the Paper mailed April 22, 2004. Applicants argue that the Depui et al reference, while containing both an NSAID and a proton pump inhibitor, teaches the use of tablet coatings for the purpose of preventing the degradation of gastric inhibitor, not for the purpose of retarding the release of NSAID or protecting the gastrointestinal tract of a patient from damage caused by NSAID released at low ph. Applicant's arguments are not persuasive because applicant's claim 1 does not disclose a coating. The prior art teaches the same elements as applicant's claims. It is the position of this office that since the composition components are the same the dosage form would inherently provide the same release rates and effects on the gastric ph irrespective of the additional coating components.

5. Claims 7, 8, 13-20 and 51-54 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 1-6, 9-12, 21-23 and 50 are rejected.

Claims 24-49 are allowed.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James M Spear whose telephone number is 571 272 0605. The examiner can normally be reached on Monday thru Friday from 6:30 AM to 3 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page, can be reached on 571 272 0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

James M. Spear

James M Spear
Primary Examiner
Art Unit 1615

October 16, 2004

LIST OF REFERENCES CITED BY APPLICANT *(Use several sheets if necessary)*	Atty. Docket No.: 7569/73281	Appl No.: 10/158,216
	Applicant(s) Plachetka, John R.	
	Filing Date: May 31, 2002	Group: to be assigned

OIPE JUL 22 2004 PATENT & TRADEMARK OFFICE JC60

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date If Appropriate
	AA 1						
	AB 1						
	AC 1						
	AD 1						
	AE 1						
	AF 1						

FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	Subclass	Translation	
							Yes	No
	AG 1							
	AH 1							
	AI 1							
	AJ 1							

OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)

	AK 1	HOWDEN, "Clinical Pharmacology of Omeprazole," *Clin. Pharmacokinet. 20(1)*:38-49 (1991) abstract.
	AL 1	PILBRANT, *et al.*, "Development of an Oral Formulation of Omeprazole," *Scand. J. Gastroenterol. 20(Suppl. 108)*:113-120 (1985).
	AM1	SHARMA, "Comparison of 24-Hour Intragastric pH Using Four Liquid Formulations of Lansoprazole and Omeprazole," *Am. J. Health-Syst. Pharm. 56(Supp. 4)*:S18-S21 (1999).
	AN 1	
	AO 1	
	AP 1	
	AQ 1	
	AR 1	

Examiner JAMES M. SPEAR	Date Considered 10-16-2004

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IPR2015-01344
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LIST OF REFERENCES CITED BY APPLICANT *(Use several sheets if necessary)*	Atty. Docket No.: 7569/73281	Appl No.: 10/158,216
	Applicant(s) Plachetka, John R.	
	Filing Date: May 31, 2002	Group: to be assigned AU 1615

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date If Appropriate
	AA 1	4,554,276	Nov. 19, 1985	LaMattina	514	272	Oct. 3, 1983
	AB 1	4,676,984	Jun. 30, 1987	Wu, *et al.*	424	157	Aug. 14, 1985
	AC 1	4,704,278	Nov. 3, 1987	Wu, *et al.*	424	157	Aug. 8, 1986
	AD 1	4,757,060	Jul. 12, 1988	Lukacsko, *et al.*	514	160	Apr. 29, 1986
	AE 1	4,766,117	Aug. 23, 1988	Crawford, *et al.*	514	219	Dec. 12, 1986
	AF 1	4,786,505	Nov. 22, 1988	Lovgren, *et al.*	424	468	Apr. 20, 1987

FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	Subclass	Translation Yes	Translation No
	AG 1	WO 85/03443	15 August 1985	WIPO	A61K	45/06		
	AH 1	GB 2 105 193	23 March 1983	United Kingdom	A61K	31/34		
	AI							
	AJ							

OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)

	AK 1	Bigard, *et al.*, "Complete Prevention by Omeprazole of Aspirin Induced Gastric Lesions in Healthy Subjects," *GUT 29(5)*:A712, T49 (1988).
	AL 1	Bombardier, *et al.*, "Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis," *N. Engl. J. Med. 343*:1520-1528 (2000).
	AM1	Brown, *et al.*, "Prevention of the Gastrointestinal Adverse Effects of Nonsteroidal Anti-Inflammatory Drugs," *Pract. Drug Safety 21*:503-512 (1999).
	AN 1	Cullen, *et al.*, "Primary Gastroduodenal Prophylaxis with Omeprazole for Non-Steroidal Anti-Inflammatory Drug Users," *Aliment. Pharmacol. Ther. 12*:135-140 (1998).
	AO 1	Hawkey, "Progress in Prophylaxis Against Nonsteroidal Anti-Inflammatory Drug-Associated Ulcers and Erosions," *Am. J. Med. 104*:67S-74S (1998).
	AP 1	Hawkey, *et al.*, "Omeprazole Compared with Misoprostol for Ulcers Associated with Nonsteroidal Anti-Inflammatory Drugs," *N. Engl. J. Med. 338*:727-734 (1998).
	AQ 1	Howden, "Clinical Pharmacology of Omeprazole," *Clin. Pharmacokinet. 20*:38-49 (1991).
	AR 1	Katz, *et al.*, "Gastric Acidity and Acid Breakthrough with Twice-Daily Omeprazole or Iansoprazole," *Aliment. Pharmacol. Ther 14*:709-714 (2000).

Examiner James M. Spear	Date Considered 04-15-2004

APR 24 2003 PATENT & TRADEMARK OFFICE

APR 25 2003 TECH CENTER 1600/2900

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IPR2015-01344
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LIST OF REFERENCES CITED BY APPLICANT (Use several sheets if necessary)	Atty. Docket No.: 7569/73281	Appl No.: 10/158,216
	Applicant(s) Plachetka, John R.	
	Filing Date: May 31, 2002	Group: to be assigned AU 1615

OIPE JC174 APR 2 6 2003 PATENT & TRADEMARK OFFICE

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date If Appropriate
JS	AA 2	5,037,815	Aug. 6, 1991	Lukacsko, *et al.*	514	162	Sep. 8, 1988
	AB 2	5,204,118	Apr. 20, 1993	Goldman, *et al.*	424	489	Apr. 29, 1992
	AC 2	5,417,980	May 23, 1995	Goldman, *et al.*	424	464	Jun. 29, 1994
	AD 2	5,466,436	Nov. 14, 1995	Stables	514	161	Dec. 17, 1993
	AE 2	5,716,648	Feb. 10, 1998	Halskov, *et al.*	424	682	Dec. 21, 1995
JS	AF 2	6,365,184 B1	Apr. 2, 2002	Depui, *et al.*	424	469	Dec. 23, 1999

FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	Subclass	Translation Yes	Translation No
	AG							
	AH							
	AI							
	AJ							

OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)

JS	AK 2	Kephart, *et al.*, "Coprescribing of Nonsteroidal Anti-Inflammatory Drugs and Cytoprotective and Antiulcer Drugs in Nova Scotia's Senior Population," *Clin. Ther. 17*:1159-1173 (1995).
	AL 2	Lad, *et al.*, "Management of Nonsteroidal Anti-Inflammatory Drug-Induced Gastroduodenal Disease by Acid Suppression," *Can. J. Gastroenterol 13*:135-142 (1999).
	AM2	Mattsson, *et al.*, "Omeprazole Provides Protection Against Experimentally Induced Gastric Mucosal Lesions," *Eur. J. Pharmacol. 91*:111-114 (1983).
	AN 2	Oddsson, *et al.*, "Endoscopic Findings in the Stomach and Duodenum after Treatment with Enteric-Coated and Plain Naproxen Tablets in Healthy Subjects," *Scand. J. Gastroenterol. 25*:231-234 (1990).
	AO 2	Scheiman, "NSAID-Induced Peptic Ulcer Disease: A Critical Rview of Pathogenesis and Management," *Dig. Dis. 12*:210-222 (1994).
	AP 2	Selway, "Potential Hazards of Long-Term Acid Suppression," *Scand. J. Gasatroenterol. 25(Supp. 178)*:85-92 (1990).
	AQ 2	Silverstein, *et al.*, "Gastrointestinal Toxicity with Celecoxib vs. Nonsteroidal Anti-Inflammatory Drugs for Osteoarthritis and Rheumatoid Arthritis; The CLASS Study: A Randomized Controlled Trial," *JAMA 284*:1247-1255 (2000).
JS	AR 2	Tronstad, *et al.*, "Gastroscopic Findings after Treatment with Enteric-Coated and Plain Naproxen Tablets in Healthy Subjects," *Scand. J. Gastroenterol. 20*:239-242 (1985).

Examiner James M. Spear	Date Considered 04-15-2004

Patent Owner Ex. 2005
IPR2015-01344
Page 79 of 613

LIST OF REFERENCES CITED BY APPLICANT *(Use several sheets if necessary)*		Atty. Docket No.: 7569/73281	Appl No.: 10/158,216
		Applicant(s) Plachetka, John R.	
		Filing Date: May 31, 2002	Group: to be assigned AU 1615

OIPE APR 2 4 2003 PATENT & TRADEMARK OFFICE

RECEIVED APR 25 2003 TECH CENTER 1600/2900

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date If Appropriate
	AA						
	AB						
	AC						
	AD						
	AE						
	AF						

FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	Subclass	Translation Yes	Translation No
	AG							
	AH							
	AI							
	AJ							

OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)

JS	AK 3	Wolfe, *et al.*, "Gastrointestinal Toxicity of Nonsteroidal Anti-Inflammatory Drugs," *N. Engl. J. Med. 340*:1888-1899 (1999).
JS	AL 3	Yeomans, *et al.*, "A Comparison of Omeprazole with Ranitidine for Ulcers Associated with Nonsteroidal Anti-Inflammatory Drugs," *N. Engl. J. Med. 338*:719-726 (1998).
JS	AM3	Yeomans, *et al.*, "New Data on Healing of Nonsteroidal Anti-Inflammatory Drug-Associated Ulcers and Erosions," *Am. J. Med. 104*:56S-61S (1998).
	AN	
	AO	
	AP	
	AQ	
	AR	

Examiner James M. Spear	Date Considered 04-15-2004

Patent Owner Ex. 2005
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Index of Claims

Application No.	Applicant(s)
10/158,216	PLACHETKA, JOHN R.
Examiner	**Art Unit**
James M Spear	1615

√	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

Claim		Date
Final	Original	10/16/04
	1	✓
	2	↑
	3	|
	4	|
	5	↓
	6	✓
	7	O
	8	O
	9	✓
	10	✓
	11	✓
	12	✓
	13	O
	14	↑
	15	|
	16	|
	17	|
	18	|
	19	↓
	20	O
	21	✓
	22	✓
	23	✓
	24	II
	25	↑
	26	|
	27	|
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	29	|
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	45	|
	46	|
	47	|
	48	↓
	49	II
	50	✓

Claim		Date
Final	Original	10/16/04
	51	O
	52	O
	53	O
	54	O
	55	
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OIPE JC60
JUL 22 2004
PATENT & TRADEMARK OFFICE

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IFW

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*ADMITTED TO D.C. BAR; D.C. PRACTICE OF ALL OTHERS LIMITED TO FEDERAL COURTS AND AGENCIES

July 22, 2004

Commissioner of Patents
U.S. Patent and Trademark Office
220 20th Street South
Customer Window, **MS Amendment**
Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

Re: Response to Office Action and
Second Supplemental Information Disclosure Statement
Appl. No.: 10/158,216
Filed: May 31, 2002
Title: **Pharmaceutical Compositions for the Coordinated Delivery of NSAIDs**
Inventor(s): Plachetka, John R.
Atty. Dkt.: 7569/73281

Dear Sir:

The following documents are being forwarded herewith for appropriate action by the U.S. Patent and Trademark Office:

1. Response to Office Action Under 37 C.F.R. § 1.111;
2. Second Supplemental Information Disclosure Statement;
3. List of References Cited By Applicant;
4. References AK1-AM1; and
5. Return postcard.

OIPE
JUL 22 2004
PATENT & TRADEMARK OFFICE
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CALCULATION OF ADDITIONAL FEES

Applicant(s) have calculated additional fees as follows (**small entity status is claimed**):

	No. After Amendment	No. Previously Paid for	No. Extra	Rate	Fee
Total Claims Fee	166	166=	0	$ 9.00	0.00
Independent Claims Fee	5	5 =	0	$ 43.00	0.00
Multiple Dependent Claims Fee (Previously Paid)	0	0	0	$ 145.00	0.00
Total Additional Claims Fee					0.00
Fee for Submission of an Information Disclosure Statement					180.00
TOTAL FEES DUE					180.00

The Commissioner is hereby authorized to charge the fees listed above to our Deposit Account No. 06-1135 under Order No. 7569/73281. The Commissioner is also hereby authorized to charge any fee deficiency with respect to this filing and any other fee required in connection with the present case, or credit any overpayment, to our Deposit Account No. 06-1135 under Order No. 7569/73281.

It is respectfully requested that the enclosed postcard be stamped with the date the enclosed documents are received by the PTO and that it be returned as soon as possible.

Very truly yours,

FITCH, EVEN, TABIN & FLANNERY

Michael A. Sanzo
Reg. No. 36,912
Attorney for Applicant

MAS:ct
Enclosures

OIPE JC60
JUL 22 2004
PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of:	
Plachetka, John R.	Group Art Unit: 1615
Appl. No.: 10/158,216	Examiner: Spear, J.
Filed: May 31, 2002	Atty. Dkt.: 7569/73281
For: **Pharmaceutical Compositions for the Coordinated Delivery of NSAIDs**	

Response to Office Action Under 37 C.F.R. § 1.111

Commissioner for Patents
U.S. Patent and Trademark Office
220 20th Street S.
Customer Window, **MS Amendment**
Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

Sir:

In response to the Office Action dated April 22, 2004, Applicant respectfully requests reconsideration of the above-captioned application in view of the comments below.

There are no amendments to the claims or specification.

Remarks/Arguments begin on page 2 of the present document.

07/23/2004 HGUTEMA1 00000024 061135 10158216
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Remarks

I. Status of the Application and Claims

As filed on May 31, 2002, the present application had a total of 50 claims. A Preliminary Amendment was filed by Applicant on October 17, 2003 in which original claims 1 and 23 were amended and new claims 51-54 were added. Thus, claims 1-54 are now pending in the application.

II. Consideration of Preliminary Amendment

The present Office Action states that it is responsive to the communication filed by Applicant on May 31, 2002. This suggests that the Examiner did not consider the Preliminary Amendment filed on October 17, 2003. However, the Office Action also recognizes that there are 54 claims pending in the application which would suggest the opposite. For the purposes of the present response, Applicant will assume that the Examiner did receive and consider the Preliminary Amendment. If this assumption is incorrect, then Applicant will be happy to resubmit the Preliminary Amendment upon notification.

III. Request for Acknowledgement of Consideration of Cited Art

Accompanying the present Office Action were several lists of references that Applicant had included in information disclosure statements filed on April 24, 2003 and on August 23, 2003. These lists have been initialed by the Examiner to indicate that each reference was considered. However, two pages of references that were submitted with the April 24 information disclosure statement were not included. These are numbered as pages 2 and 3 and cite references AA2-AF2 and AK2-AM3. Applicants respectfully request that initialed copies of these missing pages be included with the next communication from the Examiner. If, for any reason, these pages or the references have become lost, Applicant will be happy to resubmit copies as a courtesy.

The Rejections

I. Rejection of Claims Under 35 U.S.C. § 102(b)

On page 2 of the Office Action, claims 1-5, 9, 10, 11, 21, 22 and 50 are rejected under 35 U.S.C. § 102(b) as being anticipated by Goldman, *et al.* (U.S. 5,204,118). The Examiner

alleges that the reference discloses pharmaceutical compositions containing an acid inhibitor and an NSAID. It is also alleged that the effective dosages reported in Goldman are the same as required in Applicant's claims and that the reference recites the same H2 blockers and proton pump inhibitors.

Applicant respectfully traverses this rejection.

All of Applicant's claims have requirements not only with respect to the type of active ingredients present in compositions or methods, but also with respect to the way in which active ingredients are delivered in relation to one another. Specifically, claim 1 requires that there be a single unit dosage form containing both an acid inhibitor and an NSAID and that, upon administration to a patient, the dosage form deliver these drugs in a coordinated fashion such that the acid inhibitor is released first and the NSAID is not released until after the gastric pH of the patient is 3.5 or higher. Applicant submits that these characteristics are not disclosed or suggested Goldman.

The importance of delivering drugs in the claimed manner is discussed in the specification of the present application. Specifically, a major factor contributing to NSAID-associated gastrointestinal lesions is the presence of a highly acidic environment in the stomach and upper small intestine of patients. By preventing NSAID from being released until the surrounding environment becomes more basic, the pharmaceutical composition defined in claim 1 provides for safer delivery. Dependent claims 2-21 all incorporate the requirement for coordinated sequential delivery and pH-controlled release of NSAID. Similarly, method claims 22 and 23 involve the administration of pharmaceutical compositions with essentially the same characteristics. Thus, none of these claims are suggested by Goldman.

Similar considerations apply with respect to the other claims in the application. Claim 24 is directed to a method in which patients are administered an acid inhibitor for the purpose of raising gastric pH and administered an NSAID that is coated with a polymer that only dissolves at a pH of 3.5 or greater. Claim 37 is essentially the same as claim 24 except that it

requires that NSAID be coated with a polymer that dissolves at a rate such that NSAID is not released until gastric pH is 3.5 or greater. Claims that are dependent upon claim 24 (*i.e.*, claims 25-36) and claim 37 (*i.e.*, claims 38-49) incorporate these requirements as well. Finally, claims 50-54, all refer back to claims which require that the release of NSAID be delayed until after gastric pH is 3.5 or higher.

In light of the above considerations, Applicant submits that the Goldman reference does not anticipate the claims of the present application. It is therefore respectfully requested that the rejection of claims under 35 U.S.C. § 102(b) be withdrawn.

II. Rejection of Claims Under 35 U.S.C. § 102(e)

On pages 2 and 3 of the Office Action, the Examiner rejects claims 1, 2, 5, 6, 9-12, 21, 23, 24, 28-30, 32-35, 41-43, 45-48 and 50-54 under 35 U.S.C. § 102(e) as being unpatentable over Depui, *et al.* (U.S. 6,613,354).

Applicant respectfully traverses this rejection.

Although the Depui reference discloses compositions containing both an NSAID and a proton pump inhibitor, it teaches the use of tablet coatings for the purpose of preventing the degradation of *gastric inhibitor*, not for the purpose of retarding the release of NSAID or protecting the gastrointestinal tract of a patient from damage caused by NSAID released at low pH. The concept of using an agent to prevent NSAID release until local pH is at least 3.5 is missing. Applicant therefore respectfully requests that the Examiner reconsider and withdraw the rejection based upon Depui.

III. Rejection of Claims Under 35 U.S.C. § 103

On pages 3 and 4 of the Office Action, claims 1-54 are rejected under 35 U.S.C. § 103 as being unpatentable over Depui, *et al.*, Lerner, *et al.* (U.S. 6,231,888) and Chen, *et al.* (U.S. 6,544,556). The Examiner alleges that the Depui reference discloses pharmaceutical compositions containing an acid inhibitor and an NSAID, but concedes that it does not disclose COX-2 inhibitors or barrier coatings susceptible to pH variations. Lerner is cited as

disclosing COX-2 inhibitors and Chen as disclosing dosage forms which dissolve at particular pHs. The Examiner argues that one of skill in the art would be motivated to combine the references to provide optimum efficiency and improve patient compliance.

Applicant respectfully traverses this rejection.

As discussed above, the Depui reference fails to disclose dosage forms or procedures in which an acid inhibitor is used for the purpose of raising the pH of the gastrointestinal tract of a patient and which is combined with an NSAID that is only released after this pH rises above 3.5. In addition, Depui provides no motivation to use pH sensitive dosage forms for delivering NSAIDs because it does not recognize that the damage caused to a patient's gastrointestinal lining by these agents is pH dependent.

Chen does disclose dosage forms which contain an NSAID and a proton pump inhibitor. This reference also suggests that dosage forms containing inhibitors may have either pH-dependent or pH-independent coatings. However, there is no suggestion for a dosage form in which there is sequential release such that the proton pump inhibitor is released first and NSAID is not released until gastrointestinal pH rises above 3.5. As with the reference by Depui, Chen appears to be primarily concerned with coating the acid inhibitor to prevent it from degrading when exposed to acid and does not recognize any advantage in regulating the release of NSAID in the pH-controlled manner required by Applicant's claims.

In light of the above considerations,, Applicant submits that: a) there is no motivation to combine Chen with Depui; and b) even if these references are combined, the resulting teachings could not be used to construct a tablet or carry out a method with the requirements set forth in the presently pending claims.

The reference by Lerner does nothing to cure the defects of Chen and Depui described above. In other words, the coordinated delivery of acid inhibitor followed by NSAID and the use of coatings that prevent the release of NSAID until surrounding pH reaches at least 3.5 would still be missing from the combination of all three references.

Conclusion

In light of the discussion above, Applicant submits that all of the Examiner's rejections have been overcome. It is therefore respectfully requested that these rejections be withdrawn and that the claims presently pending in the application be allowed.

If, in the opinion of the Examiner, a phone call may help to expedite the prosecution of this application, the Examiner is invited to call Applicant's undersigned attorney at (202) 419-7013.

Respectfully submitted,

FITCH, EVEN, TABIN & FLANNERY

By: Michael A. Sanzo

Michael A. Sanzo
Reg. No. 36,912
Attorney for Applicant

Date: July 12, 2004
1801 K Street, NW, Suite 401L
Washington, DC 20006
(202) 419-7013

OIPE JC60
JUL 22 2004
PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of:	
Plachetka, John R.	Art Unit: 1615
Appl. No.: 10/158,216	Examiner: Spear, J.
Filed: May 31, 2002	Atty. Dkt.: 7569/73281
For: **Pharmaceutical Compositions for the Coordinated Delivery of NSAIDs**	

Second Supplemental Information Disclosure Statement

Commissioner of Patents
U.S. Patent and Trademark Office
220 20th Street S.
Customer Window, **MS Amendment**
Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

Sir:

Submitted herewith is a listing of documents known to Applicant and/or his attorney in compliance with the requirements of 37 C.F.R. § 1.56. Copies of the listed documents are also enclosed.

Applicant does not waive any rights to appropriate action to establish patentability over any of the listed documents should they be applied as references against the claims of the present application. This statement should not be construed as a representation that more material information does not exist or that an exhaustive search of the relevant art has been made.

Consideration of the cited documents and making the same of record in the prosecution of the above-captioned application are respectfully requested.

The Director is hereby authorized to charge the fee for the filing of this Information Disclosure Statement to our Deposit Account No. 06-1135 under Order No. 7569/73281.

Respectfully submitted,

FITCH, EVEN, TABIN & FLANNERY

By: Michael A. Sanzo

Michael A. Sanzo
Attorney for Applicant
Reg. No. 36,912

Date July 22, 2004

1801 K Street, N.W., Suite 401L
Washington, D.C. 20006-1201
Phone: (202) 419-7013

LIST OF REFERENCES CITED BY APPLICANT *(Use several sheets if necessary)*	Atty. Docket No.: 7569/73281	Appl No.: 10/158,216
	Applicant(s) Plachetka, John R.	
	Filing Date: May 31, 2002	Group: to be assigned

OIPE JUL 22 2004 PATENT & TRADEMARK OFFICE TC600

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date If Appropriate
	AA 1						
	AB 1						
	AC 1						
	AD 1						
	AE 1						
	AF 1						

FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	Subclass	Translation	
							Yes	No
	AG 1							
	AH 1							
	AI 1							
	AJ 1							

OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)

	AK 1	HOWDEN, "Clinical Pharmacology of Omeprazole," *Clin. Pharmacokinet. 20(1)*:38-49 (1991) abstract.
	AL 1	PILBRANT, *et al.*, "Development of an Oral Formulation of Omeprazole," *Scand. J. Gastroenterol. 20(Suppl. 108)*:113-120 (1985).
	AM1	SHARMA, "Comparison of 24-Hour Intragastric pH Using Four Liquid Formulations of Lansoprazole and Omeprazole," *Am. J. Health-Syst. Pharm. 56(Supp. 4)*:S18-S21 (1999).
	AN 1	
	AO 1	
	AP 1	
	AQ 1	
	AR 1	

Examiner	Date Considered

V&E1449
5/94

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PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 1, 2001

Application or Docket Number: 10158216

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS	50	
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	122 minus 20=	* 92
INDEPENDENT CLAIMS	3 minus 3 =	*
MULTIPLE DEPENDENT CLAIM PRESENT		☒

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐	RATE	FEE	OR	OTHER THAN SMALL ENTITY	RATE	FEE
	BASIC FEE	370.00	OR		BASIC FEE	740.00
	X$ 9=		OR		X$18=	1656.00
	X42=		OR		X84=	
	+140=		OR		+280=	280
	TOTAL		OR		TOTAL	2676.00

CLAIMS AS AMENDED - PART II

2/22/4

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 2470	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY	RATE	ADDITIONAL FEE	OR	OTHER THAN SMALL ENTITY	RATE	ADDITIONAL FEE
	X$ 9=		OR		X$18=	
	X42=		OR		X84=	
	+140=		OR		+280=	
	TOTAL ADDIT. FEE		OR		TOTAL ADDIT. FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE	OR	RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE	OR	RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

FORM PTO-875 (Rev. 8/01) U.S. Government Printing Office: 2001 — 484-484/58268 Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/158,216	05/31/2002	John R. Plachetka	7569/73281	5014

7590 04/22/2004

Michael A Sanzo
Fitch Even Tabin & Flannery
1801 K Street NW Suite 4011
Washinton, DC 20006-1201

EXAMINER	
SPEAR, JAMES M	
ART UNIT	**PAPER NUMBER**
1615	

DATE MAILED: 04/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/158,216	PLACHETKA, JOHN R.	
	Examiner	Art Unit	
	James M Spear	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 May 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/03, 8/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 1-5, 9, 10, 11, 21, 22 and 50 are rejected under 35 U.S.C. 102(b) as being anticipated by Goldman et al. US 5,204,118. See examples 1-6 and 12, claims 1-4. The reference clearly shows a pharmaceutical composition comprised of an acid inhibitor and a non-steroidal anti-inflammatory drug (NSAID). The particular H2 blockers and proton pump inhibitors are the same as applicants'. The effective dosage amounts are the same as applicants'. The composition of Goldman would therefore inherently impart the same effects on the gastric ph as applicants'. Particular dosage forms including capsules are shown in column 7, lines 56-60.

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1, 2, 5, 6, 9-12, 21, 23, 24, 28-30, 32-35, 41-43, 45-48, and 50-54 are rejected under 35 U.S.C. 102(e) as being anticipated by Depui et al US 6,613,354, B2.

See examples 4 and 9. The reference shows dosage forms such as layered tablets (Figure 3) comprised of proton pump inhibitors such as omeprazole, lansoprazole, pantoprazole, pariprazole, leminoprazole, etc. Columns 6-7. Particular NSAIDS in addition to those in the examples are disclosed in column 8, lines 42-50. Since the particular composition components are the same the dosage form would inherently provide the same release rates and effects on the gastric ph.

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Depui et al US 6,613,354 B2 in view of Lerner et al US 6,231,888 B1 and Chen et al US 6,544,556 B1

4. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Depui et al shows pharmaceutical compositions comprised of an acid inhibitor and a nonsteroidal anti-inflammatory drug as explained above. The reference does not show non-steroidal anti-inflammatory drugs that are Cox-2 inhibitors and modified barrier coatings susceptible to ph variations. Lerner et al is relied on for teaching it is well known to combine or exchange applicants particular NSAIDs including Cox-2 inhibitors. See column 10, lines 43-68, and claims 1-3. The formulations may further comprise acid inhibitors. Column 11, lines 29-35. Chen et al teaches dosage forms wherein the positioning of particular elements in the dosage form determines the rate of dissolution. See columns 11-12. The coatings would therefore dissolve at a different ph. The prior art teaches equivalent NSAIDs, acid inhibitors and enteric coatings as disclosed by applicant. It would be reasonable for one skilled in the art to determine modifications to the particular combination to elicit the desired release rate of active ingredients. It would have been obvious to one of ordinary skill in the art to change the position and rate of release of enteric coatings of the Depui et al compositions as taught by Chen et al. The motivation being a desire to provide optimum efficacy and improve patient compliance. See Chen et al column 12, lines 14-32. Depui et al Summary.

Claims 1-54 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James M Spear whose telephone number is 571 272 0605. The examiner can normally be reached on Monday thru Friday from 6:30 AM to 3 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page, can be reached on 571 272 0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

James M. Spear

James M Spear
Primary Examiner
Art Unit 1615

April 17, 2004

LIST OF REFERENCES CITED BY APPLICANT (Use several sheets if necessary)	Atty. Docket No.: 7569/73281	Appl. No.: 10/158,216
	Applicant(s) Plachetka, John R.	
	Filing Date: May 31, 2002	Group: 1614

OTIPE JC141 AUG 25 2003 PATENT & TRADEMARK OFFICE

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U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date If Appropriate
JS	A 1	4,255,431	Mar. 10, 1981	Junggren, *et al.*	424	263	Apr. 5, 1979
	A 2	4,508,905	Apr. 2, 1985	Junggren, *et al.*	546	271	Apr. 6, 1983
	A 3	4,562,261	Dec. 31, 1985	Hirata, *et al.*	548	184	Apr. 5, 1984
	A 4	4,619,934	Oct. 28, 1986	Sunshine, *et al.*	514	277	Jul. 8, 1985
	A 5	4,965,065	Oct.23, 1990	Lukacsko, *et al.*	424	10	Feb. 6, 1987
	A 6	5,043,358	Aug. 27, 1991	Lukacsko, *et al.*	514	653	Sep. 4, 1990
	A 7	5,260,333	Nov. 9, 1993	Lukacsko, *et al.*	514	471	Apr. 9, 1992
	A 8	5,364,616	Nov. 15, 1994	Singer, *et al.*	424	52	Dec. 22, 1993
	A 9	5,373,022	Dec. 13, 1994	Fawzi, *et al.*	514	570	Sep. 8, 1992
	A 10	5,514,663	May 7, 1996	Mandel	514	33	Oct. 19, 1993
	A 11	5,631,022	May 20, 1997	Mandel, *et al.*	424	456	Jul. 6, 1995
	A 12	5,643,960	Jul. 1, 1997	Breitner, *et al.*	514	570	Apr. 15, 1994
	A 13	5,686,105	Nov. 11, 1997	Kelm, *et al.*	424	452	May 17, 1995
	A 14	5,955,451	Sep. 21, 1999	Lichtenberger, *et al.*	514	78	Sep. 24, 1996
	A 15	6,013,281	Jan. 11, 2000	Lundberg, *et al.*	424	468	Mar. 8, 1996
	A 16	6,025,395	Feb. 15, 2000	Breitner, *et al.*	514	570	Apr. 14, 1997
	A 17	6,160,020	Dec. 12, 2000	Ohannesian, *et al.*	514	629	Jun. 19, 1998
	A 18	6,126,816	Dec. 19, 2000	Bohlin, *et al.*	514	338	Jan. 18, 1999
	A 19	6,207,188 B1	Mar. 27, 2001	Gustavsson, *et al.*	424	464	Jun. 29, 1998
	A 20	6,395,298 B1	May 28, 2002	Flanagan, *et al.*	424	479	Sep. 24, 1999
	A 21	6,485,747 B1	Nov. 26, 2002	Flanagan, *et al.*	424	479	Oct. 11, 1999
	A 22	6,544,556 B1	Apr. 8, 2003	Chen, *et al.*	424	469	Sep. 11, 2000
	A 23	2001/0025107 A1	Sep. 27, 2001	Barberich, *et al.*	546	273.7	May 11, 2001
	A 24	2001/0036473 A1	Nov. 1, 2001	Scott, *et al.*	424	463	Apr. 17, 2001
	A 25	2001/0044410 A1	Nov. 22, 2001	Gelber, *et al.*	514	27	Jan. 5, 2001
	A 26	2002/0012676 A1	Jan. 31, 2002	Lundeberg, *et al.*	424	400	Oct. 6, 1999
JS	A 27	2002/0042433 A1	Apr. 11, 2002	Yelle, *et al.*	514	338	Oct. 17, 2001

Examiner James M. Spear | Date Considered 04-15-2004

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	Applicant(s) Plachetka, John R.	
	Filing Date: May 31, 2002	Group: GROUP 1700

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	A 29	2002/0045184 A1	Apr. 18, 2002	Chen	435	6	Oct. 2, 2001
	A 30	2002/0086029 A1	Jul. 4, 2002	Lundberg, *et al.*	424	184.1	Dec. 18, 2001
	A 31	2002/0111370 A1	Aug. 15, 2002	Bergman, *et al.*	514	338	Dec. 20, 2001
	A 32	2002/0155153 A1	Oct. 24, 2002	Depui, *et al.*	424	452	Mar. 4, 2002
	A 33	2003/0008903 A1	Jan. 9, 2003	Barberich, *et al.*	514	338	Aug. 12, 2002
	A 34	2003/0113375 A1	Jun. 19, 2003	Lundberg, *et al.*	424	474	Sep. 4, 2002
JS	A 35	2003/0129235 A1	Jul. 10, 2003	Chen, *et al.*	424	470	Oct. 28, 2002
	A 36						
	A 37						
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	Applicant(s) Plachetka, John R.	
	Filing Date: May 31, 2002	Group: 1614

OIPE AUG 25 2003 PATENT & TRADEMARK OFFICE

RECEIVED AUG 28 2003 GROUP 1700

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Examiner Initial		Document Number	Date	Country	Class	Subclass	Abst./Trans. Yes	Abst./Trans. No
	B 1	WO 93/12817	Jul. 8, 1993	WIPO	A61K	45/06		
	B 2	WO 94/07541	Apr. 14, 1994	WIPO	A61K	49/00		
	B 3	WO 98/22117	May 28, 1998	WIPO	A61K	33/24		
	B 4	WO 99/00380	Jan. 7, 1999	WIPO	C07D	401/12		
	B 5	WO 99/12524	Mar. 18, 1999	WIPO	A61K	9/20		
	B 6	WO 00/71122	Nov. 30, 2000	WIPO	A61K	31/44		
	B 7	WO 00/72838 A1	Dec. 7, 2000	WIPO	A61K	31/04		
	B 8	WO 03/017980 A1	Mar. 6, 2003	WIPO	A61K	9/16		
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	B 14							
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	Applicant(s) Plachetka, John R.	
	Filing Date: May 31, 2002	Group: 1614

OIPE 3641 AUG 25 2003 PATENT & TRADEMARK OFFICE

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Examiner Initial		OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)
JS	C 1	English language abstract for DE 198 01 811, Reference B13 above.
	C 2	DENT, "Why Proton Pump Inhibition Should Heal and Protect Against Nonsteroidal Anti-inflammatory Drug Ulcers," *Am. J. Med. 104*:52S-55S (1998).
	C 3	KIMMEY, *et al.*, "Role of H_2-Receptor Blockers in the Prevention of Gastric Injury Resulting from Nonsteroidal Anti-inflammatory Agents," *Am. J. Med. 84*:49-52 (1988).
	C 4	LEE, *et al.*, "Omeprazole Prevents Indomethacin-Induced Gastric Ulcers in Rabbits," *Aliment. Pharmacol. Ther. 10*:571-576 (1996).
	C 5	LICHTENBERGETR, *et al.*, "Nonsteroidal Anti-inflammatory Drug and Phospholipid Prodrugs: Combination Therapy with Antisecretory Agents in Rats," *Gastroenterology 111*:990-995 (1996).
	C 6	SAVARINO, *et al.*, "Effect of One-Month Treatment with Nonsteroidal Antiinflammatory Drugs (NSAIDs) on Gastric pH of Rheumatoid Arthritis Patients," *Digestive Diseases and Sciences 43*:459-463 (1998).
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	C 8	
	C 9	
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	Applicant(s) Plachetka, John R.	
	Filing Date: May 31, 2002	Group: to be assigned AU 1615

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Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date If Appropriate
	AA 1	4,554,276	Nov. 19, 1985	LaMattina	514	272	Oct. 3, 1983
	AB 1	4,676,984	Jun. 30, 1987	Wu, *et al.*	424	157	Aug. 14, 1985
	AC 1	4,704,278	Nov. 3, 1987	Wu, *et al.*	424	157	Aug. 8, 1986
	AD 1	4,757,060	Jul. 12, 1988	Lukacsko, *et al.*	514	160	Apr. 29, 1986
	AE 1	4,766,117	Aug. 23, 1988	Crawford, *et al.*	514	219	Dec. 12, 1986
	AF 1	4,786,505	Nov. 22, 1988	Lovgren, *et al.*	424	468	Apr. 20, 1987

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	AG 1	WO 85/03443	15 August 1985	WIPO	A61K	45/06		
	AH 1	GB 2 105 193	23 March 1983	United Kingdom	A61K	31/34		
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	AL 1	Bombardier, *et al.*, "Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis," *N. Engl. J. Med. 343*:1520-1528 (2000).
	AM1	Brown, *et al.*, "Prevention of the Gastrointestinal Adverse Effects of Nonsteroidal Anti-Inflammatory Drugs," *Pract. Drug Safety 21*:503-512 (1999).
	AN 1	Cullen, *et al.*, "Primary Gastroduodenal Prophylaxis with Omeprazole for Non-Steroidal Anti-Inflammatory Drug Users," *Aliment. Pharmacol. Ther. 12*:135-140 (1998).
	AO 1	Hawkey, "Progress in Prophylaxis Against Nonsteroidal Anti-Inflammatory Drug-Associated Ulcers and Erosions," *Am. J. Med. 104*:67S-74S (1998).
	AP 1	Hawkey, *et al.*, "Omeprazole Compared with Misoprostol for Ulcers Associated with Nonsteroidal Anti-Inflammatory Drugs," *N. Engl. J. Med. 338*:727-734 (1998).
	AQ 1	Howden, "Clinical Pharmacology of Omeprazole," *Clin. Pharmacokinet. 20*:38-49 (1991).
	AR 1	Katz, *et al.*, "Gastric Acidity and Acid Breakthrough with Twice-Daily Omeprazole or Iansoprazole," *Aliment. Pharmacol. Ther 14*:709-714 (2000).

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	Applicant(s) Plachetka, John R.	
	Filing Date: May 31, 2002	Group: to be assigned AU 1615

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U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date If Appropriate
JS	AA 2	5,037,815	Aug. 6, 1991	Lukacsko, *et al.*	514	162	Sep. 8, 1988
JS	AB 2	5,204,118	Apr. 20, 1993	Goldman, *et al.*	424	489	Apr. 29, 1992
	AC 2	5,417,980	May 23, 1995	Goldman, *et al.*	424	464	Jun. 29, 1994
	AD 2	5,466,436	Nov. 14, 1995	Stables	514	161	Dec. 17, 1993
	AE 2	5,716,648	Feb. 10, 1998	Halskov, *et al.*	424	682	Dec. 21, 1995
JS	AF 2	6,365,184 B1	Apr. 2, 2002	Depui, *et al.*	424	469	Dec. 23, 1999

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		Document Number	Date	Country	Class	Subclass	Translation Yes	Translation No
	AG							
	AH							
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JS	AK 2	Kephart, *et al.*, "Coprescribing of Nonsteroidal Anti-Inflammatory Drugs and Cytoprotective and Antiulcer Drugs in Nova Scotia's Senior Population," *Clin. Ther. 17*:1159-1173 (1995).
	AL 2	Lad, *et al.*, "Management of Nonsteroidal Anti-Inflammatory Drug-Induced Gastroduodenal Disease by Acid Suppression," *Can. J. Gastroenterol 13*:135-142 (1999).
	AM2	Mattsson, *et al.*, "Omeprazole Provides Protection Against Experimentally Induced Gastric Mucosal Lesions," *Eur. J. Pharmacol. 91*:111-114 (1983).
	AN 2	Oddsson, *et al.*, "Endoscopic Findings in the Stomach and Duodenum after Treatment with Enteric-Coated and Plain Naproxen Tablets in Healthy Subjects," *Scand. J. Gastroenterol. 25*:231-234 (1990).
	AO 2	Scheiman, "NSAID-Induced Peptic Ulcer Disease: A Critical Rview of Pathogenesis and Management," *Dig. Dis. 12*:210-222 (1994).
	AP 2	Selway, "Potential Hazards of Long-Term Acid Suppression," *Scand. J. Gasatroenterol. 25(Supp. 178)*:85-92 (1990).
	AQ 2	Silverstein, *et al.*, "Gastrointestinal Toxicity with Celecoxib vs. Nonsteroidal Anti-Inflammatory Drugs for Osteoarthritis and Rheumatoid Arthritis; The CLASS Study: A Randomized Controlled Trial," *JAMA 284*:1247-1255 (2000).
JS	AR 2	Tronstad, *et al.*, "Gastroscopic Findings after Treatment with Enteric-Coated and Plain Naproxen Tablets in Healthy Subjects," *Scand. J. Gastroenterol. 20*:239-242 (1985).

Examiner James M. Spear	Date Considered 04-15-2004

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LIST OF REFERENCES CITED BY APPLICANT *(Use several sheets if necessary)*	Atty. Docket No.: 7569/73281	Appl No.: 10/158,216
	Applicant(s) Plachetka, John R.	
	Filing Date: May 31, 2002	Group: to be assigned AU 1615

OIPE JC174 APR 2 6 2003 PATENT & TRADEMARK OFFICE

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U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date If Appropriate
	AA						
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FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	Subclass	Translation Yes	Translation No
	AG							
	AH							
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JS	AK 3	Wolfe, *et al.*, "Gastrointestinal Toxicity of Nonsteroidal Anti-Inflammatory Drugs," *N. Engl. J. Med. 340*:1888-1899 (1999).
JS	AL 3	Yeomans, *et al.*, "A Comparison of Omeprazole with Ranitidine for Ulcers Associated with Nonsteroidal Anti-Inflammatory Drugs," *N. Engl. J. Med. 338*:719-726 (1998).
JS	AM3	Yeomans, *et al.*, "New Data on Healing of Nonsteroidal Anti-Inflammatory Drug-Associated Ulcers and Erosions," *Am. J. Med. 104*:56S-61S (1998).
	AN	
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Examiner James M. Spear	Date Considered 04-15-2004

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Index of Claims

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10/158,216	PLACHETKA, JOHN R.	
Examiner	**Art Unit**	
James M Spear	1615	

√	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
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Claim		Date
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	10/158,216	PLACHETKA, JOHN R.	
	Examiner	Art Unit	
	James M Spear	1615	

SEARCHED			
Class	Subclass	Date	Examiner
424	464 451	4-17-04	JSpear
	472		
	474		

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
WEST-searched For dosage forms comprised of a combination acid inhibitor and a NSAID,	4-17-04	JSpear

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WEST Search History

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DATE: Saturday, April 17, 2004

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☐	L20	l19 and (acid adj inhibitor)	14
☐	L19	(nsaid same cox$).clm.	58
☐	L18	(nsaid same cox$).ti.	10
☐	L17	(celecoxib) same (acid adj inhibior)	0
☐	L16	(celecoxib same rabeprazole).ti.	0
☐	L15	(celecoxib same pantoprazole).ti.	0
☐	L14	(celecoxib same lansoprazole).ti.	0
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☐	L12	(celecoxib same omeprazole).clm.	9
☐	L11	(cox$ same acid).ti.	22
☐	L10	(cox$ same omeprazole)	19
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☐	L5	(layer same tablet).clm.	554
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☐	L3	6365184.pn.	1
☐	L2	6365184.pn.	1
	DB=PGPB,USPT,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=AND		
☐	L1	(acid adj inhibitor) same nsaid	19

END OF SEARCH HISTORY

Patent Owner Ex. 2005
IPR2015-01344
Page 110 of 613

PALM INTRANET

Day : Thursday
Date: 4/8/2004
Time: 12:08:00

Inventor Name Search Result

Your Search was:

Last Name = PLACHETKA
First Name = JOHN

Application#	Patent#	Status	Date Filed	Title	Inventor Name 20
60436000	Not Issued	020	12/26/2002	MULTILAYER DOSAGE FORMS CONTAINING NSAIDS AND TRIPTANS	PLACHETKA, JOHN R.
60294588	Not Issued	159	06/01/2001	PHARMACEUTICAL COMPOSITIONS FOR THE COORDINATED DELIVERY OF NSAIDS	PLACHETKA, JOHN R.
60137450	Not Issued	159	06/02/1999	DIHYDROERGOTAMINE COMPOSITIONS FOR INTRANASAL ADMINISTRATION	PLACHETKA , JOHN R.
60126333	Not Issued	159	03/26/1999	HIGH POTENCY DIHYDROERGOTAMINE COMPOSITION	PLACHETKA , JOHN R.
60078001	Not Issued	159	03/13/1998	PROPHYLAXIS AND TREATMENT OF MIGRAINE HEADACHES WITH THROMBOXANE SYNTHETASE INHIBITORS AND/OR RECEPTOR ANTAGONISTS	PLACHETKA , JOHN R.
60024129	Not Issued	159	08/16/1996	FORMULATION OF 5HT AGONISTS	PLACHETKA , JOHN R.
10741592	Not Issued	019	12/22/2003	MULTILAYER DOSAGE FORMS CONTAINING NSAIDS AND TRIPTANS	PLACHETKA, JOHN R.
10414493	Not Issued	030	04/16/2003	METHODS OF TREATING HEADACHES USING 5-HT AGONISTS IN COMBINATION WITH LONG-ACTING NSAIDS	PLACHETKA, JOHN R.
10281982	Not Issued	071	10/29/2002	HIGH POTENCY DIHYDROERGOTAMINE COMPOSITIONS	PLACHETKA, JOHN R.

Patent Owner Ex. 2005
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Page 111 of 613

10255036	Not Issued	071	09/26/2002	TREATMENT OF MIGRAINE HEADACHE	PLACHETKA, JOHN R.
10158216	Not Issued	030	05/31/2002	PHARMACEUTICAL COMPOSITIONS FOR THE COORDINATED DELIVERY OF NSAIDS	PLACHETKA, JOHN R.
09559753	6586458	150	04/27/2000	METHODS OF TREATING HEADACHES USING 5-HT AGONISTS IN COMBINATION WITH LONG-ACTING NSAIDS	PLACHETKA, JOHN R.
09546387	Not Issued	160	04/10/2000	FORMULATION OF 5-HT AGONISTS	PLACHETKA, JOHN R.
09526474	6495535	150	03/15/2000	HIGH POTENCY DIHYDROERGOTAMINE COMPOSITIONS	PLACHETKA, JOHN R.
09517751	6479551	150	03/03/2000	TREATMENT OF MIGRAINE HEADACHE	PLACHETKA, JOHN R.
09253278	Not Issued	161	02/19/1999	FORMULATION OF 5-HT AGONISTS WITH COX-2 INHIBITORS	PLACHETKA , JOHN R.
09151912	6060499	150	09/11/1998	ANTI-MIGRAINE METHODS AND COMPOSITIONS USING 5-HT AGONISTS WITH LONG-ACTING NSAIDS	PLACHETKA , JOHN R.
08966506	6077539	150	11/10/1997	TREATMENT OF MIGRAINE HEADACHE	PLACHETKA , JOHN R.
08907826	5872145	150	08/14/1997	FORMULATION OF 5-HT AGONIST AND NSAID FOR TREATMENT OF MIGRAINE	PLACHETKA , JOHN R.
08748332	Not Issued	161	11/12/1996	TREATMENT OF MIGRAINE HEADACHE	PLACHETKA , JOHN R.

Inventor Search Completed: No Records to Display.

Search Another: Inventor

Last Name plachetka **First Name** john

Search

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October 17, 2003

Commissioner of Patents
U.S. Patent and Trademark Office
2011 South Clark Place
Customer Window
Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

Re: Preliminary Amendment
Appl. No.: 10/158,216
Filed: May 31, 2002
Title: **Pharmaceutical Compositions for the Coordinated Delivery of NSAIDs**
Inventor(s): Plachetka, John R.
Atty. Dkt.: 7569/73281 (formerly 71896/284951)

Dear Sir:

The following documents are being forwarded herewith for appropriate action by the U.S. Patent and Trademark Office:

1. Preliminary Amendment; and
2. Return postcard.

CALCULATION OF ADDITIONAL FEES

Applicant(s) have calculated additional fees as follows (**small entity status is claimed**):

	No. After Amendment	No. Previously Paid for	No. Extra	Rate	Fee
Total Claims Fee	166	122=	44	$ 9.00	396.00
Independent Claims Fee	5	5 =	0	$ 43.00	0.00
Multiple Dependent Claims Fee (Previously Paid)	0	0	0	$ 145.00	0.00
Total Additional Claims Fee					396.00
TOTAL FEES DUE					396.00

The Commissioner is hereby authorized to charge the fees listed above to our Deposit Account No. 06-1135 under Order No. 7569/73281. The Commissioner is also hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 06-1135 under Order No. 7569/73281.

It is respectfully requested that the enclosed postcard be stamped with the date the enclosed documents are received by the PTO and that it be returned as soon as possible.

Very truly yours,

FITCH, EVEN, TABIN & FLANNERY

Michael A. Sanzo

Michael A. Sanzo
Reg. No. 36,912
Attorney for Applicant

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of:

Plachetka, John R.	Group Art Unit: to be assigned
Appl. No.: 10/158,216	Examiner: to be assigned
Filed: May 31, 2002	Atty. Dkt.: 7569/73281 (formerly 71896/284951)
For: **Pharmaceutical Compositions for the Coordinated Delivery of NSAIDs**	

Preliminary Amendment

Commissioner for Patents
U.S. Patent and Trademark Office
2011 South Clark Place
Customer Window
Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

Sir:

In advance of prosecution, please amend the above-captioned application as described herein.

Amendments to the specification begin on page 2 of the present document.

Amendments to the claims begin on page 3 of the present document.

Remarks begin on page 11 of the present document.

Amendments to the Specification

Please amend page 1 of the specification by adding the following text immediately after the title of the application and before the "Field of the Invention" section that begins on line 4:

-- **Cross Reference to Related Applications**

The present application claims priority to U.S. provisional application 60/294,588, filed on June 1, 2001. --

Amendments to the Claims

Please amend claims 1, and 23 and add new claims 51-54 as shown below in the "list of claims."

List of Claims

1. (Currently amended) A pharmaceutical composition in unit dose form suitable for oral administration to a patient, comprising:

   (a) an acid inhibitor present in an amount effective to raise the gastric pH of said patient to at least 3.5 upon the administration of one or more of said unit dosage forms;

   (b) a non-steroidal anti-inflammatory drug (NSAID) in an amount effective to reduce or eliminate pain or inflammation in said patient upon administration of one or more of said unit dosage forms;

   and wherein said unit dosage form provides for ~~the~~ coordinated release ~~of said acid inhibitor followed by said NSAID~~ such that said acid inhibitor is released first and said NSAID is not released until the gastric pH of said patient is 3.5 or higher.

2. (Original) The pharmaceutical composition of claim 1, wherein said acid inhibitor is selected from: a proton pump inhibitor and an H2 blocker.

3. (Original) The pharmaceutical composition of claim 2, wherein said acid inhibitor is an H2 blocker selected from the group consisting of: cimetidine; ranitidine; ebrotidine; pabutidine; lafutidine; loxtidine and famotidine.

4. (Original) The pharmaceutical composition of claim 3, wherein said H2 blocker is famotidine, present in said unit dosage form in an amount of between 5 mg and 100 mg.

5. (Original) The pharmaceutical composition of claim 1, wherein said acid inhibitor is a proton pump inhibitor selected from the group consisting of: omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole.

6. (Original) The pharmaceutical composition of claim 5, wherein said proton pump inhibitor is pantoprazole, present in said unit dosage form in an amount of between 10 mg and 200 mg.

7. (Original) The pharmaceutical composition of claim 1, wherein said NSAID is a cyclooxygenese-2 (COX-2) inhibitor.

8. (Original) The pharmaceutical composition of claim 7, wherein said COX-2 inhibitor is selected from the group consisting of celecoxib; rofecoxib; meloxicam; piroxicam; valdecoxib, parecoxib, etoricoxib, CS-502, JTE-522; L-745,337; and NS398.

9. (Original) The pharmaceutical composition of claim 1, wherein said NSAID is selected from the group consisting of: aspirin; acetaminophen; ibuprofen; flurbiprofen; ketoprofen; lornoxicam; naproxen; oxaprozin; etodolac; indomethacin; ketorolac; and nabumetone.

10. (Original) The pharmaceutical composition of claim 9, wherein said NSAID is naproxen present in an amount of between 50 mg and 1500 mg.

11. (Original) The pharmaceutical composition of claim 10, wherein said naproxen is present in an amount of between 200 mg and 600 mg.

12. (Original) The pharmaceutical composition of claim 1, wherein said unit dosage form is a multilayer tablet.

13. (Original) The pharmaceutical composition of claim 12, wherein said unit dosage form is a trilayer tablet having an outer layer of said acid inhibitor and an inner core of said NSAID.

14. (Original) The pharmaceutical composition of claim 12, wherein said unit dosage form is a bilayer tablet having an outer layer of said acid inhibitor and an inner core of said NSAID.

15. (Original) The pharmaceutical composition of any one of claims 12-14, wherein said tablet has an inner core of said NSAID surrounded by a barrier coating that does not dissolve unless the pH of the surrounding medium is 3.5 or greater.

16. (Original) The pharmaceutical composition of any one of claims 12-14, wherein said tablet has an inner core of said NSAID surrounded by a barrier coating that does not dissolve unless the pH of the surrounding medium is 4 or greater.

17. (Original) The pharmaceutical composition of any one of claims 12-14, wherein said tablet has an inner core of said NSAID surrounded by a barrier coating that does not dissolve unless the pH of the surrounding medium is 5 or greater.

18. (Original) The pharmaceutical composition of any one of claims 12-14, wherein said tablet has an inner core of said NSAID surrounded by a barrier coating that dissolves at a rate such that said NSAID is not released until the pH of the surrounding medium is 3.5 or greater.

19. (Original) The pharmaceutical composition of any one of claims 12-14, wherein said tablet has an inner core of said NSAID surrounded by a barrier coating that dissolves at a rate such that said NSAID is not released until the pH of the surrounding medium is 4 or greater.

20. (Original) The pharmaceutical composition of any one of claims 12-14, wherein said tablet has an inner core of said NSAID surrounded by a barrier coating that dissolves at a rate such that said NSAID is not not released until the pH of the surrounding medium is 5 or greater.

21. (Original) The pharmaceutical composition of claim 1, wherein said unit dosage form is a capsule.

22. (Original) A method of treating a patient for pain or inflammation, comprising administering to said patient the pharmaceutical composition of any one of claims 1-14.

23. (Currently amended) The method of claim 22, wherein ~~said patient is treated for~~ said pain or inflammation is due to either osteoarthritis or rheumatoid arthritis.

24. (Original) A method of treating a patient for pain or inflammation, comprising:
    (a) orally administering to said patient an acid inhibitor at a dose effective to raise the gastric pH of said patient to at least 3.5; and
    (b) orally administering to said patient an NSAID that is coated in a polymer that only dissolves at a pH of 3.5 or greater.

25. (Original) The method of claim 24, wherein said acid inhibitor is an H2 blocker.

26. (Original) The method of claim 25, wherein said H-2 blocker is selected from the group consisting of: cimetidine; ranitidine; ebrotidine; pabutidine; lafutidine; loxtidine and famotidine.

27. (Original) The method of claim 26, wherein said H2 blocker is famotidine administered at a dose of between 5 mg and 100 mg.

28. (Original) The method of claim 24, wherein said acid inhibitor is a proton pump inhibitor.

29. (Original) The method of claim 28, wherein said proton pump inhibitor is selected from the group consisting of: omeprazole, esomeprazole, lansoprazole, rabeprazole and pantoprazole.

30. (Original) The method of claim 29, wherein said proton pump inhibitor is pantoprazole administered at a dose of between10 mg and 200 mg.

31. (Original) The method of any one of claims 24 - 30, wherein said NSAID is a COX-2 inhibitor selected from the group consisting of: celecoxib; rofecoxib; meloxicam; piroxicam; valdecoxib, parecoxib, etoricoxib, CS-502, JTE-522; L-745,337; and NS398.

32. (Original) The method of any one of claims 24 – 30, wherein said NSAID is selected from the group consisting of: aspirin; acetaminophen; ibuprofen; flurbiprofen; ketoprofen; lornoxicam; naproxen; oxaprozin; etodolac; indomethacin; ketorolac; and nabumetone.

33. (Original) The method of claim 32, wherein said NSAID is naproxen administered at a dose of between 50 mg and 1500 mg.

34. (Original) The method of claim 33, wherein said naproxen is administered at a dose of between 200 mg and 600 mg.

35. (Original) The method of claim 24, wherein said acid inhibitor and said NSAID are delivered as part of a single dosage form providing for the coordinated release of therapeutic agents.

36. (Original) The method of claim 35, wherein said single dosage form is a bilayer tablet with an outer layer comprising an H2 blocker and an inner core comprising an NSAID.

37. (Original) A method of treating a patient for pain or inflammation, comprising:

(a) orally administering to said patient an acid inhibitor at a dose effective to raise the gastric pH of said patient to at least 3.5; and

(b) concurrently administering to said patient an NSAID that is coated in a polymer that dissolves at a rate such that said NSAID is not released until said gastric pH is at 3.5 or higher.

38. (Original) The method of claim 37, wherein said acid inhibitor is an H2 blocker.

39. (Original) The method of claim 38, wherein said H-2 blocker is selected from the group consisting of: cimetidine; ranitidine; ebrotidine; pabutidine; lafutidine; loxtidine and famotidine.

40. (Original) The method of claim 39, wherein said H2 blocker is famotidine administered at a dose of between 5 mg and 100 mg.

41. (Original) The method of claim 37, wherein said acid inhibitor is a proton pump inhibitor.

42. (Original) The method of claim 41, wherein said proton pump inhibitor is selected from the group consisting of: omeprazole, esomeprazole, lansoprazole, rabeprazole and pantoprazole.

43. (Original) The method of claim 42, wherein said proton pump inhibitor is pantoprazole administered at a dose of between 10 mg and 200 mg.

44. (Original) The method of any one of claims 37 - 43, wherein said NSAID is a COX-2 inhibitor selected from the group consisting of: celecoxib; rofecoxib; meloxicam; piroxicam; valdecoxib, parecoxib, etoricoxib, CS-502, JTE-522; L-745,337; and NS398.

45. (Original) The method of any one of claims 37 - 43, wherein said NSAID is selected from the group consisting of: aspirin; acetaminophen; ibuprofen; flurbiprofen; ketoprofen; lornoxicam; naproxen; oxaprozin; etodolac; indomethacin; ketorolac; and nabumetone.

46. (Original) The method of claim 45, wherein said NSAID is naproxen administered at a dose of between 50 mg and 1500 mg.

47. (Original) The method of claim 46, wherein said naproxen is administered at a dose of between 200 mg and 600 mg.

48. (Original) The method of claim 47, wherein said acid inhibitor and said NSAID are delivered as part of a single dosage form providing for the coordinated release of therapeutic agents.

49. (Original) The method of claim 48, wherein said single dosage form is a bilayer tablet with an outer layer comprising an H2 blocker and an inner core comprising an NSAID.

50. (Original) A method of improving compliance in patients requiring frequent daily dosages of an acid inhibitor and an NSAID comprising administering said dosages in a coordinated unit dosage form in accordance with claim 1.

51. (New) The pharmaceutical composition of any one of claims 1-11, wherein said NSAID is surrounded by an enteric coating that does not dissolve until the pH of the surrounding medium is 3.5 or higher, and said acid inhibitor is either not surrounded by an enteric coating or it surrounded by an enteric coating that dissolves when the surrounding medium is at a pH below 3.5.

52. (New) The pharmaceutical composition if claim 51, wherein essentially all of said NSAID is present in a core and is separated from said acid inhibitor by said enteric coating.

53. (New) A method of treating a patient for pain or inflammation, comprising administering to said patient the pharmaceutical composition of claim 51.

54. (New) The method of claim 53, wherein said pain or inflammation is due to either osteoarthritis or rheumatoid arthritis.

Remarks

I. Status of the Application and Claims

As originally filed, the present application had a total of 50 claims. Applicants have added new claims 51-54 herein. Thus, the claims pending in the application after the entry of the present amendments will be claims 1-54.

II. The Amendments

The specification of the application was amended to cross-reference the related provisional application relied upon for priority.

Support for the amendment to claim 1 can be found, *inter alia*, on page 5 of the specification, lines 3-17.

Support for new claims 51 and 52 may be found, *inter alia*, on page 10 of the application, line 27 – page 11, line 14. Further support may be found in the various examples provided on pages 11-29.

Support for new claims 53 and 54 may be found, *inter alia*, on page 5 of the application, lines 19-25.

None of the amendments made herein add new matter to the application and their entry is therefore respectfully requested.

Conclusion

In light of the amendments made herein, Applicants believe that the present application is now in condition for immediate allowance. Early notice to this effect is earnestly solicited. If, in the opinion of the Examiner, a phone call may help to expedite the

prosecution of this application, the Examiner is invited to call Applicants' undersigned attorney at (202) 419-7013.

Respectfully submitted,

FITCH, EVEN, TABIN & FLANNERY

Michael A. Sanzo

By:_____
Michael A. Sanzo
Reg. No. 36,912
Attorney for Applicants

Date: October 17, 2003
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*ADMITTED TO D.C. BAR; D.C. PRACTICE OF ALL OTHERS LIMITED TO FEDERAL COURTS AND AGENCIES

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August 25, 2003

Commissioner of Patents
U.S. Patent and Trademark Office
2011 South Clark Place
Customer Window
Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

Re: Supplemental Information Disclosure Statement
Appl. No.: 10/158,216
Filed: May 31, 2002
Title: **Pharmaceutical Compositions for the Coordinated Delivery of NSAIDs**
Inventor(s): Plachetka, John R.
Atty. Dkt.: 7569/73281 (formerly 71896/284951)

Dear Sir:

The following documents are being forwarded herewith for appropriate action by the U.S. Patent and Trademark Office:

1. Supplemental Information Disclosure Statement;
2. PTO Form 1449 - List of References Cited by Applicant;
3. References A1-A35, B1-B13, and C1-C7; and
4 One return postcard.

Applicant does not believe that any fee is due for the filing of this IDS. However, the Commissioner is hereby authorized to charge any fee deficiency to our Deposit Account No. 06-1135 under Order No. 7569/73281.

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Very truly yours,

FITCH, EVEN, TABIN & FLANNERY

Michael A. Sanzo

Michael A. Sanzo
Reg. No. 36,912
Attorney for Applicant

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OIPE JC141 AUG 25 2003 PATENT & TRADEMARK OFFICE

In re patent application of:

Plachetka, John R.

Appl. No.: 10/158,216

Filed: May 31, 2002

For: **Pharmaceutical Compositions for the Coordinated Delivery of NSAIDs**

Art Unit: to be assigned

Examiner: to be assigned

Atty. Dkt.: 7569/73281
(Formerly 71896/284951)

Supplemental Information Disclosure Statement

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Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

Sir:

Submitted herewith is a listing of documents known to Applicant and/or his attorney in compliance with the requirements of 37 C.F.R. § 1.56. Copies of the listed documents are also enclosed.

In accordance with 37 C.F.R. § 1.98(a)(3), Applicant's undersigned attorney submits the following concise explanation of the relevance of the non-English language documents cited on the accompanying form:

Reference B13, German patent document DE 198 01 811, describes an oral pharmaceutical composition containing an antisecretory compound. The composition can be used in the treatment of esophagitis, gastritis, duodenitis, gastric ulcers and duodenal ulcers. An English language abstract corresponding to this document is cited on the accompanying list of references as document C1.

Applicant does not waive any rights to appropriate action to establish patentability over any of the listed documents should they be applied as references against the claims of the present application. This statement should not be construed as a representation that more material information does not exist or that an exhaustive search of the relevant art has been made.

Consideration of the cited documents and making the same of record in the prosecution of the above-captioned application are respectfully requested.

Applicant does not believe that any fee is due for the filing of this IDS. However, the Commissioner is hereby authorized to charge any fee deficiency to our Deposit Account No. 06-1135 under Order No. 7569/73281.

Respectfully submitted,

FITCH, EVEN, TABIN & FLANNERY

By: Michael A. Sanzo

Michael A. Sanzo
Attorney for Applicant
Reg. No. 36,912

Date August 25, 2003

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Washington, D.C. 20006-1201
Phone: (202) 419-7013

LIST OF REFERENCES CITED BY APPLICANT *(Use several sheets if necessary)*	Atty. Docket No.: 7569/73281	Appl. No.: 10/158,216
	Applicant(s) Plachetka, John R.	
	Filing Date: May 31, 2002	Group: 1614

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U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date If Appropriate
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(54) Title: THERAPEUTIC COMBINATIONS USEFUL IN THE TREATMENT OF GASTROESOPHAGEAL REFLUX DISEASE

(57) Abstract

The invention concerns combinations of proton pump inhibitors and CCK-B/gastrin antagonists in pharmaceutical compositions that are useful in the treatment of peptic disorders such as ulcers and gastroesophageal reflux disease and in the treatment of Zollinger-Ellison Syndrome.

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THERAPEUTIC COMBINATIONS USEFUL IN THE TREATMENT OF GASTROESOPHAGEAL REFLUX DISEASE

BACKGROUND OF THE INVENTION

Although gastrin exerts many pharmacological effects throughout the gastrointestinal (GI) tract, it appears that its main physiological functions are stimulation of acid secretion in the stomach, and stimulation of mucosal growth in the stomach, small intestine, and colon.

The secretory activity of the gastrin-producing G-cell of the gastric antrum depends on the intragastric pH, on the presence or absence of food in the stomach lumen, and on the activity of several epigastric endocrine, paracrine, or neuronal systems. Thus, abolition of acid secretion, as in the achlorhydria of pernicious anemia, is accompanied by a marked hypergastrinemia where gastrin levels may reach those seen in patients with gastrinoma, or with Zollinger Ellison syndrome (Yalow, R. S. and Berson, S. A., Radioimmunoassay of gastrin, Gastroenterology 58:1-14 (1970); McGuigan, J. E. and Trudeau, W. L., Serum gastrin concentrations in pernicious anemia, New Engl J Med 282:358-61 (1970); Creutzfeld, W., Arnold, R., Creutzfeld, C., Feurle, G., and Ketterer, H., Gastrin and G-cells in the antral mucosa of patients with pernicious anemia, acromegaly and hyperthyroidism and in a Zollinger-Ellison tumor of the pancreas, Eur J Clin Invest 1:461-79 (1971); Ganguli, P. C., Cullen, D. R., and Irvine, W. J., Radioimmunoassay of plasma gastrin in pernicious anaemia, achlorhydria without pernicious

anaemia, hypochlorhydria, and in controls, Lancet i:155-58 (1971)).

Hyperfunction of the G-cell in achlorhydria of pernicious anemia or after vagotomy is associated with increases in G-cell number in the antral mucosa, but the hyperplasia of the G-cell is a consequence of achlorhydria itself, and is independent of the degree of hypergastrinemia. However, in other gastric mucosal cells such as the acid-secreting parietal cell, or the histamine-forming enterochromaffin-like cell (ECL-cell), where gastrin has a trophic function, the hyperplasia of achlorhydria will be dependent on hypergastrinemia (Becker, H. D., Arnold, R., Börger, H. W., Creutzfeld, C., Schafmayer, A., and Creutzfeld, W., Influence of truncal vagotomy on serum and antral gastrin and G-cells, Gastroenterology 72:811 (1977); Delince, P., Williams, G., and de Graef, J., Antral gastrin cell proliferation after vagotomy in rats, Digestion 18:27-34 (1978); Arnold, R., von Hülst, M., Neuhof, C., Schwarting, H., Becker, H. D., and Creutzfeld, W., Antral gastrin-producing G-cells and somatostatin-producing D-cells in different states of acid secretion, Gut 23:285-91 (1982); Larsson, H., Carlsson, E., Håkabnson, R., Mattsson, M., Nilsson, G., Seensalu, R., Wallmark, B., and Sundler, F., Time course of development and reversal of gastric endocrine cell hyperplasia after inhibition of acid secretion. Studies with omeprazole and ranitidine in intact and adrenalectomized rats. Gastroenterology 95:1477-86 (1988); Håkanson, R., Oscarson, J., and Sundler, F., Gastrin and the trophic control of gastric mucosa, Scand J Gastroenterol 21(suppl. 118):18-30 (1986)).

The most powerful pharmacological agents for blocking acid secretion, clinically or experimentally, are the H_2-antagonists and the benzimidazole proton-pump inhibitors. The action of the former class of agent is by antagonism of the receptors for the histamine that has a dominant role in producing secretion of H^+-ions by the parietal cell; the latter group inhibit acid secretion by a direct action at sulphydryl groups of the H^+/K^+-ATPase of the parietal cell membrane. Treatment with either class of compound will produce achlorhydria, and a resulting hypergastrinemia; this in turn will affect the growth of GI mucosal cells. This effect has been most thoroughly investigated with omeprazole, or related compounds, in the rat stomach, but it is reported that treatment with the H_2-antagonist ranitidine is equally effective in producing hyperplasia of ECL-cells, and that toxicological studies in rats with omeprazole, or H_2-antagonists have revealed that chronic treatments were associated with increased incidence of carcinoid tumors. (Creutzfeld, W., Stöckman, F., Conlon, J. M., Fölsch, U. R., Bonatz, G., and Wulfrath, M., Effect of short and long-term feeding of omeprazole on rat gastric endocrine cells, Digestion 35(suppl. 1):84-97 (1986); Allen, J. M., Bishop, A. E., Daley, M. J., Larsson, H., Carlsson, E., Polack, J. M., and Bloom, S. R., Effect of inhibition of acid secretion on the regulatory peptides in the rat stomach, Gastroenterology 90:970-077 (1986); Larsson, H., Carlsson, E., Mattsson, H., Lundell, L., Sundler, F., Sundell, G., Wallmark, B., Watanabe, T., and Håkonson, R., Plasma gastrin and gastric enterochromaffin-like cell activation and proliferation. Studies with omeprazole and ranitidine in intact and adrenalectomized rats, Gastroenterology

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It is clear that with long-term therapy utilizing powerful blockers of acid secretion where hypergastrinemia is apparent, there may be consequences for either the growth, or turnover rate of GI mucosal cells, with the hypersecretion of gastrin a causal factor. It is also clear that if any of the effects of the hypergastrinemia of iatrogenic achlorhydria may be of serious clinical consequences, and they are to be avoided, there will be a clinical role for any agent that is a selective blocker of the release of gastrin, or a selective blocker of the action of gastrin at its receptor.

Although antagonists of gastrin-releasing peptide ("bombesin antagonists") are known, no agent has been available that will produce a powerful and selective block of the release of gastrin.

SUMMARY OF THE INVENTION

The instant invention concerns pharmaceutical compositions containing a CCK-B/gastrin antagonist or a long-acting and potent H_2 antagonist and an ATP'ase proton pump inhibitor with or without a pharmaceutically acceptable carrier.

CCK_B antagonists (gastrin antagonists) include but are not limited to:

L-365-091 which is 1-((3-((((4-chlorophenyl)-amino)carbonyl)amino)-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)acetyl)-pyrrolidine; and

(S)-5-[(10,11-dihydrodibenzo[a,d]cyclohepten-5-yl)amino]4-[(1H-indol-2-yl)carbonyl]amino]-5-oxo-pentanoic acid.

Other compounds useful in the compositions and methods of the instant invention are:

L-365,260 which is (R)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepine-3-yl)-N'-(3-methylphenyl)urea,

Butanoic acid, 4-[[2-[[3-(1H-indol-3-yl)-2-methyl-1-oxo-2-[[[(1,7,7-trimethylbicyclo[2.2.1]hept-2-yl)oxy]carbonyl]amino]propyl]amino]-1-phenylethyl]-amino]-4-oxo-, [1S-[1α,2β[S*(S*)],4β]]-,

[R-[R*,S*-(E)]]-4-[[2-[[3-(1H-indol-3-yl)-2-methyl-1-oxo-2-[[(tricyclo[3.3.1.$1^{3,7}$]dec-2-yloxy)-carbonyl]amino]propyl]amino]-3-phenylpropyl]amino]-4-oxo-2-butenoic acid,

[R-(R*,R*)]-4-[[2-[[3-(1H-indol-3-yl)-2-methyl-1-oxo-2-[[(tricyclo[3.3.1.$1^{3,7}$]dec-2-yloxy)carbonyl]-amino]propyl]amino-1-phenylethyl]amino]-4-oxo-butanoic acid,

[R-[R*,R*-(E)]-4-[[2-[[3-(1H-indol-3-yl)-2-methyl-1-oxo-2-[[(tricyclo[3.3.1.$1^{3,7}$]dec-2-yloxy)-

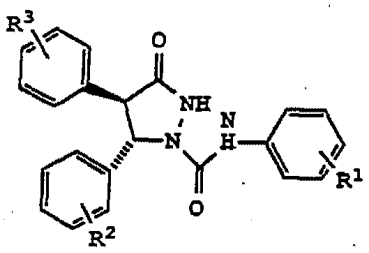
carbonyl]amino]propyl]amino]-1-phenylethyl]amino]-4-oxo-2-butenoic acid,

LY-262,690 which is *trans*-1-Pyrazolidinecarboxamide, 5-(2-chlorophenyl)-3-oxo-4-phenyl-N-[4-(trifluoromethyl)phenyl]-,

LY-262,691 which is *trans*-5-(2-chlorophenyl)-3-oxo-4-phenyl-N-[4-(bromo)phenyl]-1-pyrazolidinecarboxamide, and

trans-1-pyrazolidinecarboxamide-N-(4-bromophenyl)-5-(2-chlorophenyl)-3-oxo-4-phenyl-.

Other compounds useful in the instant invention are pyrazolidinones of formula



or a pharmaceutically acceptable salt thereof wherein

R^1 is 2,3-dichloro,
3,4-$(CH_2)_4$,
4-CF_3, or
4-Br;

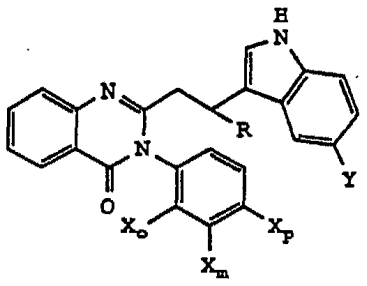
R^2 is hydrogen,
2-chloro,
2,3-dichloro, or
CN; and

R^3 is hydrogen -trans or -cis.

These are disclosed in Drugs of the Future 16(7):631-740 (1991). The compounds are made as described in Synthetic Examples 1 and 2 below.

Other compounds useful in the compositions and methods of treatment of the instant invention and

quinazolinones disclosed in J. Med. Chem. 34:1505-1508 (1991) of formula



or a pharmaceutically acceptable salt thereof wherein

X_0 is hydrogen, fluorine, chlorine, methoxy, or trifluoromethyl;

X_n is hydrogen, fluorine, chlorine, bromine, methyl ethyl isopropyl, methoxy, trifluoromethyl, propoxy, isopropoxy, cyclopentyloxyl, MeS, or NMe_2;

X_p is hydrogen, methoxy, ethoxy, isopropoxy, isopropyl, MeS, or NMe_2; or X_m and X_p together are $-OCH_2O-$;

Y is hydrogen, methyl, methoxy, fluorine, chlorine, or bromine; and

R is hydrogen or methyl.

Although several synthetic routes are available for preparing the above series, the compounds are also made as described in Synthetic Example 3 below.

Proton pump inhibitors include but are not limited to: omeprazole, BY308, SK&F 95601 which is 2-[[(3-chloro-4-morpholino-2-pyridyl)methyl]sulfinyl]-5-methoxy-(1H)-benzimidazole; and SK&F 96067 which is 3-butyryl-4-(2-methylphenylamino)-8-methoxyquinoline.

The instant invention also includes a method of treating peptic disorders such as gastroesophageal reflux disease and ulcers.

The instant invention also includes a method of treating Zollinger-Ellison Syndrome.

The compositions of the instant invention contain from 0.1 mg/kg to 10 mg/kg of a CCK-B antagonist and from 10 mg to 360 mg of an ATP'ase proton pump inhibitor.

Especially preferred is a composition of [R-(R*,R*)]-4-[[2-[[3-(1H-indol-3-yl)-2-methyl-1-oxo-2-[[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-amino]propyl]amino-1-phenylethyl]amino]-4-oxo-butanoic acid and omeprazole.

BRIEF DESCRIPTION OF DRAWINGS

Figure I shows serum gastrin levels in venous blood from rats.

Figure II shows enterochromaffin-like cell (ECL) proliferation in the corpus of rat gastric mucosa.

DETAILED DESCRIPTION

Irreversible proton pump inhibitors such as omeprazole, BY308, and others are extremely effective in gastroesophageal reflux disease (GERD), as indeed are the longer acting and potent H_2 antagonists, as well as in all other peptic disorders caused or aggravated by gastric acid. A long-acting H_2 antagonist means dosing usually is once per day; that is once in 24 hours, usually nocturnally. Unfortunately, the compounds cause carcinoid tumors in animals because of the elevated levels of gastrin. This problem means that the duration of treatment

with, for example, omeprazole in GERD is restricted. Omeprazole is indicated for short-term treatment (4-8 weeks). [Physicians' Desk Reference (1991)].

Reversible inhibitors of the gastric (H^+ and K^+)-ATP'ase, such as SK&F 96067 are also included in the instant invention.

Gerd is a chronic problem and the relief to sufferers provided by existing treatments renders them dependent on permanent therapy.

Proton pump inhibitors are also useful in the treatment of ulcers but the same problems pertain to the use of the drugs for ulcer treatment.

Proton pump inhibitors are also useful in the long-term treatment of Zollinger-Ellison syndrome.

The pharmaceutical compositions of the instant invention that contain combinations of an ATP'ase proton pump inhibitor and a CCK-B antagonist are useful for all of the above problems.

At high doses of omeprazole, for example, which totally suppress gastric acid secretion and raise gastrin blood levels very significantly, a CCK-B antagonist blocks the cellular hypertrophy of gastric mucosal cells.

Gastrin antagonists coadministered with proton pump inhibitors offer great therapeutic advantage over H_2 antagonists. Gastrin has been implicated as a growth factor in many areas of the gastrointestinal and respiratory tracts.

Studies have shown that achlorhydria causes a marked hypergastrinemia due to hypertrophy, hyperplasia, and hyperfunction of the gastrin-cell (G-cell) mass in the gastric mucosa. This increased gastrin secretion, in turn, has been suggested to be the underlying cause of a proliferation of the number, size, and activity of the enterochromaffin-like (ECL)

cells in the gastric or duodenal mucosa in achlorhydric animals. Thus, it appears that gastric carcinoid tumors formed from ECL cell hyperplasia in omeprazole-treated rats are related to the achlorhydria and secondary hypergastrinemia produced by the drug. If this is the case then treatment with gastrin antagonists should inhibit this omeprazole-induced phenomenon.

Other gastrin-dependent tumors include a human small cell carcinoma of the lung, which was recently reported to contain CCK-B/gastrin receptors, and a mouse carcinoid tumor of the colon.

CCK-B/gastrin antagonist compounds of the instant invention are able to block acid secretion in the rat in response to stimulation by pentagastrin (Hayward, N. J., Harding, M., Lloyd, S. A. C., McKnight, A. T., Hughes, J., and Woodruff, G. N., The effect of CCK_B gastrin antagonists on stimulated gastric acid secretion in the anesthetized rat, Br J Pharmacol, 104: 973-977 (1991).

Some of the compounds that are CCK-B antagonists and useful in the instant invention are fully described in European Application Publication Number 0405537 (United States Serial Number 07/545,222, filed June 28, 1990), United States Serial Numbers 07/726,656, 07/726655, 07/726,654, 07/726,653, 07/726,652, and 07/726,651, all filed on July 12, 1991 by Horwell, et al. All of the above United States applications are hereby incorporated by reference.

Other compounds which are CCK-B/gastrin antagonists and useful in the instant invention are fully described in United States Patent 4,820,834, which is hereby incorporated by reference.

Proton pump inhibitors such as BY 308, 5-trifluoromethyl-2-[4-methoxy-3-methyl-2-pyridyl-methyl]-thio-[1H]-benzimidazole, which are described and claimed in United States Patent 4,472,409, are useful in the instant invention. The patent is hereby incorporated by reference.

Proton pump inhibitors such as omeprazole, 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, which are described and claimed in United States Patent 4,255,431, are useful in the instant invention. The patent is hereby incorporated by reference.

Other useful proton pump inhibitors include but are not limited to:

[[4-(2,2,2-trifluoroethoxy)-3-methyl-2-pyridyl]-methyl]sulfenamide;

(Z)-5-methyl-2-[2-(1-naphthyl)ethenyl]-4-piperidinopyridine HCl;

2-(4-cyclohexyloxy-5-methylpyridin-2-yl)-3-(1-naphthyl)-1-propanol;

methyl 2-cyano-3-(ethylthio)-3-(methylthio)-2-propenoate;

2-((4-methoxy-2-pyridyl)methylsulphinyl)-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole sodium;

5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole;

2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methylsulfinyl]-1H-benzimidazole, sodium;

2-[[[4-(2,2,3,3,4,4,4-heptafluorobutoxy)-2-pyridyl]methyl]sulfinyl]-1H-thieno[3,4-d]imidazole;

2-[[[4-(2,2,2-trifluoroethoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole;

2-[[[4-(2,2,2-trifluoroethoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole;

2-methyl-8-(phenylmethoxy)-imidazo(1,2-A)-pyridine-3-acetonitrile;

(2-((2-dimethylaminobenzyl)sulfinyl)-benzimidazole);

4-(N-allyl-N-methylamino)-1-ethyl-8-((5-fluoro-6-methoxy-2-benzimidazolyl)sulfinylmethyl)-1-ethyl-1,2,3,4-tetrahydroquinolone;

2-[[(2-dimethylaminophenyl)methyl]sulfinyl]-4,7-dimethoxy-1H-benzimidazole;

2-[(2-(2-pyridyl)phenyl)sulfinyl)-1H-benzimidazole;

(2-[(2-amino-4-methylbenzyl)sulfinyl]-5-methoxybenzo[d]imidazole;

(4-(2-methylpyrrol-3-yl)-2-guanidisothiazole);

4-(4-(3-(imidazole)propoxy)phenyl)-2-phenylthiazole;

(E)-2-(2-(4-(3-(dipropylamino)butoxy)phenyl)-ethenyl)benzoxazole;

(E)-2-(2-(4-(3-(dipropylamino)propoxy)phenyl)-ethenyl)-benzothiazole;

Benzeneamine, 2-[[(5-methoxy-1H-benzimidazol-2-yl)sulfinyl]methyl]-4-methyl-;

Pumilacidin A;

2,3-dihydro-2-methoxycarbonylamino-1,2-benzisothiazol-3-one;

2-(2-ethylaminophenylmethylsulfinyl)-5,6-dimethoxybenzimidazole;

2-methyl-8-(phenylmethoxy)imidazo[1,2-a]pyridine-3-acetonitrile;

3-amino-2-methyl-8-phenylmethoxyimidazo[1,2-a]-pyrazine HCl;

2-[[(3-chloro-4-morpholino-2-pyridyl)methyl]-sulfinyl]-5-methoxy-(1H)-benzimidazole;

[3-butyryl-4-(2-methylphenylamino)-8-methoxy-quinoline];

2-indanyl 2-(2-pyridyl)-2-thiocarbamoylacetate HCl;

2,3-dihydro-2-(2-pyridinyl)-thiazolo(3,2-a)-benzimidazole;

3-cyanomethyl-2-methyl-8-(3-methyl-2-butenyloxy)-(1,2-a)imidazopyridine;

Zinc L-carnosine.

Figure I concerns serum gastrin levels. It shows levels of gastrin-like immunoreactivity in venous blood from rats, before and after 1, 4, 7, or 14 days of treatment with vehicles (veh/veh: isotonic saline 3 subcutaneous injections at 8-hour intervals, methocel orally at 8:00 a.m.) Compound 1 which is [R-[R*,S*-(E)]]-4-[[2-[[3-(1H-indol-3-yl)-2-methyl-1-oxo-2-[[(tricyclo[3.3.1.$1^{3,7}$]dec-2-yloxy)-carbonyl]amino]propyl]amino]-3-phenylpropyl]amino]-4-oxo-2-butenoic acid, 18 mg/kg thrice daily (veh/1189), BY 308 40 mg/kg orally in methocel (308/veh) or BY 308 and Compound 1.

Days of treatment are along the X-axis and serum gastrin (pg/md) on the Y-axis.

 is veh/veh;  is veh/compound 1;
 is 308/veh; and  308/compound 1.

Figure II concerns ECL-cell proliferation in the corpus. It shows the uptake of ^{3}H-thymidine into enterochromaffin-like cells (ECL-cell) of rat gastric mucosa after 14 days of treatments (as Figure 1); and labelled ECL-cells as a percentage of total ECL-cell count in the field ("labelling index").

 is Methocel/NaCl;  is Methocel/compound 1;
 is BY308/NaCl; and  is BY308/compound 1.

Female Sprague-Dawley rats were used with free access to lab diet and water. Groups of 10 animals were treated three times daily with 18 mg/kg of compound 1 for 14 days as follows:

S.C. saline (x3) + oral Methocel (8 am)
S.C. saline (x3) + BY 308 40 mg/kg in methocel (8 am)
S.C. Compound 1 in saline + oral methocel
S.C. Compound 1 in saline + BY 308 40 mg/kg

Two animals were used from the Compound 1 groups, for preparation with gastric fistulae, to confirm that the acid secretory response to pentagastrin remained blocked after long-term treatment with the gastrin antagonist.

Blood was drawn from the retro-orbital venous plexus before treatment on Days 0, 1, 4, 7, and 14 for assay of serum gastrin and CCK levels.

Three days before sacrifice ^{3}H-thymidine was infused into a tail vein (1 µCi/g body weight as a bolus injection, followed by continuous infusion for 8 hours of 0.25 µCi/g/h), for subsequent measurement of ECL-cel labeling index by autoradiography.

Optimal tissue preservation was achieved by perfusion fixation in Bouin's fixative for 8 minutes, and by fixation for 24 hours of excised tissue blocks in Bouin's solution, with embedding in paraffin wax. For estimation of cell density, 5 µm sections were cut; 2 µm for autoradiography (Eissele, R., Rosskopf, B., Koop, H., Adler, G., and Arnold, R., Proliferation of endocrine cells in rat stomach caused by drug-induced achlorhydria, Gastroenterology, in press (1991)).

Antral G-cells were visualized after removal of the paraffin wax by immunostaining for gastrin using

the avidin-biotin-peroxidase complex technique (Hsu, S. M., Raine, L., and Fanger, H., Use of avidin-biotin-peroxidase complex (ABC) in immunoperoxidase techniques; a comparison between ABC and unlabeled antibody (PAP) procedures, J Histochem Cytochem 29:577-780 (1981)).

ECL-cell density was evaluated in sections of oxyntic mucosa by the silver impregnation method or by immunostaining for chromogranin for autoradiographic studies (Grimelius, L., A silver nitrate stain for A_2 cells of human pancreatic islets, Acta Soc Med Ups 73:271-294 (1968)).

Gastrin levels in unfixed sections of antrum and somatostatin in the fundus were measured by radioimmunoassay. Unfixed samples of pancreas were taken to assay for enzyme and DNA levels by standard methods.

Treatment with the proton-pump inhibitor BY 308 (Koop, H., Schubert, B., Schwarting, H., Schikierka, D., Eissele, R., Willemer, S., and Arnold, R., Increased visualization of antral gastrin-producing G-cells after acute stimulation of gastrin release in the rat, Eur J Clin Invest 17:111-16 (1987)) produced the expected rise in serum gastrin levels, irrespective of the presence or absence of co-treatment with Compound 1. The compound had no effect by itself on gastrin levels (Figure 1). Levels of gastrin in antral sections were also increased in the groups treated with BY 308, but somatostatin in the fundus was not affected by any treatment.

Antral mucosal G-cells were increased from 56/mm (saline + methocel), or 60\mm (([R-[R*,S*-(E)]]-4-[[2-[[3-(1H-indol-3-yl)-2-methyl-1-oxo-2-[[(tricyclo-[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]amino]propyl]amino]-3-

phenylpropyl]amino]-4-oxo-2-butenoic acid, + methocel) to 75/mm and 88/mm in the corresponding groups given BY 308. The increases by BY 308 were statistically significant at the 2% level. That is, the increase in G-cell number is attributable to the achlorhydria, and is obtained in either group treated with BY 308.

In keeping with previous data from this group that ECL-cell density is not much affected until exposure to BY 308 extends beyond the third week of treatment, in the present 2-week study ECL-cell number was not significantly affected by any treatment (density around 200/mm). As in the earlier study by this group, however, the ^{3}H-thymidine labeling index, as an indicator of cell turnover, was increased from between 0.3% and 0.5% of cells in vehicle-treated controls to between 3% and 4% in the group treated for 14 days with the proton-pump inhibitor. This increase was abolished in the group also given Compound 1 for the 14-day period; by itself the compound had no effect on ECL-cell labeling index (Figure 2).

The above experiments show that in the female rat in achlorhydria with chronic treatment with the proton pump inhibitor BY 308, the resultant hypergastrinemia is unaffected by cotreatment with a dose of Compound 1 high enough to guarantee complete blockade of the gastrin receptor on the parietal cell. The 14-day treatment with the high dose of Compound I did not affect gastrin levels.

The 14-day treatment with BY 308 showed there was a substantial increase in the incorporation of thymidine into the ECL-cells of the fundic mucosa, indicating an increased rate of cell division. The increased thymidine labeling index was completely blocked by Compound 1, indicating that the effect is

truly a consequence of the hypergastrinemia of achlorhydria.

These results show CCK_B/gastrin antagonists are expected to have clinical utility in the periphery, in the management of gastrin-dependent hyperplasias.

The compositions or combinations of the present invention are usually administered in a standard pharmaceutical composition. The present invention therefore provides pharmaceutical compositions comprising a compound which is a CCK-B/gastrin antagonist (or a long-acting and potent H_2 antagonist) or a pharmaceutically acceptable salt thereof and a proton pump inhibitor or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, if desired.

The composition can be given orally formulated as liquids, for example, syrups, suspensions or emulsions, tablets, capsules, and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound of pharmaceutically acceptable salt in a suitable liquid carrier(s), for example, ethanol, glycerine, nonaqueous solvent, for example, polyethylene glycol, oils, or water with a suspending agent, preservative, flavoring or coloring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose, and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a

dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example, aqueous gums, celluloses, silicates, or oils, and the dispersion or suspension, then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example, polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil, or sesame oil. Alternatively, the solution can be lyophilized and then reconstituted with a suitable solvent just prior to administration.

A typical suppository formulation comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent such as polymeric glycols, gelatins, or cocoa butter or other low melting vegetable or synthetic waxes or fats.

Preferably the composition is in unit dose form such as a tablet or capsule.

Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

The pharmaceutically acceptable compositions of the invention will normally be administered to a subject for the treatment of peptic disorders and other conditions caused or exacerbated by gastric acidity. The daily dosage regimen for an adult patient may be, for example, an oral dose of between 1 mg and 500 mg, preferably between 1 mg and 250 mg, or an intravenous, subcutaneous, or intramuscular dose

of between 0.1 mg and 100 mg, preferably between 0.1 mg and 25 mg, of the compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example, for a week or more.

The dosing regimen will be within the skill or a skilled physician.

In addition, the composition of the present invention can be coadministered with further active ingredients such as antacids (for example, magnesium carbonate or hydroxide and aluminum hydroxide), nonsteroidal antiinflammatory drugs (for example, indomethacin, aspirin, or naproxen), steroids, or nitrite scavengers (for example, ascorbic acid or aminosulphonic acid), or other drugs used for treating gastric ulcers (for example, pirenzepine, prostanoids, for example, 16,16-dimethyl PGE_2, or histamine H_2-antagonists (for example, cimetidine, ranitidine, famotidine, and nazatidine).

EXAMPLE 1

Tablet		
(1) Compound 1	30 mg	
(2) Corn starch	20 mg	
(3) Lactose	85.2 mg	
(4) Micro crystalline cellulose	60 mg	
(5) Light anhydrous silicic acid	1.8 mg	
(6) Magnesium stearate	3.0 mg	
(7) Magnesium hydroxide	30 mg	
(8) L-Cysteine	20 mg	
	250 mg	(One Tablet)

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EXAMPLE 2

Capsule	
(1) Compound 1	30 mg
(2) Corn starch	40 mg
(3) Lactose	74 mg
(4) Hydroxypropylcellulose	6 mg
(5) Magnesium carbonate	50 mg
(6) Water	(0.1 mL)
	200 mg

EXAMPLE 3

A syrup containing 2% (weight per volume) of active substance was prepared from the following ingredients:

Omeprazole	2.0 g
Saccharin	0.6 g
Sugar	30.0 g
Glycerin	5.0 g
Flavoring agent	0.1 g
Ethanol 96%	10.0 mL

Distilled water (sufficient to obtain a final volume of 100 mL), sugar, saccharin, and the acid addition salt were dissolved in 60 g of warm water. After cooling, glycerin and a solution of flavoring agents dissolved in ethanol were added. Water was added to the mixture to obtain a final volume of 100 mL.

The above given active sustance may be replaced with other pharmaceutically acceptable acid addition salts.

SYNTHETIC EXAMPLE 1

Trans-5-(2-chlorophenyl)-3-oxo-4-phenyl-N-[4-(bromophenyl]-1-pyrazolidinecarboxamide

Step 1. Preparation of αphenyl-2-chlorocinnamic acid

Method used: Org. Syn. Coll. IV:777 (1963).

Phenylacetic acid (54.46 g, 0.4 M) was dissolved in acetic anhydride (80 mL). O-chlorobenzaldehyde (56.23 g, 0.4 M) was added slowly, with stirring. This was followed by the slow addition of triethylamine (40 mL). The reaction mixture was stirred at reflux for 5 hours. The reaction mixture was steam distilled until the distillate was no longer cloudy. The distillate was discarded. The aqueous residue was cooled. The solution was decanted from the gummy solid. This solid was dissolved in a 10% K_2CO_3 solution. The basic solution was charcoaled then filtered through a pooled Super cell. The filtrate was made acidic (pH 1) with 10% HCl, cooled, and the solid filtered. The product was recrystallized from 50% ethanol/H_2O to yield 52.14 g of white solid, mp 158-161°C.

Step 2. Preparation of αphenyl-2-chlorocinnamic acid methyl ester

αPhenyl-2-chlorocinnamic acid (26.29 g (0.102 M) was dissolved in methanol (300 cc). Anhydrous HCl was bubbled through the reaction mixture with stirring for 15 minutes. The reaction mixture was refluxed for 2 hours, then HCl was bubbled through the reaction mixture for another 15 minutes. The reaction was stirred at reflux overnight. The methanol was removed in vacuo and the residue taken up in ether. The ether solution was washed with H_2O, saturated $NaHCO_3$ solution, and brine. It was then dried over $MgSO_4$. The ether solution was concentrated in vacuo to yield

an oil that quickly solidified to yield 27.13 g of product, mp 67-69°C.

Step 3. Preparation of 4-(O'-chlorophenyl)-5-phenyl-3-pyrazolidine

The ester from Step 2 (27.05 g, 0.0993 M) was dissolved in ethanol (75 cc). Eighty-five percent hydrazine hydrate (5.76 g, 0.0993 M) was added. The reaction mixture was stirred at reflux for 24 hours, then cooled. H_2O was added slowly with stirring. The product oiled out. The ethanol water was decanted from the oil. The oil was taken up in ether. The ether solution was washed with cold water, then dried over $MgSO_4$. The ether solution was concentrated in vacuo. A small amount of ether was added to the residue. The white solid was filtered and dried in vacuo to yield 9.56 g of product, mp 123-124°C.

Step 4. Preparation of trans-5-(2-chlorophenyl)-3-oxo-4-phenyl-N-[4-(bromophenyl]-1-pyrazolidine-carboxamide

The pyrazolidone obtained in Step 3 (2.73 g, 0.01 M) was dissolved in THF (100 mL). p-Bromophenyl isocyanate (1.98 g, 0.01 M) was added. The reaction mixture was stirred overnight at room temperature. The clear solution was concentrated in vacuo to yield 4.73 g of a white solid. The solid was boiled in isopropyl ether. The insoluble solid was filtered from the warm ether and dried to yield 3.71 g of the product, mp 189-190°C.

Analysis for $C_{22}H_{17}BrClN_3O_2$ (MW 470.762):

Calcd.: C, 56.13; H, 3.64; N, 8.91.

Found: C, 56.43; H, 3.87; N, 8.71.

IR NMR and MS consistent for the desired product.

SYNTHETIC EXAMPLE 2

Trans-5-(2-chlorophenyl)-3-oxo-4-phenyl-N-[4-(trifluoromethyl)phenyl]-1-pyrazolidinecarboxamide

Substituting αααtrifluoro-p-tolyl isocyanate (1.87 g, 0.01 M) for p-bromophenyl isocyanate in Step 4, one obtains 3.6 g of the product, mp 193-194°C.

Analysis for $C_{23}H_{17}ClF_3N_3O_2$ (MW 459.859):

Calcd.: C, 60.07; H, 3.73; N, 9.14.

Found: C, 60.16; H, 3.81; N, 9.09.

IR, NMR and MS consistent for the desired product.

SYNTHETIC EXAMPLE 3

3-nitrophenol (50.0 g, 360 mmol), isopropyl iodide (76.19 g, 450 mmol), and K_2CO_3 (60 g) were combined and heated at reflux under N_2 overnight in acetone (400 mL). After solvent removal in vacuo, the residue was partitioned between EtOAc and H_2O. The separated organic layer was washed with 1 N NaOH, brine, dried over Na_2SO_4, and concentrated in vacuo to provide 56 g (86%) of 3-isopropoxynitrobenzene as a clear yellow oil.

A mixture of the above product (8.5 g, 50 mmol), PtO_2 (0.3 g), and EtOH (200 mL) was hydrogenated (40 psi H_2) at room temperature for 1.5 hours in a Paar shaker. The mixture was filtered through Celite and concentrated in vacuo to furnish 7.08 g of the desired aniline. This material was combined with isatoic anhydride (7.35 g, 45 mmol) and heated at 90°C for 2 hours. Upon cooling and addition of hexanes, the product crystallized to give 10.19 g (83%) of 2-amino-N-(3-isopropoxyphenyl)benzamide as a white solid. An analytical sample was obtained by recrystallization from 20% EtOAc/hexanes, mp 79-86°C; ^1H NMR ($CDCl_3$) δ 1.36 (6H, d, J=6.1 Hz), 4.59 (1H, h,

J=6.1 Hz), 5.2 (2H, bs), 6.6-6.8 (3H, m), 7.0-7.1 (1H, m), 7.2-7.4 (3H, m), 7.47 (1H, d, J=7.7 Hz), 7.80 (1H, bs); IR ($CHCl_3$) 1664, 1611, 1524, 1490 cm^{-1}; MS (FD) 270 (M^+). Anal. ($C_{16}H_{18}N_2O_2$) C, H, N.

A solution of 3-[(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)methyl]-5-bromoindole (4.12 g, 12 mmol) prepared according to the method of Farlow, et al (Farlow, D. S.; Flaugh, M. E.; Horvath, S. D.; Lavignino, E. R.; Pranc, P. Two Efficient Syntheses of Indole-3-Propionic Esters and Acids. Further Applications of Meldrum's Acid. Org. Prep. Proced. Int. 13:39-48 (1981), the above benzamide (3.48 g, 13 mmol) and pyridinium p-toluenesulfonate (1.64 g, 6.5 mmol) in 50 mL of pyridine was heated at reflux for 3.5 days. The reaction mixture was concentrated in vacuo, chromatographed (SiO_2, 30% EtOAc/hexanes), and crystallized to give 2.13 g (36%) of compound 22, mp 179-181°C; ^1H NMR ($CDCl_3$) δ 1.31 (3H, d, J=6.0 Hz), 1.34 (3H, d, J=6.1 Hz), 2.8 (2H, m), 3.2 (2H, m), 4.53 (1H, h, J=6.0 Hz), 6.7-7.6 (9H, m), 7.8 (2H, m), 8.2-8.4 (2H, m); IR (KBr) 1671 cm^{-1}; MS (FAB) 502, 504 ($M^+ + H$). Anal. ($C_{27}H_{24}N_3O_2Br$) C, H, N.

CLAIMS

1. A pharmaceutical composition containing a CCK-B/gastrin antagonist and an ATP'ase proton pump inhibitor with or without a pharmaceutically acceptable carrier.

2. A pharmaceutical composition according to Claim 1 wherein the CCK-B antagonist is one or more selected from

[R-(R*,R*)]-4-[[2-[[3-(1H-indol-3-yl)-2-methyl-1-oxo-2-[[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]amino]propyl]amino-1-phenylethyl]amino]-4-oxo-butanoic acid,

[R-[R*,R*-(E)]-4-[[2-[[3-(1H-indol-3-yl)-2-methyl-1-oxo-2-[[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]amino]propyl]amino]-1-phenylethyl]amino]-4-oxo-2-butenoic acid,

Butanoic acid, 4-[[2-[[3-(1H-indol-3-yl)-2-methyl-1-oxo-2-[[[(1,7,7-trimethylbicyclo-[2.2.1]hept-2-yl)oxy]carbonyl]amino]propyl]-amino]-1-phenylethyl]amino]-4-oxo-, [1S-[1α,2β[S*(S*)],4β]]-, and

[R-[R*,S*-(E)]]-4-[[2-[[3-(1H-indol-3-yl)-2-methyl-1-oxo-2-[[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]amino]propyl]amino]-3-phenyl-propyl]amino]-4-oxo-2-butenoic acid.

3. A pharmaceutical composition according to Claim 1 wherein the CCK-B antagonist is (R)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepine-3-yl)-N'-(3-methylphenyl)urea.

4. A pharmaceutical composition according to Claim 1 wherein th CCK-B antagonist is *trans*-1-

pyrazolidinecarboxamide, 5-(2-chlorophenyl)-3-oxo-4-phenyl-N-[4-(trifluoromethyl)phenyl]-.

5. A pharmaceutical composition according to Claim 1 wherein the ATP'ase proton pump inhibitor is one or more selected from: BY308, omeprazole, SK&F 95601 and SK&F 96067.

6. A pharmaceutical composition according to Claim 1 wherein the CCK-B antagonist is [R-(R*,R*)]-4-[[2-[[3-(1H-indol-3-yl)-2-methyl-1-oxo-2-[[(tricyclo[3.3.1.$1^{3,7}$]dec-2-yloxy)carbonyl]-amino]propyl]amino-1-phenylethyl]amino]-4-oxo-butanoic acid and the proton pump inhibitor is omeprazole.

7. A method for treating peptic disorders in a patient suffering therefrom which comprises administering a composition according to Claim 1.

8. A method according to Claim 7 wherein the peptic disorder is gastroesophageal reflux.

9. A method according to Claim 7 wherein the peptic disorder is ulcer.

10. A method for treating Zollinger-Ellison Syndrome in a patient suffering therefrom which comprises administering a composition according to Claim 1.

11. A pharmaceutical composition according to Claim 1 containing from 0.1 mg/kg to 10 mg/kg of a CCK-B antagonist and from 10 mg to 360 mg of an ATP'ase proton pump inhibitor.

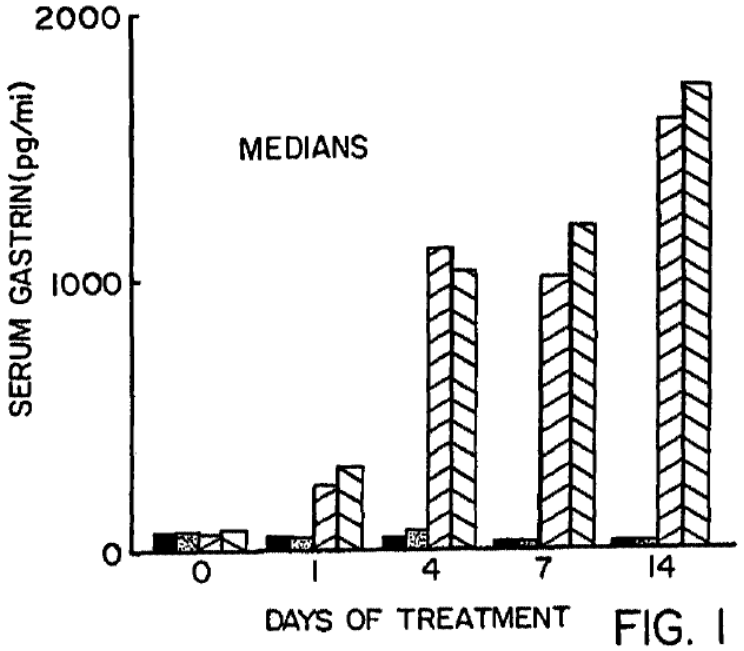

2000
1000
0
SERUM GASTRIN(pg/ml)
MEDIANS
0
1
4
7
14
DAYS OF TREATMENT

FIG. 1

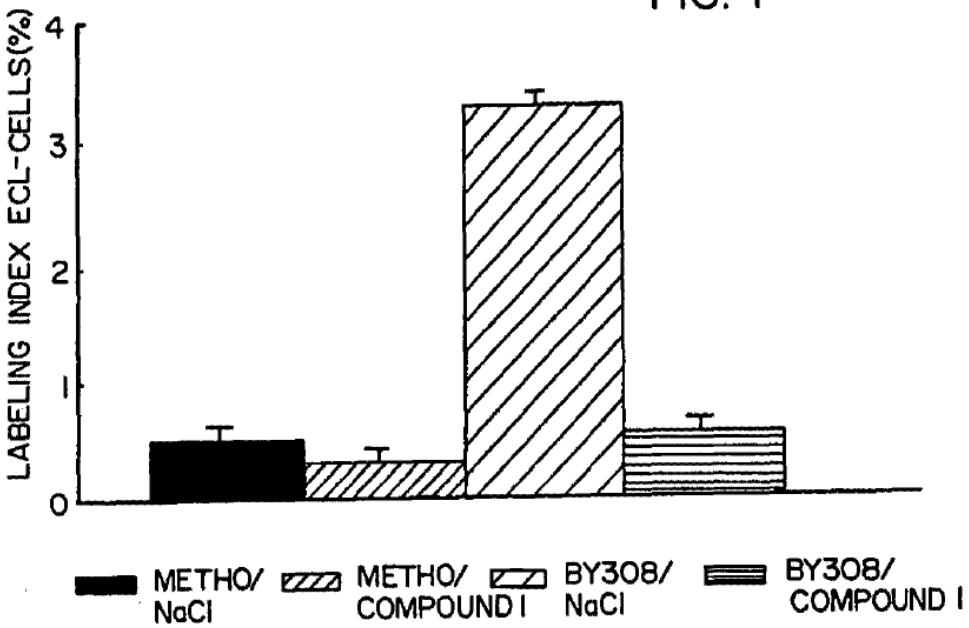

LABELING INDEX ECL-CELLS(%)
4
3
2
1
0
METHO/ NaCl
METHO/ COMPOUND I
BY308/ NaCl
BY308/ COMPOUND I

FIG. 2

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/10692

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K45/06; A61K31/44; //(A61K31/44,31:405)

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category[10]	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	FEBS LETT, VOL. 281, NO. 1-2, PAGE(S) 20-2, 1991, DIMALINE R ET AL. 'Histidine decarboxylase gene expression in rat fundus is regulated by gastrin.' see page 22, column 1, line 2 - line 13 ---	1,5
A	EP,A,0 272 876 (GLAXO GROUP LIMITED) 29 June 1988 see abstract ---	1-11
A	BRITISH JOURNAL OF PHARMACOLOGY vol. 104, no. 4, December 1991, page 973-977 HAYWARD ET AL. 'The effect of CCK-B gastrin antagonists on stimulated gastric acid secretion in the anaesthetized rat' see abstract -----	1-11

[10] Special categories of cited documents:

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
18 MARCH 1993	30. 03. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT FFICE	LEHERTE C.F.M.

Form PCT/ISA/210 (second sheet) (January 1985)

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/10692

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
ALTHOUGH CLAMIS 7-10 ARE DIRECTED TO A METHOD OF TREATMENT OF THE HUMAN/ ANIMAL BODY THE SEARCH HAS BEEN CARRIED OUT AND BASED ON THE ALLEGED EFFECTS OF THE COMPOUND/COMPOSITION.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

US 9210692
SA 68014

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0272876	29-06-88	AU-B- 618943	16-01-92
		AU-A- 8261587	23-06-88
		JP-A- 63246337	13-10-88

EPO FORM P0779

For more details about this annex : see Official Journal of the European Patent ffice, No. 12/82

B2

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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Published
With international search report.

(54) Title: IBUPROFEN-H_2 ANTAGONIST COMBINATIONS

(57) Abstract

This invention relates to pharmaceutical compositions for use in the treatment of pain and inflammation and in the relief of indigestion, sour stomach, heartburn and other gastrointestinal disorders in mammals, including humans, by administering compositions comprising (i) an analgesically and anti-inflammatory effective amount of a salt of (S)-ibuprofen substantially free of (R)-ibuprofen wherein the salt is selected from (S)-ibuprofen-(S)-lysine and (S)-ibuprofen-(R)-lysine; and (ii) an amount effective in the relief of indigestion, sour stomach, heartburn, overindulgence and other gastrointestinal disorders of at least one of the H_2 antagonists.

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TITLE OF THE INVENTION
IBUPROFEN-H_2 ANTAGONIST COMBINATIONS

BACKGROUND OF THE INVENTION

The non-steroidal anti-inflammatory drugs (NSAID) have been utilized in the treatment of pain/inflammation and a number of other symptoms including stiffness that are associated with painful conditions affecting muscles, bones, and joints. NSAIDs have been prescribed to relieve back pain, arthritic pain, gout, menstrual pain, headaches, mild pain following surgery, and pain from soft tissue injuries such as sprains and strains. NSAIDs are within the broader class of non-narcotic analgesics which also includes acetyl salicyclic acid (aspirin) and acetaminophen. NSAIDs, except for acetaminophen, are generally considered to exert their effect by blocking the production of prostaglandins at the site of pain, irritation or injury so that the pain signal does not reach the brain.

Ibuprofen (2-(4-isobutylphenyl)propionic acid) is a well known and commonly employed NSAID. Amino acid salts of racemic ibuprofen including the lysine or arginine salt are also known pain relievers. See U.S. Pat. No. 4,279,926. Recently, it has been found that a faster onset of pain relief and an enhanced analgesic response can be obtained by utilizing the single enantiomer (S)-ibuprofen (also known as (+)-ibuprofen or dexibuprofen) rather than the racemic mixture of ibuprofen. See U.S. Patent 4,877,620.

H_2 antagonists are commonly prescribed to treat and prevent ulcers in the walls of the stomach, duodenum or esophagus. H_2 antagonists are also used to treat non-ulcerative conditions. Damage to the mucus lining surrounding these tissues enables destructive action of stomach acids which erodes the underlying tissue. Commonly known H_2 antagonists for the treatment of ulcers include cimetidine, ranitidine, nizatidine, roxatidine and famotidine.

Combinations of ibuprofen with H_2 antagonists have been disclosed. See EPO App. No. 426479A which discloses a pharmaceutical composition for treating the symptoms of

overindulgence (headache and acid indigestion) using H_2 antagonists including famotidine and an analgesic effective amount of a NSAID including ibuprofen wherein the term is defined to include administration of both the racemic mixture or the pure S enantiomer of ibuprofen. There is a need to employ a compound with faster acting and enhanced analgesic capability such as (i) an analgesically and anti-inflammatory effective amount of a salt of (S)-ibuprofen substantially free of (R)-ibuprofen wherein the salt is selected from (S)-ibuprofen-(S)-lysine and (S)-ibuprofen-(R)-lysine; in combination with an H_2 antagonist such as famotidine to treat and prevent the pain and discomfort associated with headaches, indigestion, sour stomach, heartburn or other gastrointestinal disorders. There is a need to employ a combination wherein an advantage is that the (S)-ibuprofen lysine salt is more stable than the free acid of ibuprofen and is extremely soluble in water to give substantially neutral (versus acidic) aqueous solutions. The ibuprofen/lysine salt is therefore more suitable for administration to patients than the free acid because of its enhanced solubility in water (and in plasma) and because of its neutrality. Because of these improved and advantageous physical properties, administration of the combination is more effective in the treatment of pain, inflammation, and overindulgence. In addition, an advantage of the (S)-ibuprofen-(S)-lysine in the combination claimed in the instant invention is that this salt is neutral and not acidic and, therefore, unlike the prior art disclosures of H_2 antagonist and ibuprofen, does not both acerbate and treat stomach conditions simultaneously.

The present invention provides both faster onset and enhanced relief of aches and pains associated with the body, head and stomach to provide broad and concurrent symptomatic relief. The combination with famotidine is especially advantageous since (S)-ibuprofen-lysine does not interfere with the metabolism of famotidine nor does famotidine interfere with the metabolism of alcohol.

DETAILED DESCRIPTION OF THE INVENTION

This invention claims pharmaceutical compositions for use in the treatment of pain and inflammation and the treatment of mild stomach and esophagus disorders including the treatment of heartburn. The composition comprises:

(i) an analgesically and anti-inflammatory effective amount of a salt of (S)-ibuprofen substantially free of (R)-ibuprofen wherein the salt is selected from (S)-ibuprofen-(S)-lysine and (S)-ibuprofen-(R)-lysine; and

(ii) an amount effective in relief of gastrointestinal or esophagus disorders of at least one of the H_2 antagonists.

This invention is also directed to a method of treating pain and inflammation and concurrently treating indigestion, sour stomach, heartburn, overindulgence and other gastrointestinal disorders in mammals, including humans, in need thereof, comprising administering to such organism:

(i) an analgesically and anti-inflammatory effective amount of a salt of (S)-ibuprofen substantially free of (R)-ibuprofen wherein the salt is selected from (S)-ibuprofen-(S)-lysine and (S)-ibuprofen-(R)-lysine; and

(ii) an amount effective in relief of gastrointestinal or esophagus disorders of at least one of the H_2 antagonists.

This invention is further directed to a method of eliciting an onset hastened and enhanced response for the treatment of pain and inflammation and the treatment of gastrointestinal or esophagus disorders in mammals, including humans, in need thereof, comprising administering to such organism:

(i) an analgesically and anti-inflammatory effective amount of a salt of (S)-ibuprofen substantially free of (R)-ibuprofen wherein the salt is selected from (S)-ibuprofen-(S)-lysine and (S)-ibuprofen-(R)-lysine; and

(ii) an amount effective in relief of gastrointestinal or esophagus disorders of at least one of the H_2 antagonists.

Substantially free of (R)-ibuprofen means that the ratio of (S)-ibuprofen to (R)-ibuprofen is at least 90:10.

Salts of (S)-ibuprofen include pharmaceutically acceptable salts such as alkali metals (sodium or potassium), alkaline earth metals (calcium), or salts with other metals such as magnesium, aluminum, iron, zinc, copper, nickel or cobalt.

Pharmaceutically acceptable salts of (S)-ibuprofen further include the amino acid salts, particularly the basic amino acids such as lysine or arginine. Specifically included within the composition of the instant invention is (S)-ibuprofen-(S)-lysine and (S)-ibuprofen-(R)-lysine.

The term mammals or mammalian organism includes but is not limited to man, dog, cat, horse and cow.

The term treatment encompasses the complete range of therapeutically positive effects associated with pharmaceutical medication including reduction of, alleviation of and relief from the symptoms or illness which affect the organism.

(S)-ibuprofen may be prepared following the procedures disclosed in U.S. Patent 4,877,620. Metal salts of ibuprofen may be obtained by contacting a hydroxide, or carbonate with ibuprofen. Amino acid salts of ibuprofen may be obtained by contacting an amino acid in solution with ibuprofen. U.S. Patent No. 4,994,604 describes a process for the formation and resolution of (S)-ibuprofen-(S)-lysine that employs preferential crystallization to separate a pair of diastereomeric salts, (S)-ibuprofen-(S)-lysine and (R)-ibuprofen-(S)-lysine. The basic procedure involves (a) contacting (R),(S)-ibuprofen and (S)-lysine in an aqueous-organic solvent mixture; (b) separating any suspended solid from the mixture; and (c) cooling the clear mixture until the mixture is supersaturated with respect to each of the (S)-ibuprofen-(S)-lysine and (R)-ibuprofen-(S)-lysine salts; (d) contacting the supersaturated mixture with a slurry of (S)-ibuprofen-(S)-lysine in an aqueous-organic solvent; and (e) separating the formed crystalline (S)-ibuprofen-(S)-lysine.

Specifically, the racemic ibuprofen starting material is mixed with an organic solvent that is miscible with water. The (S)-

lysine is mixed with water and the ibuprofen and lysine solutions are combined.

The mixture is agitated for a time period sufficient to crystallize all the salts, if any, in excess of the solubility limit. The suspended salts are separated to obtain a clear mother liquor which is generally saturated with respect to the diastereomeric salts (S)-ibuprofen-(S)-lysine and (R)-ibuprofen-(S)-lysine. Filtration may be employed to effect the separation. The liquor is then cooled to a temperature at which it is supersaturated with respect to each of the diastereomeric salts. It is preferred that the liquor be cooled to the point at which maximum supersaturation is obtained with respect to each salt without nucleation of either crystallizable species. Typically the temperature of the mother liquor must be lowered by about 5°C to reach maximum supersaturation without precipitation of either salt. However, the degree of cooling will depend on the particular solvent composition. The supersaturated liquor is then passed into a vessel containing a slurry of (S)-ibuprofen-(S)-lysine, hereafter referred to as the (S,S) salt, in the same solvent system employed above for the mixture of racemic ibuprofen and (S)-lysine. In the presence of the (S,S) salt crystals acting as a seed, the supersaturation of the (S,S)-salt in the feed liquor is released by the growth of further crystals of the (S,S)-salt. Conversely, there is little or no change in the (R)-ibuprofen-(S)-lysine supersaturation because the growth rate of the (R,S) crystals is essentially zero in the absence of any initial (R,S) salt seed. The (S,S) crystals are then separated by filtration or centrifugation and washed with aqueous-organic solvent to yield (S)-ibuprofen-(S)-lysine of purity approximating 98%.

The pharmaceutical compositions of the present invention are useful in the rapid and enhanced treatment of pain and inflammation and in the treatment of various mild gastrointestinal disorders including indigestion, sour stomach, overindulgence and heartburn. In particular, the (S)-ibuprofen-(S)-lysine combined with an H_2 antagonist such as famotidine is useful for the treatment of pain, inflammation, and the various gastrointestinal disorders such as indigestion, sour stomach, or

heartburn. The utilization of (S)-ibuprofen and in particular (S)-ibuprofen-(S)-lysine in an analgesic/H_2 antagonist combination offers significant advantages over the combination of racemic ibuprofen and an H_2 antagonist or (S)-ibuprofen and an H_2 antagonist.

(S)-ibuprofen and in particular the (S)-lysine salt of (S)-ibuprofen provides a faster onset of pain and inflammation relief and an enhanced degree of relief compared to racemic ibuprofen. These benefits contribute to overall enhanced and faster relief of symptoms associated with headaches and other aches and pains that often accompany gastrointestinal disorders and overindulgence when the (S)-ibuprofen-(S)-lysine is combined with an H_2 antagonist such as famotidine.

The absence or reduction of (R)-ibuprofen also provides significant benefits. The allergic contraindications sometimes associated with ibuprofen administration are absent or reduced in a (R)-ibuprofen-free or substantially-free composition. An additional advantage may be that less metabolic energy will be used to convert the inactive (R)-ibuprofen to the active (S)-ibuprofen. In addition, a reduced burden may be placed on the urogenital system since administration of the pure (S)-ibuprofen eliminates the need to excrete the (R)-ibuprofen or its metabolites. The absence of the (R)-enantiomer also reduces or eliminates the incorporation of this molecule into fatty tissue. The renal burden and renal toxicities sometimes associated with racemic ibuprofen therapy may be reduced or eliminated in a (S)-ibuprofen composition that is substantially free of the (R) enantiomer.

H_2 antagonists are well known in the treatment of ulcers and other gastrointestinal disorders and may be used in combination with (S)-ibuprofen-(S)-lysine. H_2 antagonists used for ulcer therapy fall into four major structural classes: imidazole derivatives; substituted furans; aminoalkylphenoxy derivatives and guanidinothiazole compounds. Famotidine (N'-(aminosulfonyl)-3-[[[2-[(diamino-methylene)amino]-4-thiazolyl]methyl]thio] propanimidamide), a member of the latter class, is a competitive inhibitor of histamine H_2-receptors and its primary pharmacological activity is the inhibition of

gastric acid secretion. Famotidine suppresses both the acid concentration and the volume of gastric acid secretion. Famotidine is well tolerated and has minimal side effects and thus advantageously may be used in the present invention in combination with (S)-ibuprofen-(S)-lysine. Famotidine is also the most potent and selective H_2 antagonist. The combination of famotidine and (S)-ibuprofen-(S)-lysine provides a combination which simultaneously and selectively provides relief from headaches, pain, inflammation, and discomfort and injury to the stomach, esophagus, or duodenum from excess production of gastric acid. Furthermore, famotidine may not interact with alcohol so that it may be administered prior to or during ingestion of meals or beverages which contain alcohol. The combination of (S)-ibuprofen-(S)-lysine with famotidine provides rapid and enhanced relief of pain while also providing long acting relief from and treatment of gastrointestinal disorders associated with gastric acid secretion.

The absence of inactive enantiomers, particularly (R)-ibuprofen provides for significant size and weight advantages in a combination dosage form, particularly a sustained release dosage form. Where a sustained release dosage of ibuprofen may have required 800 to 1000 mg, the employment of (S)-ibuprofen-(S)-lysine reduces the weight to 400 to 500 mg, and provides for a more practical size tablet for an ibuprofen/H_2 antagonist combination. In particular, the combination of famotidine which is a highly potent H_2 antagonist with (S)-ibuprofen-(S)-lysine reduces the size and weight of all pharmaceutical delivery forms or combination formulations and therefore improves patient compliance or tolerance. The tablet or capsule form of this combination is more readily swallowable by patients in need of treatment thereof.

An effective amount of (S)-ibuprofen, or a salt thereof, for use in a unit dose composition of this invention may range from 50-800 mg of (S)-ibuprofen equivalents. The preferred amount of (S)-ibuprofen is about 100 to 400 mg. The amount of a salt such as (S)-ibuprofen-(S)-lysine is determined based on the amount of (S)-ibuprofen contained therein.

The H_2 antagonist employed herein may be selected from any of the commercially available or known H_2 antagonists such as cimetidine, ranitidine, roxatidine, nizatidine or famotidine. Famotidine is advantageously used in the present invention in combination with (S)-ibuprofen-(S)-lysine. The amount of famotidine used in the present invention in humans may range from 2.5 mg/day to 40 mg/day. Advantageously, 2.5 to 20 mgs/day is administered in combination with 100 to 400 mg of (S)-ibuprofen-(S)-lysine. The combination claimed in the instant invention is advantageously administered orally. However, in patients with hypersecretory conditions, intractable ulcers, or in patients who are unable to take oral medication, the claimed combination may be administered intravenously in a suitable dosage within the limits described for oral treatment.

The present composition may be administered in the form of tablets, caplets, gelcaps, capsules, elixirs, syrups, or suspensions. For oral administration, the active ingredients may be admixed with a pharmaceutically acceptable diluent such as lactose, sucrose, cellulose, dicalcium phosphate, calcium sulfate, mannitol, and, in a liquid composition, ethyl alcohol. Acceptable emulsifying or suspending agents such as PVP, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, guar gum, agar, bentonite, carboxymethylcellulose sodium, polyethylene glycol and waxes, may also be admixed with the active components. Where necessary, lubricants such as magnesium stearic acid talc or magnesium stearate, and disintegrators or superdisintegrators such as starch, sodium starch glycolate or cross-linked PVP may also be included. Electrolytes such as dicalcium phosphate, sodium benzoate, sodium acetate and sodium chloride may also be used.

The active components may also be formulated in sustained release or effervescent formulations. These formulations depending upon whether they are sustained release or effervescent may be employed in oral, dermal, rectal or vaginal administrations. The sustained release formulations also include layered formulations which

provide for distinct release ratio and thus may be more effective in allowing for short and long term relief.

The following examples illustrate the compositions of the present invention which may be readily prepared and as such are not to be considered as limiting the invention set forth in the claims.

EXAMPLE 1

(S)-Ibuprofen lysine/famotidine Tablet

(S)-ibuprofen-(S)-lysine	342 mg
famotidine	40 mg
PVP	15 mg
Avicel PH101	40 mg
Magnesium Stearate	4 mg

EXAMPLE 2

(S)-Ibuprofen lysine/famotidine Tablet

(S)-ibuprofen-(S)-lysine	342 mg
famotidine	20 mg
PVP	15 mg
Avicel PH101	40 mg
Magnesium Stearate	4 mg

EXAMPLE 3

(S)-Ibuprofen lysine/famotidine Tablet

(S)-ibuprofen-(S)-lysine	342 mg
famotidine	15 mg
PVP	15 mg
Avicel PH101	40 mg
Magnesium Stearate	4 mg

EXAMPLE 4

(S)-Ibuprofen lysine/famotidine Tablet

(S)-ibuprofen-(S)-lysine	342 mg
famotidine	10 mg
PVP	15 mg
Avicel PH101	40 mg
Magnesium Stearate	4 mg

EXAMPLE 5

(S)-Ibuprofen lysine/famotidine Tablet

(S)-ibuprofen-(S)-lysine	342 mg
famotidine	5 mg
PVP	15 mg
Avicel PH101	40 mg
Magnesium Stearate	4 mg

EXAMPLE 6

(S)-Ibuprofen lysine/famotidine Sustained Release

(S)-ibuprofen-(S)-lysine	400 mg
famotidine	40 mg
PVP	30 mg
Avicel PH101	80 mg
Magnesium Stearate	8 mg
Methocel E10MCR	66 mg
Methocel K100MLV	200 mg

EXAMPLE 7

(S)-Ibuprofen (S)-lysine/famotidine Sustained Release

(S)-ibuprofen-(S)-lysine	400 mg
famotidine	20 mg
PVP	30 mg
Avicel PH101	80 mg
Magnesium Stearate	8 mg
Methocel E10MCR	66 mg
Methocel K100MLV	200 mg

EXAMPLE 8

(S)-Ibuprofen-(S)-lysine/famotidine Solution

(S)-ibuprofen-(S)-lysine	342 mg
famotidine	10 mg
g.s. syrup	5 ml

EXAMPLE 9

(S)-Ibuprofen-(S)-lysine/famotidine Solution

(S)-ibuprofen-(S)-lysine	342 mg
famotidine	20 mg
g.s. syrup	5 ml

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WHAT IS CLAIMED IS:

1. A pharmaceutical composition for use in the treatment of pain and inflammation and the treatment of gastrointestinal disorders such as indigestion, sour stomach, overindulgence and heartburn in a mammals, including humans comprising:

(i) an analgesically and anti-inflammatory effective amount of a salt of (S)-ibuprofen substantially free of (R)-ibuprofen wherein the salt is selected from (S)-ibuprofen-(S)-lysine and (S)-ibuprofen-(R)-lysine; and

(ii) an amount effective in the relief of gastrointestinal disorders and in inhibition of gastric acid secretion of an H_2 receptor antagonist.

2. The composition of Claim 1 wherein the ibuprofen is present as (S)-ibuprofen-(S)-lysine.

3. The composition of Claim 1 comprising at least 50 mg of (S)-ibuprofen-(S)-lysine.

4. The composition of Claim 1 wherein the H_2 antagonist is selected from: cimetidine, ranitidine, roxatidine, nizatidine or famotidine or a pharmaceutically acceptable salt thereof.

5. The composition of claim 4 wherein the H_2 antagonist is famotidine.

6. The composition of claim 5 comprising between 5 mg to 40 mgs of famotidine.

7. A method of treating pain and inflammation and treating gastrointestinal disorders such as indigestion, sour stomach, overindulgence and heartburn in a mammalian organism in need of such treatment, comprising administering to such organism:

(i) an analgesically and anti-inflammatory effective amount of a salt of (S)-ibuprofen substantially free of (R)-ibuprofen wherein the salt is selected from (S)-ibuprofen-(S)-lysine and (S)-ibuprofen-(R)-lysine; and

(ii) an amount effective in the treatment of gastrointestinal disorders or associated symptoms of at least one of the H2 antagonists.

8. A method according to Claim 7 wherein the composition administered to a mammalian organism in need thereof comprises:

(i) an analgesically and anti-inflammatory effective amount of (S)-ibuprofen-(S)-lysine;

(ii) an amount effective in the inhibition of gastric acid secretion of famotidine.

9. A method of eliciting an onset enhanced and hastened response for the treatment and prevention of pain and inflammation and the treatment of gastrointestinal disorders such as indigestion, sour stomach, symptoms associated with overindulgence and heartburn in a mammalian organism in need of such treatment, comprising administering to such organism:

(i) an analgesically and anti-inflammatory effective amount of a salt of (S)-ibuprofen substantially free of (R)-ibuprofen wherein the salt is selected from (S)-ibuprofen-(S)-lysine and (S)-ibuprofen-(R)-lysine; and

(ii) an amount effective in the treatment of gastrointestinal disorders or associated symptoms of at least one of the H2 antagonists.

10. A method according to claim 9 wherein the composition administered to a mammalian organism in need thereof comprises:

(i) an analgesically and anti-inflammatory effective amount of (S)-ibuprofen-(S)-lysine;

(ii) an amount effective in the inhibition of gastric acid secretion of famotidine.

11. A method of reducing the side effects associated with the administration of an ibuprofen/H_2 antagonist combination which comprises the administration of (i) an analgesically and anti-inflammatory effective amount of a salt of (S)-ibuprofen substantially free of (R)-ibuprofen wherein the salt is selected from (S)-ibuprofen-(S)-lysine and (S)-ibuprofen-(R)-lysine; and at least one of the H_2 antagonists.

12. A method according to Claim 11 wherein the composition administered to a mammalian organism in need thereof comprises:

(i) an analgesically and anti-inflammatory effective amount of (S)-ibuprofen-(S)-lysine;

(ii) an amount effective in the inhibition of gastric acid secretion of famotidine.

13. A method of reducing the size and weight of a pharmaceutically effective amount of an ibuprofen/H_2 antagonist combination dosage form which comprises combining (i) an analgesically and anti-inflammatory effective amount of a salt of (S)-ibuprofen substantially free of (R)-ibuprofen wherein the salt is selected from (S)-ibuprofen-(S)-lysine and (S)-ibuprofen-(R)-lysine; and at least one of the H_2 antagonists.

14. A method according to Claim 13 wherein the composition administered to a mammalian organism in need thereof comprises:

(i) an analgesically and anti-inflammatory effective amount of (S)-ibuprofen-(S)-lysine;

(ii) an amount effective in the inhibition of gastric acid secretion of famotidine.

15. A method of treating gastrointestinal disorders, overindulgence and pain before or during ingestion of a meal accompanied by alcoholic beverages, comprising:
administration of a combination of (i) an analgesically and anti-inflammatory effective amount of a salt of (S)-ibuprofen substantially free of (R)-ibuprofen wherein the salt is selected from (S)-ibuprofen-(S)-lysine and (S)-ibuprofen-(R)-lysine and (ii) famotidine wherein the famotidine does not interact with ethanol from the ingestion of the alcoholic beverage.

16. A method according to Claim 15 wherein the composition administered to a mammalian organism in need thereof comprises:
(i) an analgesically and anti-inflammatory effective amount of (S)-ibuprofen-(S)-lysine;
(ii) an amount effective in the inhibition of gastric acid secretion of famotidine.

17. A method of providing rapid relief of pain and inflammation with (i) an analgesically and anti-inflammatory effective amount of a salt of (S)-ibuprofen substantially free of (R)-ibuprofen wherein the salt is selected from (S)-ibuprofen-(S)-lysine and (S)-ibuprofen-(R)-lysine; and providing long lasting relief of gastrointestinal disorders associated with the secretion of gastric acid with a pharmaceutically effective amount of famotidine.

18. A method according to Claim 17 wherein the composition administered to a mammalian organism in need thereof comprises:
(i) an analgesically and anti-inflammatory effective amount of (S)-ibuprofen-(S)-lysine;
(ii) an amount effective in the inhibition of gastric acid secretion of famotidine.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/08947

A. CLASSIFICATION OF SUBJECT MATTER

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/10; 514/331 370, 400, 471

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,994,604 (Tung et al.) 19 February 1991, see Abstract and column 1, lines 10-25.	1-18
Y	US, A, 5,009,895 (Lui) 23 April 1991, see column 2, lines 20-27.	1-18
Y	GB, A, 2,105,193 (Marriott et al.) 23 March 1983, see page 1, lines 5-27.	1-18
Y	EP, A, 426,479 (Goldman et al.) 08 May 1991, see Abstract.	1-18

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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(57) Abstract

The present invention relates to methods and compositions for treating a gastrointestinal disorder caused or mediated by *Helicobacter pylori* comprising bismuth, a gastropathic amount of a non-steroidal anti-inflammatory drug, and a therapeutically effective amount of each of one or more antimicrobials. The inventions may further comprise therapeutically effective amounts of one or more anti-secretory drugs.

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COMPOSITIONS FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS CONTAINING BISMUTH, AND NSAID AND ONE OR MORE ANTIMICROBIALS

BACKGROUND OF THE INVENTION

Upper abdominal pain and other gastrointestinal disorders are common and chronic problems for a vast number of the population. Of the individuals examined and diagnosed by their physicians, many can be shown to have diseases such as peptic or other ulcers, or non-ulcer dyspepsia. Until the mid 1980s, these conditions were thought to be caused by stress, diet or other environmental factors. Research now indicates that *Helicobacter pylori*, (hereinafter referred to as "*H. pylori*") a bacterium found exclusively in the gastric mucus of humans, plays a major role in the pathogenesis of these diseases and other gastrointestinal disorders.

Various methods and agents have been used to treat and/or eradicate gastrointestinal disorders caused by *H. pylori*. These include the administration of antacids, H_2 antagonists, and antimicrobials such as antibiotics. U.S. Patent No. 5,256,684 to Marshall, issued October 26, 1993 discloses a method for treating an infectious upper gastrointestinal tract disorder resulting from *Campylobacter pyloridis* comprising the administration of bismuth and an antimicrobial. U.S. Patent No. 5,476,669 to Borody, issued December 19, 1995 discloses a method for preventing the recurrence of duodental ucler associated with *Campylobacter pylori* infection comprising the administration of bismuth, metronidazole, and either tetracycline or penicillins.

In addition, speculation on the benefits of other methods for treating *H. pylori* is also available in the art. An example of such is found in Tanaka, S., et al., "Gastroprotective Effect of Ranitidine Bismuth Citrate Is Associated With Increased Mucus Bismuth Concentration In Rats", Gut, 39:164-171 (1996). However, given the prevalence and incidence of infection with *H. pylori*, and the difficulty in treating many patients suffering from such gastrointestinal disorders caused or mediated by *H. pylori*, a continuing need exists for safe and effective treatments against *H. pylori*, preferably which would be effective as mass treatment therapies in large populations of *H. pylori* carriers.

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Compositions and methods have been discovered by the present invention for the treatment of gastrointestinal disorders caused or mediated by *H. pylori* comprising the administration of bismuth salts, (other than salts formed between an H_2 receptor antagonist and a complex of bismuth with a carboxylic acid), a non-steroidal anti-inflammatory drug, and one or more antimicrobials. The present invention also comprises the optional administration of one or more antisecretory agents. It is believed that the administration of bismuth with a non-steroidal anti-inflammatory drug enhances gastric mucus bismuth concentrations. Thus, an object of the present invention is to provide safe and effective compositions and methods of treating gastrointestinal disorders caused or mediated by *H. pylori*.

SUMMARY OF THE INVENTION

The present invention relates to a composition for treating a gastrointestinal disorder caused or mediated by *Helicobacter pylori* comprising from about 50 milligrams to about 5000 milligrams, per day, of bismuth; a gastropathic amount of a non-steroidal anti-inflammatory drug; a therapeutically effective amount of each of one or more antimicrobials; and pharmaceutically acceptable carriers.

The present invention also relates to a method for treatment of a human or lower animal subject having a gastrointestinal disorder caused or mediated by *Helicobacter pylori* comprising administering to the subject from about 50 milligrams to about 5000 milligrams of bismuth, per day, for from about 1 to about 42 days, a gastropathic amount of a non-steroidal anti-inflammatory drug for up to 14 days, and a therapeutically effective amount of each of one or more antimicrobials for from about 1 to about 21 days.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to methods and compositions for treating a gastrointestinal disorder caused or mediated by *Helicobacter pylori* comprising bismuth, a non-steroidal anti-inflammatory drug and one or more antimicrobials. The inventions may optionally comprise therapeutically effective amounts of one or more antisecretory agents. The compositions also comprise pharmaceutically acceptable carreiers. The present invention and the essential and optional components therein are described fully below.

Helicobacter pylori

H. pylori, are spiral bacteria which reside in the stomach. When first identified in the early 1980s, *H. pylori* was referred to by the name *Campylobacter pyloridis*. In recent years, these bacteria have been implicated as a causative factor for gastritis, non-ulcerative dyspepsia, and various ulcers of the gastrointestinal tract. These organisms are described in detail in the following publications, all of which are incorporated herein

by reference in their entireties: Korman, M.G., Tygat, G.N., "*Helicobacter pylori* and Peptic Ulcer", Scandinavian Journal of Gastroenterology, Suppl., 210:92-96 (1995); Marshall, B. J., "*Helicobacter pylori*", American Journal of Gastroenterology, 89(8 Suppl):S116-128 (Aug. 1994); Calam, J., "*Helicobacter pylori*", European Clinical Investigation, 24(8):501-510 (Aug. 1994); NIH Consensus Conference, "*Helicobacter pylori* in Peptic Ulcer Disease. NIH Consensus Development Panel on *Helicobacter pylori* in Peptic Ulcer Disease", JAMA, 272(1):65-69 (July 6, 1994); and Marshall, B. J., Warren, J. R., "Unidentified Curved Bacilli in the Stomach of Patients with Gastritis and Peptic Ulceration", The Lancet, 1311-1315 (1984).

Gastrointestinal Disorder

The term "gastrointestinal disorder", as used herein, encompasses any infection, disease or other disorder of the body, typically of the upper and/or lower gastrointestinal tract, caused or mediated by *H. pylori*. An individual having such a gastrointestinal disorder may be symptomatic or asymptomatic. Such disorders include, for example, *H. pylori* disorders not manifested by the presence of ulcerations in the gastric mucosa, including chronic active or atrophic gastritis, non-ulcer dyspepsia, esophageal reflux disease and gastric motility disorders; and peptic ulcer disease, i.e., *H. pylori*-mediated pre-pyloric, marginal, gastric, duodenal and/or jejunal ulcers.

In the present invention, the presence of a gastrointestinal disorder caused or mediated by *H. pylori* is preferably determined by any of the diagnostic methods recognized and utilized by the medical community. Details concerning such methods are described more fully in the following publications, all of which are incorporated herein by reference in their entireties: Megraud, F., "Diagnosis of *Helicobacter pylori* Infection", Scandinavian Journal of Gastroenterology, Supplement, 214: 44-46, 57-60 (1996); Cutler, A. F., "Testing for *Helicobacter pylori* In Clinical Practice", American Journal of Medicine, 100(5A): 35S-39S, 39S-41S (May 20, 1996); Megraud, F., "Diagnosis of *Helicobacter pylori*", Baillieres Clinical Gastroenterology, 9(3): 507-518 (Sept. 1995); and Feldman, R. A., et al., "Accuracy of Diagnostic Methods Used for Epidemiological Studies of *Helicobacter pylori*", Alimentary Pharmacology and Therapeutics, 9 Suppl. 2:21-31 (1995).

Bismuth

The present invention involves administration of bismuth. As used herein, the quantity of bismuth is by weight of elemental bismuth.

In the present inventions, bismuth may be in the form of a pharmaceutically-acceptable salt, or may be in the form of an organic complex which contains bismuth as an active ingredient. Such organic complexes include 2,2'-spirobi[1,3,2-benzodoxabismole]. Salts formed between an H_2 receptor antagonist and a complex of

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bismuth with a carboxylic acid are not included for use in the present inventions. Preferably, bismuth is administered in the present methods as a pharmaceutically-acceptable salt. Such bismuth salts include bismuth aluminate, bismuth subcarbonate, bismuth subcitrate, bismuth citrate, tripotassium dicitrato bismuthate, bismuth subgallate, bismuth subnitrate, bismuth tartrate, bismuth subsalicylate, and mixtures thereof. Bismuth citrate, bismuth subcitrate, tripotassium dicitrato bismuthate, bismuth tartrate, bismuth subsalicylate, and mixtures thereof are preferred bismuth salts for use in this invention.

The bismuth useful herein may be administered alone, or in combination with other pharmaceutically-acceptable components in a bismuth-containing composition. A variety of such compositions containing bismuth salts are commercially available. Such compositions include DeNol, containing tripotassium dicitrato bismuthate (by Brocades); Bislumina, containing bismuth aluminate (by Mazuelos); Roter, containing bismuth subnitrate (by Roterpharma); Devrom®, containing bismuth subgallate (by The Parthenon Co., Inc.); and Pepto-Bismol®, containing bismuth subsalicylate (by The Procter & Gamble Company).

In general, bismuth may be administered in an amount of from about 50 milligrams to about 5000 milligrams per day, and preferably from about 50 milligrams to about 2500 milligrams, per day, for from about 1 to about 42 days, preferably for up to about 28 days, and most preferably for up to about 14 days.

Non-Steroidal Anti-Inflammatory Drugs

The term "NSAID", as used herein, refers to any agent which has anti-inflammatory, antipyretic and analgesic properties. Examples of NSAIDs are fully described in U.S. Patent 4,985,459 to Sunshine et al., issued January 15, 1991, incorporated by reference herein in its entirety. For detailed disclosure of the chemical structure, synthesis, side effects, etc. of non-steroidal anti-inflammatory agents, references may be had to standard texts, including Anti-Inflammatory and Anti-Rheumatic Drugs, K. D. Rainsford, Vol. I-III, CRC Press, Boca Raton (1985), and Anti-Inflammatory Agents, Chemistry and Pharmacology, 1 R. A. Scherrer, et al., Academic Press, New York (1974), both of which are incorporated by reference herein.

Specific NSAIDs useful in the present invention include, but are not limited to: the oxicams, such as piroxicam, isoxicam, tenoxicam, sudoxicam, and CP-14,304; the salicylates, such as acetylsalicylic acid, disalcid, benorylate, trilisate, safapryn, solprin, diflunisal, and fendosal; the acetic acid derivatives, such as diclofenac, fenclofenac, indomethacin, sulindac, tolmetin, isoxepac, furofenac, tiopinac, zidometacin, acematacin, fentiazac, zomepirac, clidanac, oxepinac, and felbinac; the fenamates, such as mefenamic, meclofenamic, flufenamic, niflumic, and tolfenamic acids; the propionic

acid derivatives, such as ibuprofen, naproxen, benoxaprofen, flurbiprofen, ketoprofen, fenoprofen, fenbufen, indoprofen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, and tiaprofenic; and the pyrazoles, such as phenybutazone, oxyphenbutazone, feprazone, azapropazone, and trimethazone. Mixtures of these NSAIDs may also be employed, as well as the pharmaceutically-acceptable salts and esters of these agents.

Another class of NSAIDs are disclosed in U.S. Patent No. 4,708,966, Loomans, et al., issued November 24, 1987. This patent discloses a class of non-steroidal anti-inflammatory compounds which comprise specifically substituted phenyl compounds, especially substituted 2.6-di-tert-butyl phenol derivatives. For example, compounds selected from 4-(4'-pentyn-3'-one)-2,6-di-t-butylphenol; 4-(5'-hexynoyl)-2,6-di-t-butylphenol; 4-((S)-(-)-3'-methyl-5'-hexynoyl)-2,6-di-t-butyl-phenol; 4-((R)-(+)-3'-methyl-5'-hexynoyl)-2,6-di-t-butylphenol; and 4-(3',3'-dimethoxypropionyl)-2,6-di-t-butylphenol are useful in the present invention.

Examples of preferred NSAIDs useful in the present invention include, but are not limited to: acetylsalicylic acid, ibuprofen, fenbuprofen, fenoprofen, flurbiprofen, indomethacin, ketoprofen, naproxen, their pharmaceutically-acceptable salts, enantiomers thereof, and mixtures thereof. Ibuprofen, indomethacin, acetylsalicylic acid, and naproxen are especially preferred for use in the present invention.

NSAIDs are administered in a gastropathic amount. The term "gastropathic amount", as used herein, refers to a level and frequency of administration of NSAID which is sufficient to produce gastropathy, e.g. mucosal damage as judged by fiberoptic endoscopy, in normal subjects after a one week course of therapy. Such an amount will vary depending on the particular NSAID being administered, the size and/or condition of the subject receiving treatment and/or other medical factors determined by the administering physician. The gastropathic amounts for specific NSAIDs are known in the art. For example, acetylsalicylic acid administered at a levels of about 2.4 to 3.9 grams per day for one week will consistently produce mucosal injury without causing complications. Gastropathic amounts for other NSAIDs are levels which produce comparable gastropathy to the gastropathy produced by the acetylsalicylic acid levels disclosed herein.

The following publications provide greater detail on gastropathy and NSAIDs, and are incorporated herein by reference in their entireties: Heigh, R. I., "Use of NSAIDs. An Assault on the Upper Gastrointestinal Tract", Postgraduate Medicine, 96(6):63-68 (Nov. 1, 1996); Levi, S., et al., "Non-Steroidal Anti-Inflammatory Drugs: How Do They Damage the Gut?", British Journal of Rheumatology, 33(7):605-612

(July 1994); and Bower, P. R., "Non-Steroidal Anti-Inflammatory Drugs", British Journal of Rheumatology, 32 Suppl. 4:35-38 (June 1993).

In the present invention, the duration of NSAID administration is for up to about 14 days, and preferably for from 1 about to about 10 days. The duration of administration should be less than that associated with the development of complications. Therefore, the most preferred duration of administration of the NSAID is from about 1 to about 7 days. In addition to the publications mentioned in the preceding paragraph, complications associated with NSAID usage are discussed in Fenn, G. C., "Review Article: Controversies in NSAID-induced Gastroduodenal Damage--Do They Matter?", Alimentary Pharmacology and Therapeutics, 8(1):15-26 (Feb. 1994), incorporated herein by reference in its entirety.

Antimicrobial

The present inventions also include administration of a theraputically effective amount of each of one or more antimicrobials, per day. As used herein, the term "antimicrobial" refers to one or more antimicrobial agents, other than and in addition to bismuth, which are effective against *H. pylori*. The term "therapeutically effective amount", as used herein, refers to a level which is commonly known in the art and recognized and utilized by the medical community.

Typically, according to the present invention, each of the one or more antimicrobials is administered at a level of from about 100 milligrams to about 10,000 milligrams, per day, for from about 1 to about 28 days. Preferably, each of the one or more antimicrobials is administered at a level of from about 100 milligrams to about 8000 milligrams per day, and more preferably at from about 100 milligrams to about 5000 milligrams per day. It is also preferred that each of the antimicrobials is administered for from about 1 to about 21 days, more preferably for from about 1 to about 14 days, and most preferably for from about 7 to about 10 days.

The specific dosage of antimicrobial(s) to be administered, as well as the duration of antimicrobial(s) treatment, are mutually dependent, and will also depend upon such factors as the specific antimicrobial used, the number of antimicrobials used in the treatment, the resistance pattern of the infecting organism to the antimicrobial used, the ability of the antimicrobial to reach minimum inhibitory concentrations at the site of the infection, the nature and extent of other infections (if any), the personal attributes of the subject, compliance with the treatment regimen, and the presence and severity of any side effects of the treatment. Therefore, in the case of prevention or treatment with more than one antimicrobial, the duration of administration should depend on the type of antimicrobial rather than the administration of the antimicrobials for the same number of days.

A wide variety of antimicrobials are useful in this invention. As used herein, the term "antimicrobial" refers to any naturally-occurring, synthetic or semi-synthetic compound or composition or mixture thereof, which is safe for human use as used in the methods of this invention, and is effective in killing or substantially inhibiting *H. pylori* when used according to the present inventions. Antibiotics are preferred for use herein.

Antibiotics can be generally classified by chemical composition, into the following principal groups: the aminoglycosides, such as gentamicin, neomycin, kanamycin, and streptomycin; the macrolides, such as erythromycin, clindamycin, and rifampin; the penicillins, such as penicillin G, penicillin V, ampicillin and amoxycillin; the polypeptides such as bacitracin and polymyxin; the tetracyclines such as tetracycline, chlortetracycline, oxytetracycline and doxycycline; the cephalosporins such as cephalexin and cephalothin; quinolones such as ciprofloxacin, norfloxacin and ofloxacin; and such miscellaneous antibiotics as chloramphenicol and clindamycin. These antibiotics can generally be said to function in one of four ways: inhibition of cell wall synthesis, alteration of cell wall permeability, inhibition of protein synthesis or inhibition of nucleic acid synthesis.

Other antimicrobials useful herein include the sulfonamides; nitrofurans, such nitrofurazon, nitrofurantoin, and furozolidone; metronidazole, tinidazole, and nimorazole. Antimicrobials among those useful herein are described in Remington's Pharmaceutical Sciences, 18th Edition, pp. 1173-1232 (1990), which is incorporated herein by reference.

While any of these antimicrobials may be used, penicillin, erythromycin, metronidazole, doxycycline, tinidazole, amoxycillin, ampicillin, tetracycline, nitrofurantoin, and mixtures thereof are among the preferred antimicrobials for use in the present invention.

As stated above, the specific preferred quantity of antimicrobial and duration of treatment used in the methods of this invention will, in addition to other factors, depend upon the particular antimicrobial used and its pharmacology. In general, though, the tetracyclines are preferably administered at a level of from about 100 milligrams to about 2,000 milligrams per day. Macrolides (such as erythromycin) are preferably administered at a level of from about 1,000 milligrams to about 4,000 milligrams per day. Penicillins are preferably administered at a level of from about 500 milligrams to about 3,000 milligrams per day. The aminoglycosides (such as neomycin) are preferably administered at a level of from about 100 milligrams to about 8,000 milligrams per day. Nitrofurans (such as nitrofurantoin) are administered preferably at levels of from about 100 milligrams to about 800 milligrams per day. Preferably,

metronidazole is administered at a level of from about 500 to about 2,000 milligrams per day.

The specific method of administering the antimicrobial, according to the processes of this invention, may depend upon such factors as the particular antimicrobial(s) used, the site of infection, the amount of antimicrobial(s) to be administered per day, the presence of any adverse side effects, and the interactions (if any) between the antimicrobial(s) and the bismuth. Thus, the antimicrobial(s) may be administered under the process of this invention by single daily doses, or by administration in two, three, four, or more doses per day.

Antisecretory Agents

The present invention can optionally include one or more antisecretory agents. The term "antisecretory agent", as used herein, refers to agents selected from the group consisting of H_2 receptor antagonists, proton pump inhibitors, and mixtures thereof. These agents are administered in a therapeutically effective amount. The term "therapeutically effective amount", as used herein, refers to a level which is commonly known in the art and recognized and utilized by the medical community. Such an amount will vary depending on the particular agent(s) administered, the size and/or condition of the individual receiving treatment or other medical factors determined by the administering physician.

H_2 receptor antagonists are disclosed fully in U.S. Patent No. 5,294,433 to Singer et al., issued March 15, 1994, incorporated herein by reference in its entirety. Preferred H_2 receptor antagonists include cimetidine, etintidine, ranitidine, ICIA-5165, tiotidine, ORF-17578, luptidine, donetidine, famotidine, rozatidine, pifatidine, lamtidine, BL-6548, BMY-25271, zaltidine, nizatidine, mifentidine, BMY-52368,SKF-94482, BL-6341A, ICI-162846, ramixotidine, Wy-45727, SR-58042, BMY-25405, loxidine, DA-4634, bisfentidine, sufotidine, ebrotidine, HE-30-256,D-16637, FRG-8813, FRG-8701, impromidine, L-643728, HB-4-08, and mixtures thereof..

Preferred for use in the present invention are cimetidine, ranitidine, famotidine, roxatidine, nizatidine, mifentidine, and mixtures thereof. Most preferred are cimetidine and ranitidine.

Proton pump inhibitors are described in greater detail in the following publications, which are incorporated by reference herein in their entireties: U.S. Patent No. 4,786,505 to Lovgren, issued November 22, 1988; U. S. Patent No. 4,255,431 to Junggren, issued March 10, 1981; and U.S. Patent No. 4,853,230 to Lovgren, issued August 1, 1989. Preferred for use in the present invention are omeprazole, lansoprazole, pantoprazole, and mixtures thereof. Most preferred is omeprazole.

Antisecretory agents may be administered for from about 1 to about 42 days, preferably for up to about 28 days, and most preferably for up to about 14 days.

Pharmaceutically Acceptable Carriers

The compositions of the present invention may contain optional components which affect the physical and therapeutic characteristics of the present compositions. In particular, a variety of pharmaceutically-acceptable carriers and excipients may be included, depending upon the particular dosage form to be used. Various oral dosage forms can be used, including such solid forms as tablets, capsules, granules and bulk powders. Tablets can be compressed, tablet triturates, enteric-coated, sugar coated, film-coated or multiple compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents and melting agents. Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions, and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, melting agents, coloring, and flavoring agents.

Specific examples of pharmaceutically-acceptable carriers and excipients that may be used to formulate oral dosage forms of the present invention are described in U. S. Patent 3,903,297, Robert, issued September 2, 1975, incorporated by reference herein. Techniques and compositions for making dosage forms useful herein are described in the following references, all incorporated by reference herein: 7 Modern Pharmaceutics, Chapters 9 and 10 (Banker and Rhodes, editors, 1979); an Lieberman, et al., Pharmaceutical Dosage Forms: *Tablets* (1981); and Ansel, Introduction to Pharmaceutical Dosage Forms (2d edition, 1976).

The compositions of this invention may be used according to the methods of this invention by administering the composition from 1 to 4 times per day, and preferably from 1 to 2 times per day; for from 1 to 28 days, preferably for from about 1 to about 21 days, and most preferably for from about 1 to about 14 days. The specific frequency of administration will depend upon such factors as the specific NSAID, bismuth compound or composition and antimicrobial(s) used, the levels at which the components are incorporated in the composition, the nature and severity of the condition to be treated, and the nature of any concurrent therapy, if any.

Method of Use

The methods of the present invention comprise the treatment of a human or lower animal subject having a gastrointestinal disorder caused or mediated by *Helicobacter pylori* comprising administering to the subject bismuth, a non-steroidal

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anti-inflammatory drug, and one or more antimicrobials. The present method may further comprise the administration of one or more antisecretory agents.

As used herein, the term "administering" refers to any method which, in sound medical practice delivers the compounds or compositions used in this invention to the subject to be treated in such a manner so as to be effective in the treatment of the gastrointestinal disorder. Preferably, the bismuth, NSAID, antimicrobial(s) and antisecretory agent(s), if present, are administered orally.

The present invention encompasses methods wherein the administering of bismuth, the NSAID, the antimicrobial(s) and optionally the antisecretory agent(s) are performed simultaneously (beginning and ending on the same day), concurrently (overlapping but not of the same duration of administration), or consecutively (sequential, but where the course of treatment is substantially continuous). Preferably, the bismuth, NSAID and antimicrobial are administered concurrently and administration for bismuth, the NSAID and the antimicrobial is commenced on the same day. Additionally, if one or more antisecretory agents are also present, it is preferred that the bismuth and the antisecretory agent(s) are administered simultaneously.

The following non-limiting examples illustrate the composition and methods of use of the present invention.

EXAMPLE I

An asymptomatic young volunteer identified as having *H. pylori* infection through the results of a mass screening, is treated by a method of the present invention. The subject is orally administered approximately 2500 milligrams of bismuth in the form of bismuth subcitrate ("DeNol", sold by Brocades) in four equal doses, for 28 days; approximately 100-200 milligrams of indomethacin daily, in four equal doses, for about 14 days; and approximately 1 gram of erythromycin daily, in two equal doses, for about 14 days. One to two months later, a diagnostic test performed on the volunteer shows no evidence of *H. pylori*.

In the above example, tripotassium dicitrato bismuthate, bismuth tartrate, bismuth citrate, and bismuth subnitrate are substituted, respectively, for bismuth subsalicylate, with substantially similar results.

EXAMPLE II

A human subject is suffering from chronic active gastritis. A diagnostic test reveals the presence of *H. pylori*. The individual is treated by orally administering approximately 2100 milligrams of bismuth daily, in the form of bismuth subsalicylate, ("Pepto-Bismol®", sold by The Procter & Gamble Company), in four equal doses, for about 14 days; approximately 3.9 grams of acetylsalicylic acid daily, in three equal doses, for about 14 days; approximately 20 milligrams of omeprazole daily, for 14 days;

approximately 1000 milligrams of metronidazole daily, in four equal doses, for 14 days; and approximately 2000 milligrams of tetracycline daily in four equal doses, for 14 days. Administration of all agents are commenced on the same day. One to two months later, the diagnostic test is repeated. The results show no evidence of *H. pylori*.

EXAMPLE III

A human subject is suffering from non-ulcer dyspepsia. A biopsy of the gastric mucosa is taken from the stomach of the subject. Analysis of the biopsy sample indicates the presence of urease in the sample and the presence of *H. pylori* in the stomach of the subject. The subject is given approximately 1200 milligrams of bismuth daily, (administered as bismuth subsalicylate in the composition Pepto-Bismol®, sold by The Procter & Gamble Company), in four equal doses, for about 21 days; 1200-3200 milligrams of ibuprofen daily, in three to four equal doses, for about 7 days; 150 milligrams of ranitidine daily, in two equal doses, for about 21 days; and 500 milligrams of metronidazole daily, in four equal doses, for about 14 days. Administration of all agents are commenced on the same day. A biopsy sample taken and analyzed one to two months later shows no evidence of *H. pylori*.

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WHAT IS CLAIMED IS:

1. A composition for treating a gastrointestinal disorder caused or mediated by *Helicobacter pylori* comprising:
   a) from 50 milligrams to 5000 milligrams, per day, of bismuth;
   b) a gastropathic amount of a non-steroidal anti-inflammatory drug;
   c) a therapeutically effective amount of each of one or more antimicrobials; and
   d) pharmaceutically acceptable carriers.

2. The composition of Claim 1 further comprising a therapeutically effective amount of one or more antisecretory agents selected from the group consisting of H_2 receptor antagonists, proton pump inhibitors and mixtures thereof.

3. The composition of Claim 1 or 2 wherein the antisecretory agents are selected from the group consisting of cimetidine, ranitidine, famotidine, roxatidine, nizatidine, mifentidine, omeprazole, lansoprazole, pantoprazole, and mixtures thereof.

4 The composition of any of Claims 1-3 wherein the bismuth is selected from the group consisting of bismuth aluminate, bismuth subcarbonate, bismuth subcitrate, bismuth citrate, tripotassium dicitrato bismuthate, bismuth subgallate, bismuth subsalicylate, bismuth tartrate, and mixtures thereof and is administered at a level of from 50 milligrams to 2500 milligrams, per day for up to 28 days.

5. The composition of any of Claims 1-4 wherein the non-steroidal anti-inflammatory drug is selected from the group consisting of ibuprofen, indomethacin, acetylsalicylic acid, and naproxen and wherein it is administered for up to 14 days, the one or more antimicrobials are administered for 1 to 21 days, and the one or more antisecretory agents are administered for up to 28 days.

6. The composition of any of Claims 1-5 wherein the one or more antimicrobials are selected from the group consisting of penicillin, erythromycin, metronidazole, doxycycline, tinidazole, amoxycillin, ampicillin, tetracycline, nitrofurantoin, and mixtures thereof.

7. The use of the compositions of any of Claims 1-6 for the manufacture of a composition for treatment of a human or lower animal subject having a gastrointestinal disorder caused or mediated by *Helicobacter pylori* comprising administering to the subject from 50 milligrams to 5000 milligrams of bismuth, per day, for from 1 to 42 days; a gastropathic amount of a non-steroidal anti-inflammatory drugs for up to 14 days; and a therapeutically effective amount of each of one or more antimicrobials for from 1 to 21 days.

8. The use of the compositions of any of Claims 1-7 for the manufacture of a composition comprising a therapeutically effective amount of one or more antisecretory agents which are selected from the group consisting of H_2 receptor antagonists, proton pump inhibitors and mixtures thereof.

9. The use of the compositions of any of Claims 1-8 for the manufacture of a composition wherein the antisecretory agents are selected from the group consisting of cimetidine, ranitidine, famotidine, roxatidine, nizatidine, mifentidine, omeprazole, lansoprazole, pantoprazole, and mixtures thereof and wherein the antisecretory agents are administered for up to 28 days and the one or more antimicrobials are administered for 1 to 14 days.

10. The use of the compositions of any of Claims 1-9 for the manufacture of a composition wherein the bismuth is selected from the group consisting of bismuth aluminate, bismuth subcarbonate, bismuth subcitrate, bismuth citrate, tripotassium dicitrato bismuthate, bismuth subgallate, bismuth subsalicylate, bismuth tartrate, and mixtures thereof and wherein the bismuth is administered at a level of from 50 milligrams to 2500 milligrams, per day for up to 28 days.

11. The use of the compositions of any of Claims 1-10 for the manufacture of a composition wherein the non-steroidal anti-inflammatory drug is selected from the group consisting of ibuprofen, indomethacin, acetylsalicylic acid, and naproxen and wherein the one or more antimicrobials are selected from the group consisting of penicillin, erythromycin, metronidazole, doxycycline, tinidazole, amoxycillin, ampicillin, tetracycline, nitrofurantoin, and mixtures thereof.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	GB 2 262 036 A (GLAXO GROUP LTD) 9 June 1993 see abstract	1-11
A	EP 0 437 294 A (GIST BROCADES NV) 17 July 1991 see page 3, line 18-24	1-11
A	TANAKA S ET AL: "Indomethacin increases mucus bismuth concentration in ranitidine bismuth citrate treated rats" GASTROENTEROLOGY, 108 (4 SUPPL.). 1995. A234., XP002059838 see the whole document	1-11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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Information on patent family members

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(54) Title: OMEPRAZOLE SODIUM SALT

(57) Abstract

This invention relates to a novel form of the sodium salt of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]sulfinyl]-1H-benzimidazole, known under the generic name of omeprazole sodium salt. This invention also relates to processes for its preparation of omeprazole sodium form B which is thermodynamically stable, as well as pharmaceutical compositions containing it and its use in the treatment of gastrointestinal disorders.

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OMEPRAZOLE SODIUM SALT

Field of the invention

This invention relates to a novel form of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, known under the generic name omeprazole. More specifically, it relates to a novel form of the sodium salt of omeprazole, namely a well-defined omeprazole sodium monohydrate salt, hereinafter referred to as omeprazole sodium form B, and its use in the treatment of gastrointestinal disorders, pharmaceutical compositions containing it and preparation thereof.

Background of the invention and prior art

The compound 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole having the generic name omeprazole, as well as therapeutically acceptable salts thereof, are described in EP 5129. The specific alkaline salts of omeprazole, such as the sodium salt, are disclosed in EP 124 495. The omeprazole sodium salt produced according to examples 1 and 2 of EP 124 495 is a mixture of crystal forms and amorphous material. One of the crystal forms present in this mixture, hereinafter referred to as omeprazole sodium form A, is a hydrate with one to two water molecules, of which one water molecule is strongly bound in the crystal structure while the other is easily removed by drying. The resulting dried substance containing one strongly bound water molecule is very hygroscopic and absorbs water rapidly under normal conditions.

Omeprazole is a proton pump inhibitor, *i.e.* effective in inhibiting gastric acid secretion, and is useful as an antiulcer agent. In a more general sense, omeprazole may be used for treatment of gastric-acid related diseases in mammals and especially in man.

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Brief description of the drawings

Figure 1 is an X-ray powder diffractogram of omeprazole sodium form B.

Figure 2 is an X-ray powder diffractogram of omeprazole sodium form A.

Figure 3 is an X-ray powder diffractogram of omeprazole sodium prepared according to prior art.

Description of the invention

It has surprisingly been found that the sodium salt of omeprazole exists in a number of different crystal forms. It is an object of the present invention to provide a well-defined, thermodynamically stable at ambient temperature, and industrially useful form of omeprazole sodium, namely omeprazole sodium form B. Another object of the present invention is to provide a process for the preparation of omeprazole sodium form B, substantially free from other forms of the sodium salt of omeprazole. X-ray powder diffraction (XRPD) is used as a method of differentiating omeprazole sodium form B from other forms of the sodium salt of omeprazole.

It has been found that the sodium salt of omeprazole may crystallize in at least two different crystal forms, of which omeprazole sodium form B is one. One other form is omeprazole sodium form A with one to two moles of water. Omeprazole sodium form A is one of the crystal forms present in the mixture of crystal forms and amorphous material obtained in example 1 and example 2 in EP 124 495. However, there is no omeprazole sodium form B present in the mixture of forms obtained when preparing omeprazole sodium salt as described in either example 1 or example 2 in EP 124 495.

Omeprazole sodium form B is a crystalline form exhibiting advantageous properties, such as being well-defined, stable, and being a true monohydrate crystal form. Omeprazole sodium form B is thermodynamically more stable than omeprazole sodium form A. Omeprazole sodium form B is essentially non-hygroscopic and can therefore in industrial

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processes, such as pharmaceutical manufacturing processes, be charged in a fixed amount in contrast to omeprazole sodium form A which must be charged in amounts calculated from a recent assay of omeprazole or indirectly from a recent assay of its water content. Other advantages include easier preparation and higher reproducibility between batches. This is especially important in production scale and leads to a higher production capacity.

Omeprazole sodium form A, which is thermodynamically unstable, can under certain storing conditions be completely or partly converted to omeprazole sodium form B. Omeprazole sodium form B is thereby characterized in being thermodynamically more stable than omeprazole sodium form A and any other form of omeprazole sodium prepared according to prior art. Omeprazole sodium form B is further characterized as being essentially non-hygroscopic.

With the expression "any other form" is meant anhydrates, hydrates, solvates and amorphous materials, including polymorphs disclosed in the prior art. Examples of any other forms of sodium salts of omeprazole includes, but are not limited to, anhydrates, monohydrates, dihydrates, sesquihydrates, trihydrates, alcoholates and polymorphs or amorphous forms thereof.

Omeprazole sodium form B is characterized by the positions and intensities of the peaks in the X-ray powder diffractogram, as well as by the unit cell parameters which have been calculated from the peak positions. The corresponding data for omeprazole sodium form A are totally different, whereas form B is easily distinguishable from form A.

Omeprazole sodium form B according to the present invention is characterized in providing an X-ray powder diffraction pattern exhibiting substantially the following d-values;

d-value/Å	relative intensity	d-value/Å	relative intensity
9.8	vs	3.37	w
7.8	vw	3.25	vw
6.7	s	3.17	vw
6.5	s	3.14	w
6.2	vw	3.12	m
5.9	m	3.05	w
5.8	vw	2.99	w
5.4	w	2.98	m
5.1	w	2.91	m
4.6	m	2.89	m
4.5	m	2.79	vw
4.3	s	2.62	vw
4.1	m	2.59	vw
3.96	m	2.50	vw
3.92	m	2.45	vw
3.71	s	2.40	vw
3.60	w	2.37	vw
3.43	vw	2.28	vw

Omeprazole sodium form B according to the present invention is characterized by having a monoclinic unit cell with parameters

a = 15.09 Å, b = 12.83 Å, c = 9.82 Å, $\beta = 94.4°$.

According to the invention there is further provided a process for the preparation of omeprazole sodium form B as well as a process for the preparation of omeprazole sodium form A.

Omeprazole sodium form B can also be characterized by FT-IR.

Omeprazole sodium form B is prepared by treating omeprazole with an aqueous base, $Na^+ B^-$, wherein Na denotes sodium and B denotes hydroxide or alkoxide, in an appropriate solvent, such as isopropanol optionally containing some water, at ambient temperature. Once the mixing has taken place the total mixture may be agitated, for example stirred, for a further period of time, *e.g.* about 0-2 hours, at ambient temperature. The crude mixture may optionally be filtered at this stage. Seeds of omeprazole sodium form B may be added to the crystallization solution in order to induce the crystallization. The slurry is thereafter further agitated for a time period of about 10-24 h to ensure as complete crystallization as possible. It is also possible to cool the mixture in order to complete the crystallization and thereby improving the yield. The omeprazole sodium form B is thereafter separated, for example by filtration or centrifugation, followed by washing with an appropriate solvent, preferably the same solvent as used above, and thereafter dried to constant weight.

Omeprazole sodium form B may also be prepared by recrystallizing the sodium salt of omeprazole of any form, or mixtures thereof, in an appropriate solvent such as ethanol or isopropanol, optionally containing some water.

The omeprazole sodium form B obtained according to the present invention is substantially free from other forms of sodium salts of omeprazole, such as omeprazole sodium form A.

The compound of the invention, *i.e.* omeprazole sodium form B, prepared according to the present invention is analyzed, characterized and differentiated from omeprazole sodium form A by X-ray powder diffraction, a technique which is known per se. Another suitable

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technique to analyze, characterize and differentiate omeprazole sodium form B from omeprazole sodium form A is by conventional FT-IR.

The amount of water in omeprazole sodium form B and omeprazole sodium form A is determined by thermogravimetric analysis, a technique which is known per se. The water content can also be determined by Karl Fischer.

Omeprazole sodium form B is effective as a gastric acid secretion inhibitor, and is useful as an antiulcer agent. In a more general sense, it can be used for treatment of gastric-acid related conditions in mammals and especially in man, including *e.g.* reflux esophagitis, gastritis, duodenitis, gastric ulcer and duodenal ulcer. Furthermore, it may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable *e.g.* in patients on NSAID therapy, in patients with Non Ulcer Dyspepsia, in patients with symptomatic gastro-esophageal reflux disease, and in patients with gastrinomas. The compound of the invention may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre- and postoperatively to prevent aspiration of gastric acid and to treat stress ulceration. Further, the compound of the invention may be useful in the treatment of psoriasis as well as in the treatment of *Helicobacter* infections and diseases related to these. The compound of the invention may also be used for treatment of inflammatory conditions in mammals, including man.

Any suitable route of administration may be employed for providing the patient with an effective dosage of omeprazole sodium form B according to the invention. For example, peroral or parenteral formulations and the like may be employed. Dosage forms include capsules, tablets, dispersions, solutions, suspensions and the like. Omeprazole sodium form B is, because of it being highly soluble in water, especially suitable for parenteral formulations, such as for intravenous administration.

According to the invention there is further provided a pharmaceutical composition comprising omeprazole sodium form B, as active ingredient, in association with a

pharmaceutically acceptable carrier, diluent or excipient and optionally other therapeutic ingredients. Compositions comprising other therapeutic ingredients are especially of interest in the treatment of *Helicobacter* infections. The invention also provides the use of omeprazole sodium form B in the manufacture of a medicament for use in the treatment of a gastric-acid related condition and a method of treating a gastric-acid related condition which method comprises administering to a subject suffering from said condition a therapeutically effective amount of omeprazole sodium form B.

The compositions of the invention include compositions suitable for peroral or parenteral administration. The compositions may be conveniently presented in unit dosage forms, and prepared by any methods known in the art of pharmacy.

Combination therapies comprising omeprazole sodium form B and other active ingredients in separate dosage forms may also be used. Examples of such active ingredients include anti-bacterial compounds, non-steroidal anti-inflammatory agents, antacid agents, alginates and prokinetic agents.

In the practice of the invention, the most suitable route of administration as well as the magnitude of a therapeutic dose of omeprazole sodium form B in any given case will depend on the nature and severity of the disease to be treated. The dose, and dose frequency, may also vary according to the age, body weight, and response of the individual patient. Special requirements may be needed for patients having Zollinger-Ellison syndrome, such as a need for higher doses than the average patient. Children and patients with liver diseases as well as patients under long term treatment will generally benefit from doses that are somewhat lower than the average. Thus, in some conditions it may be necessary to use doses outside the ranges stated below. Such higher and lower doses are within the scope of the present invention.

In general, a suitable dose range for parental administration is from 10 mg to 300 mg, and preferably from 20 mg to 80 mg.

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A suitable oral dosage form may cover a dose range from 5 mg to 300 mg total daily dose, administered in one single dose or equally divided doses. A preferred dosage range is from 10 mg to 80 mg.

The compound of the invention may be combined as the active component in intimate admixture with a pharmaceutical carrier according to conventional techniques, such as the oral formulations described in WO 96/01623 and EP 247 983, the disclosures of which are hereby incorporated as a whole by reference.

The examples which follow will further illustrate the preparation of the compound of the invention, i.e. omeprazole sodium form B, but are not intended to limit the scope of the invention as defined hereinabove or as claimed below.

Examples

Example 1

Preparation of omeprazole sodium form B from omeprazole

120 gram of omeprazole, 480 ml of isopropanol and 13.2 gram of NaOH(s) dissolved in 26.7 gram of water, was added to a 3-necked glass vessel. The slurry was stirred for an additional 40 minutes at ambient room temperature. The obtained solution was filtered through a clarifying filter and the filter was washed with 20 ml of isopropanol. The isopropanol wash was combined with the previous isopropanol solution containing the product. The solution was seeded with 6 gram of omeprazole sodium form B in 25 ml of isopropanol. The slurry was stirred for an additional 25 hours and the product was filtered and dried at 40°C.

Yield 84.5 %.

Example 2

Preparation of omeprazole sodium form B from omeprazole sodium form A

30 gram of omeprazole sodium form A, prepared according to example 3 below, and 25 ml of ethanol was added to a 3-necked glass vessel. The slurry was seeded with omeprazole sodium form B and then stirred for an additional 24 hours at room temperature. The product was then filtered and dried at 50°C.
Yield: 80%

Example 3

Preparation of omeprazole sodium form A from omeprazole

14.8 kg sodium hydroxide was dissolved in 42 l water in a separate vessel.

120 kg omeprazole was added to 927 l isopropanol in a 4000 l glass lined reactor. The aqueous sodium hydroxide was charged to the slurry. Omeprazole was dissolved and the clear solution was filtered in a closed pressure filter to a 1200 l glass lined reactor. The solution was heated and 228 l methanol was charged at 50 °C to initiate the crystallization. The batch was seeded with a slurry of 1.2 kg omeprazole sodium methanol wet in isopropanol. The solution was cooled from 51 °C to - 8 °C. The formed slurry was kept at - 8 to - 9 °C for 4 hours with moderate stirring. Centrifuged substance was flushed with a cool mixture of isopropanol and methanol, 76 l and 20 l respectively, and then dried in a rotary dryer at approximately 35 mbar with a jacket temperature of 65 °C. Dried substance was de-lumped in a mill.

Yield: 126.0 kg omeprazole sodium methanol wet.

A sample of the omeprazole sodium methanol wet (32.3 kg) was charged into a rotary dryer. An equilibration process with steam in order to remove methanol was performed at 39 - 87 mbar and with a jacket temperature of 50 °C. The equilibration process took 3 days. Equilibrated substance was de-lumped in a mill.

Yield: 25.7 kg

Example 4

Characterization of omeprazole sodium form B and omeprazole sodium form A using X-ray powder diffraction (XRPD)

X-ray powder diffraction analysis was performed according to standard methods which can be found in *e.g.* Bunn, C. W. (1948), Chemical Crystallography, Clarendon Press, London; or Klug, H.P. & Alexander, L. E. (1974), X-Ray Diffraction Procedures, John Wiley and Sons, New York. The unit cell parameters for form A and B have been calculated from the X-ray powder diffractograms using the program "TREOR" by Werner,P.-E., Eriksson,L. And Westdahl,M., J. Appl. Crystallogr. 18 (1985) 367 - 370. The fact that the positions of all peaks in the diffractograms for form A and form B may be calculated using the respective unit cell parameters, proves that the unit cells are correct and that the diffractograms are indicative of the pure forms. The diffractogram of omeprazole sodium form B, prepared according to Example 1 in the present application, is shown in Figure 1 and the diffractogram of omeprazole sodium form A, prepared according to Example 3, is shown in Figure 2.

The peaks, identified with d-values calculated from the Bragg formula and intensities, have been extracted from the diffractograms for form A, form B and from the diffractogram obtained from material produced according to prior art, and are given in Table 1. In this table the unit cell parameters for forms A and B are also given. The relative intensities are less reliable and instead of numerical values the following definitions are used;

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% Relative Intensity	Definition
25-100	vs (very strong)
10-25	s (strong)
3-10	m (medium)
1-3	w (weak)
<1	vw (very weak)

Some additional very weak peaks found in the diffractograms have been omitted from table 1.

Reference Example A

Preparation of omeprazole sodium according to prior art in accordance with the method described in Example 2 in EP 124 495

Omeprazole (1300 g; 3.77 mol) was added under vigorous mechanical stirring to a mixture of tetrahydrofurane (13 L) and 50% aqueous NaOH (296 g, 3.7 mol) and stirring was continued for 45 min. Trichloroethylene (5.7 L) was added and stirring was continued over night at room temperature. The mixture was cooled to +5°C and then stirred for 3 h. The precipitate was filtered off and the filter cake was washed with trichloroethylene (5 L) and dried under reduced pressure at 50°C giving omeprazole sodium salt (1314 g, 95%), m.p. 208-210 °C.

The product was analyzed using X-ray powder diffraction and gave the diffractogram depicted in Figure 3 and given above in Table 1. Some additional very weak peaks found in the diffractograms have been omitted from Table 1.

Table 1. X-ray powder diffraction data for omeprazole sodium form A, form B and according to prior art. Only peaks below 2θ = 40° have been included.
All peaks noted for form A and form B can be indexed with the unit cells given below.

Unit cell form A: a = 15.757 (3) Å b= 8.126 (1) Å c= 15.671 (6) Å β= 94.21 (2) °

Unit cell form B: a= 15.086 (6) Å b= 12.835 (4) Å c= 9.815 (3) Å β= 94.41 (3)°

Omeprazole sodium form A		Omeprazole sodium form B		Omeprazole sodium according to prior art	
d-value/Å	Relative intensity	d-value/Å	relative intensity	d-value/Å	Relative intensity
				17.8	vw
15.6	vs	9.8	vs	15.5	vs
				13.9	vw
				10.2	vw
				8.9	m
7.9	m	7.8	vw	8.0	m
7.2	m	6.7	s	7.2	m
				6.9	w
6.8	w	6.5	s	6.8	w
6.6	vw	6.2	vw		
6.5	w	5.90	m	6.5	vw
				6.4	vw
				6.2	vw
				5.91	vw
				5.83	w
				5.52	vw

Table 1, continued

Omeprazole sodium form A		Omeprazole sodium form B		Omeprazole sodium according to prior art	
d-value/Å	Relative intensity	d-value/Å	relative intensity	d-value/Å	Relative intensity
5.35	vw	5.76	vw	5.37	w
5.20	s	5.36	w	5.21	w
				5.15	m
				4.81	vw
4.70	vw	5.12	w	4.70	vw
				4.63	vw
4.40	vw	4.57	m	4.40	vw
4.29	vw	4.46	m		
				4.27	vw
4.17	vw	4.29	s	4.17	vw
3.935	s	4.11	m	3.938	w
				3.846	vw
3.831	w	3.963	m		
3.744	w	3.920	m	3.748	vw
				3.711	vw
3.611	w	3.713	s	3.610	vw
3.543	w	3.601	w	3.545	w
3.522	w	3.431	vw	3.519	vw
3.488	w	3.375	w		
				3.464	vw
3.411	vw	3.254	vw	3.410	vw
				3.304	vw
				3.256	vw
				3.151	vw

Table 1, continued

Omeprazole sodium form A		Omeprazole sodium form B		Omeprazole sodium according to prior art	
d-value/Å	Relative intensity	d-value/Å	relative intensity	d-value/Å	Relative intensity
3.125	m	3.173	vw	3.125	vw
				3.079	vw
3.021	vw	3.137	w	3.026	vw
2.919	w	3.119	m	2.911	vw
				2.854	vw
2.833	w	3.050	w		
				2.775	vw
2.676	vw	2.993	w		
2.626	vw	2.980	m		
2.606	vw	2.906	m	2.601	vw
				2.553	vw
2.534	vw	2.892	m		
2.425	vw	2.793	vw	2.430	vw
		2.624	vw		
		2.589	vw		
		2.499	vw		
		2.447	vw		
		2.402	vw		
		2.372	vw		
		2.283	vw		

CLAIMS

1. Omeprazole sodium form B, characterized in being thermodynamically stable.

2. Omeprazole sodium form B, characterized in being essentially non-hygroscopic.

3. Omeprazole sodium form B according to claim 1 or claim 2, characterized in providing an X-ray powder diffraction pattern exhibiting substantially the following d-values and intensities;

d-value/Å	relative intensity	d-value/Å	relative intensity
9.8	vs	3.37	w
7.8	vw	3.25	vw
6.7	s	3.17	vw
6.5	s	3.14	w
6.2	vw	3.12	m
5.9	m	3.05	w
5.8	vw	2.99	w
5.4	w	2.98	m
5.1	w	2.91	m
4.6	m	2.89	m
4.5	m	2.79	vw
4.3	s	2.62	vw
4.1	m	2.59	vw
3.96	m	2.50	vw
3.92	m	2.45	vw
3.71	s	2.40	vw
3.60	w	2.37	vw
3.43	vw	2.28	vw

4. Omeprazole sodium form B according to any of claims 1-3, characterized by having a monoclinic unit cell with parameters

a = 15.09 Å, b = 12.83 Å, c = 9.82 Å, β = 94.4°.

5. A process for the preparation of omeprazole sodium form B as defined in any of claims 1-4, which includes the step of;

a) preparing the sodium salt of omeprazole by addition of an aqueous base to omeprazole in a solvent mixture comprising an alcohol and water,

b) allowing the solution to crystallize, optionally using omeprazole sodium form B to induce crystallization;, and

c) isolating the omeprazole sodium form B thus obtained.

6. A process according to claim 5, wherein said aqueous base used in step a) is sodium hydroxide.

7. A process according to any of claims 5-6, wherein said alcohol used in step a) is isopropanol.

8. A process for the preparation of omeprazole sodium form B as defined in any of claims 1-4, comprising the steps of;

a) dissolving omeprazole sodium of any form, or a mixture of any forms, in a solvent mixture comprising alcohol and water;

b) allowing the solution to crystallize, optionally using omeprazole sodium form B to induce crystallization, and

c) isolating the omeprazole sodium form B thus obtained.

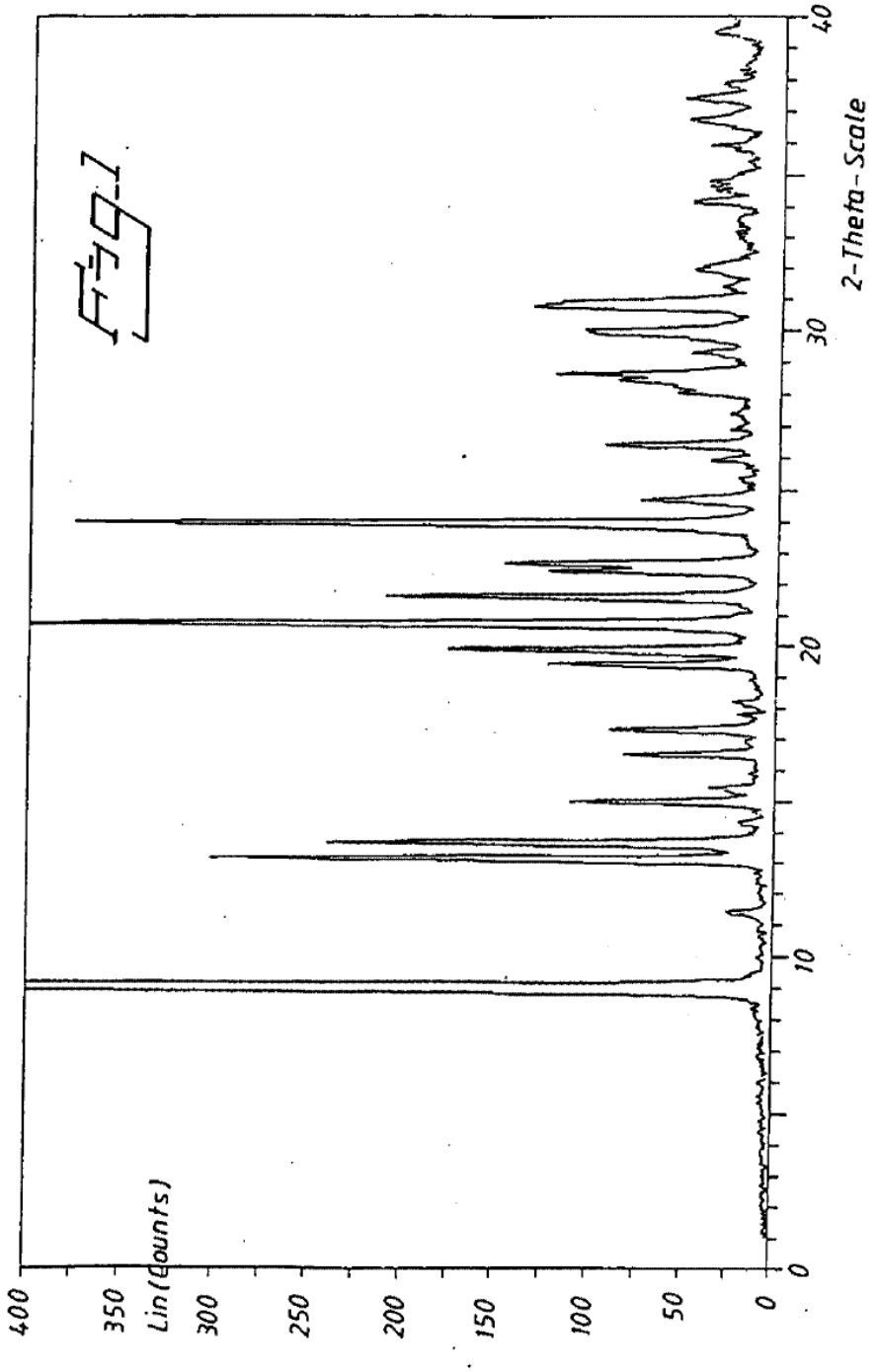
9. A pharmaceutical formulation comprising omeprazole sodium form B as defined in any of claims 1-4 in admixture with a pharmaceutically acceptable excipient.

10. A pharmaceutical formulation suitable for i.v. administration comprising omeprazole sodium form B as defined in any of claims 1-4 in admixture with a pharmaceutically acceptable excipient.

11. The use of omeprazole sodium form B as defined in any of claims 1-4, as active ingredient in the manufacture of medicament for use in treatment of gastrointestinal disorders.

12. The use of omeprazole sodium form B as defined in any of claims 1-4 in the manufacture of a pharmaceutical formulation for i.v. administration.

13 A method of treatment of gastrointestinal disorders which comprises administration of a therapeutically effective amount of omeprazole sodium form B as defined in any of claims 1-4, to a patient suffering from gastrointestinal disorders.


Fig 1
Lin(Counts)
2-Theta-Scale
0
50
100
150
200
250
300
350
400
10
20
30
40

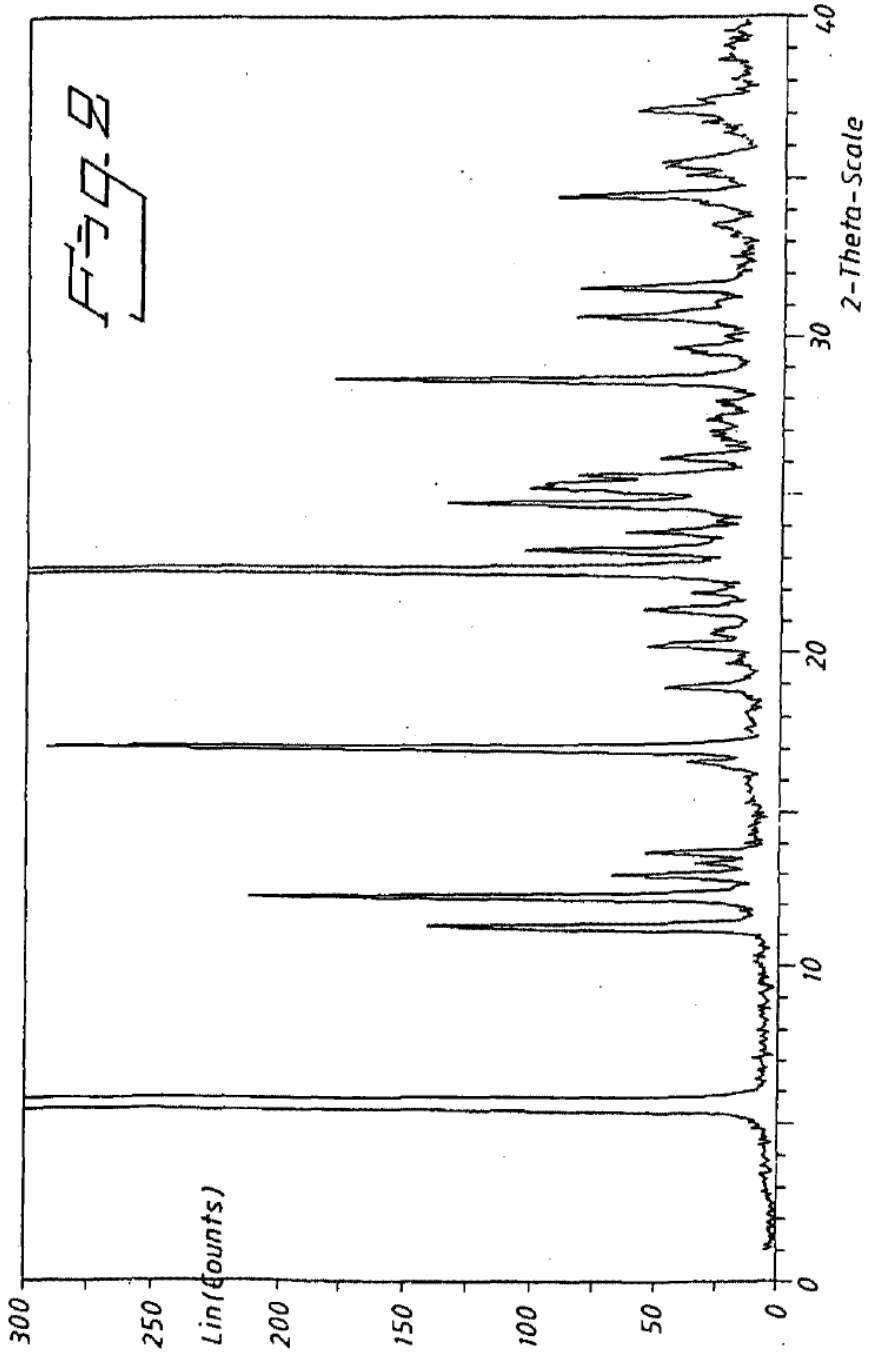
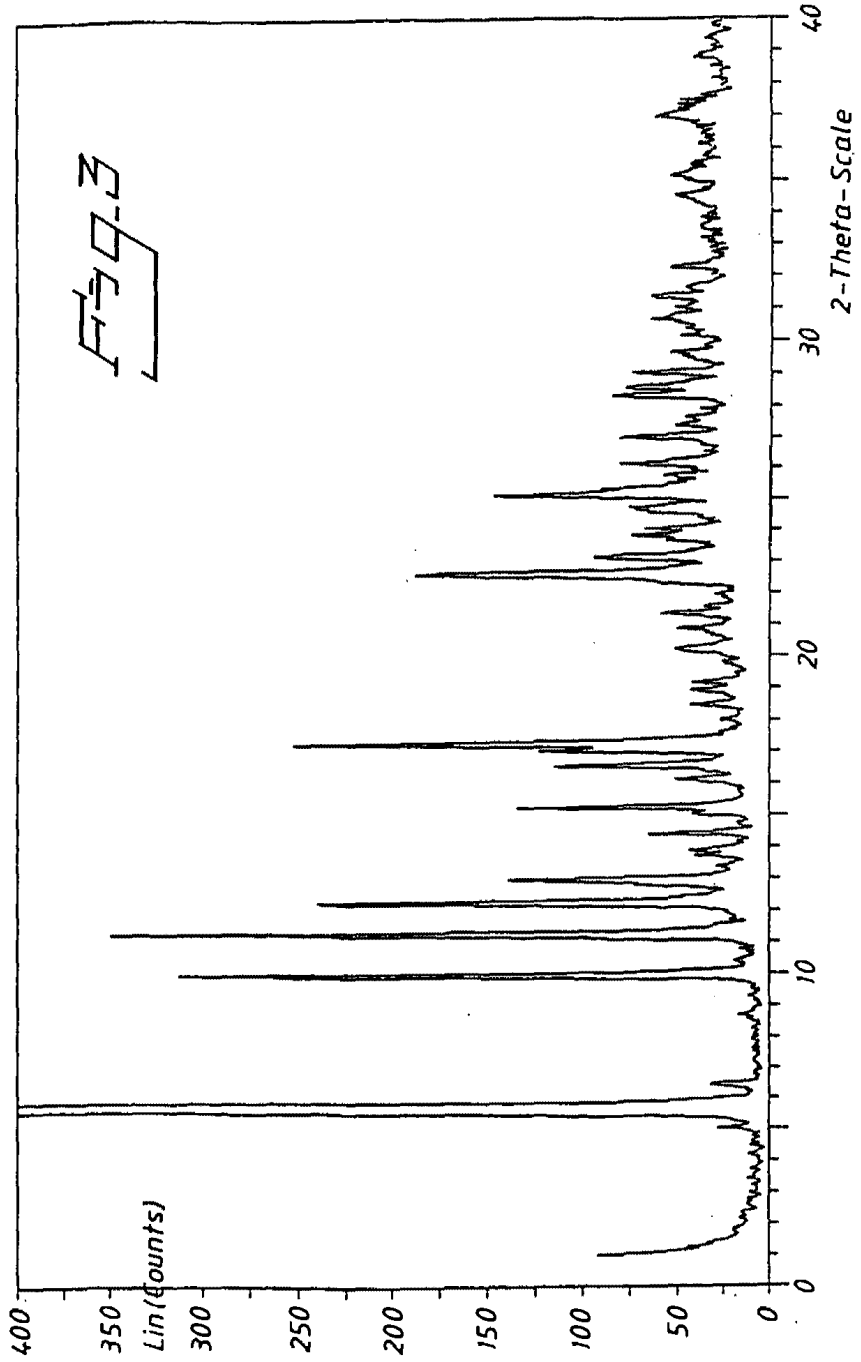

Fig 8
Lin(Counts)
0
50
100
150
200
250
300
10
20
30
40
2-Theta-Scale

Fig 3


Lin (Counts)
0
50
100
150
200
250
300
350
400
0
10
20
30
40
2-Theta-Scale

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/01124

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 401/12, A61K 31/44
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0124495 A2 (AKTIEBOLAGET HÄSSLE), 7 November 1984 (07.11.84) -- --------	1-12

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 Sept 1998	12-10-1998
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson Telephone No. +46 8 782 25 00

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/01124

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 13
because they relate to subject matter not required to be searched by this Authority, namely:
A method for treatment of the human or animal body by therapy, see rule 39.1.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
[ ] The additional search fees were accompanied by the applicant's protest.
[ ] No protest accompanied the payment of additional search fees.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

27/07/98

International application No.
PCT/SE 98/01124

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0124495 A2	07/11/84	SE 0124495 T3	
		AU 563842 B	23/07/87
		AU 2525784 A	06/09/84
		BG 44538 A	15/12/88
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		CS 8401515 A	13/06/85
		DK 99584 A	05/09/84
		DK 160044 B,C	21/01/91
		FI 83649 B	30/04/91
		FI 840851 A	05/09/84
		GB 2137616 A,B	10/10/84
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		JP 59167587 A	21/09/84
		LT 2253 A	15/11/93
		LT 94793 R	15/11/93
		PT 78191 B	05/08/86
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		US 4738974 A	19/04/88

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(81) Designated States: AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), EE, EE (Utility model), ES, FI, FI (Utility model), GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: MODIFIED RELEASE MULTIPLE-UNITS COMPOSITIONS OF NON-STEROID ANTI-INFLAMMATORY DRUG SUBSTANCES (NSAIDs)

(57) Abstract

An oral pharmaceutical modified release multiple-units composition for the administration of a therapeutically and/or prophylactically effective amount of a non-steroid anti-inflammatory drug substance (in the following abbreviated "an NSAID substance") to obtain both a relatively fast or quick onset of the therapeutic effect and the maintenance of a therapeutically active plasma concentration for a relatively long period of time. The modified release multiple-units composition comprises at least two fractions of multiple units such as a first and a second fraction. The first fraction comprises individual units which are designed to quickly release the drug substance and the second fraction comprises individual units which are designed to slowly release the drug substance to enable a delayed and extended release of the drug substance. Typically, the second fraction comprises multiple units which are coated with a sustained release coating designed to release the drug substance in such a manner that the maintenance of a therapeutically active plasma concentration for a relatively long period of time are obtained. By suitable adjustment of the release pattern of the at least first and second fraction a composition is obtained which is adapted to once- or twice-a-day administration.

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MODIFIED RELEASE MULTIPLE-UNITS COMPOSITIONS OF NON-STEROID ANTI-INFLAMMATORY DRUG SUBSTANCES (NSAIDs)

The present invention relates to an oral pharmaceutical modified release multiple-units composition for the administration of a therapeutically and/or prophylactically effective amount of a non-steroid anti-inflammatory drug substance (in the following abbreviated "an NSAID substance") to obtain both a relatively fast or quick onset of the therapeutic effect and the maintenance of a therapeutically active plasma concentration for a relatively long period of time. The modified release multiple-units composition comprises at least two fractions of multiple units such as a first and a second fraction. The first fraction comprises individual units which are designed to quickly release the drug substance and the second fraction comprises individual units which are designed to slowly release the drug substance to enable a delayed and extended release of the drug substance. Typically, the second fraction comprises multiple units which are coated with a sustained release coating designed to release the drug substance in such a manner that the maintenance of a therapeutically active plasma concentration for a relatively long period of time are obtained. By suitable adjustment of the release pattern of the at least first and second fraction a composition is obtained which is adapted to once- or twice-a-day administration.

TECHNICAL BACKGROUND

Drug levels can be maintained above the lower level of the therapeutic plasma concentration for longer periods of time by giving larger doses of conventionally formulated dosage forms. However, it is not a suitable approach to increase dosage as such doses may produce toxic and undesired high drug levels. Alternatively, another approach is to administer a drug at certain intervals of time, resulting in oscillating drug levels, the so-called peak and valley effect. This approach is generally associated with several potential problems, such as a large peak (toxic effect) and valley (non-active drug level) effect, and a lack of patient compliance leading to drug therapy inefficiency or failure. If, however, the plasma concentration is kept constant over the therapeutic level using conventional tablets, an unacceptably high daily dosage is required if the active substance is not administered very frequently.

Controlled release compositions are known which are designed to rapidly release a fraction of a total drug dose. This loading dose is an amount of a drug which will provide a desired pharmacological response as fast as possible according to the biopharmaceutical properties of the drug substance. Generally, such compositions in some more or less sophisticated manner are composed of a sustained release part and a part which either contains a free amount of the drug substance or it releases the drug substance in the same manner as if the drug substance had been formulated as a plain formulation (e.g. in the form of normal tablets or granulates). Such compositions which initially release a burst of a therapeutic agent and then release the agent at an essentially constant rate are described, e.g., in WO 95/14460 (Euroceltique S.A.) published on 1 June 1995. The composition described therein relates to a sustained release opioid formulation comprising a plurality of substrates comprising the active ingredient in a sustained release matrix or coated with a sustained release coating comprising a retardant material. The sustained release beads are then coated with an opioid in immediate release form or, in the case the composition is in the form of a gelatine capsule, an amount of free opioid (i.e. the opioid is included as such and has not been processed into a specific formulation e.g. by means of pharmaceutically acceptable excipients) is incorporated into the gelatin capsule via inclusion of a sufficient amount of opioid within the capsule. In a further alternative, the gelatine capsule itself is coated with an immediate release layer of the opioid.

Generally, the rationale which lies behind the kind of compositions which have been described to enable an immediate release of a drug substance as well as a sustained release of the drug substance is to combine a traditional formulation approach (such as, e.g., i) plain tablets which have a disintegration time in water of at the most about 15 min for uncoated tablets, cf. Ph. Eur. (the requirements for coated tablets or capsules are at the most 30 min), ii) a traditionally formulated granulate or iii) loose powder of the drug substance itself) with a controlled release approach. By doing so the immediate release part of the composition is intended to release the drug substance in a manner which corresponds to a plain tablet formulation or the like and the term "immediate" is in such a context intended to denote that the release of the drug substance is faster than the release from a sustained release composition. The immediate release is in no way intended to be faster than that of a traditional or plain composition.

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Especially in those cases where the drug substance has a low solubility in an acidic medium having a pH of from about 1 to about 3, i.e. a pH corresponding to the pH in the stomach, the traditional formulation approach will lead to a pharmaceutical composition which has a suitable fast disintegration time but not necessarily a suitable dissolution rate of the drug substance under acidic conditions, i.e. a plain tablet will rapidly disintegrate into granules but the dissolution of the drug substance from the composition and/or the disintegrated composition under acidic conditions may be unsuitable low due to the solubility properties of the drug substance itself. The availability of a drug substance with respect to absorption, i.e. entrance into the circulatory system, is dependant on the presence of the drug substance on dissolved form as it is generally accepted that only dissolved substances are capable of passing the mucous membranes in the gastro-intestinal tract. Therefore, it is important that the dissolution of the drug substance is suitably fast even under acidic conditions in order to enable an initial absorption already from the stomach so that a true fast or immediate therapeutic response is obtainable. Furthermore, if a drug substance – dependant on pH – can exist on un-ionized as well as ionized form (e.g. acetyl salicylic acid which at an acid pH below its pK_a value predominantly is present on an unloaded, i.e. un-ionized form, whereas at a pH above its pK_a value predominantly is present on ionized form). For drug substances which are weak acids it is very important to ensure a proper bioavailability of the drug substance already under acidic conditions in order to achieve a true rapid therapeutic effect. However, the various approaches disclosed with respect to achievement of a combination of a rapid and a sustained effect (e.g. in the publications mentioned above) do not seem to take the above-mentioned factors into account and, hence, there is a need for developing compositions which enable a true rapid onset of the therapeutic effect as well as a sustained effect. To this end, we have especially focused on compositions comprising a drug substance suitable for use in situations where a rapid effect is needed but also in situations where an extended effect is desirable in order to develop compositions suitable for administration less frequent than compositions on the market today, more specifically to enable administration on a once or twice daily basis. Examples of suitable drug substances are, e.g., substances which have a pain relief effect. More specifically, interesting drug substances are those belonging to the class of drug substances normally denoted NSAIDs or NSAID substances.

In EP-A-0 438 249A1 (ELAN Corporation P.L.C.) is given another example of a composition which has been designed to release naproxen immediately and sustained. However, as shown in Example 18 herein, the so-called immediate release of naproxen does not take place under acidic conditions, i.e. conditions prevailing in the stomach. Accordingly, such a composition is not within the scope of the present application.

As will be apparent from the following the present inventors have developed a composition in multiple-units form for a quick release as well and an delayed and extended release.

Multiple-units formulation techniques according to the invention aim at a modified release of a drug substance in a predetermined pattern to control the peak plasma concentration without affecting the bioavailability, i.e. the extent of drug availability. The release of an NSAID substance from a composition according to the present invention is controlled in a very flexible manner as described below. Many advantages are obtained, e.g., the frequency of undesirable side effects may be reduced, and due to the control of the time it takes to obtain the peak plasma concentration and the prolongation of the time at the therapeutically active plasma concentration, the frequency of the administration may be reduced to a dosage taken only twice or once a day. This also serves to improve patient compliance. A further advantage of the modified release multiple-units dosage form is that high local concentrations of the active substance in the gastro-intestinal system are avoided, due to the units being distributed freely throughout the gastrointestinal tract, independent of gastric emptying.

Moreover, patients suffering from pain and/or inflammatory conditions and/or related conditions very often require high daily dosages of NSAID substances. If such high dosage of an NSAID substance should be given only once a day, the release from the dosage form must be safe, predictable and reliable. The composition should also be very storage stable because an immediate release due to accidental damaging of e.g. the coating or capsule of a high dosage form may result in undesired high plasma concentrations, so-called dose dumping, which could cause undesired side effects. Furthermore, from a technical point of view, the release rate and the release pattern of the active drug substance from the composition should not significantly change during the shelf-life of the composition. Even a minor change in the release rate and/or release pattern may have a significant impact on the *in vivo* performance of the composition.

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By use of a coated multiple unit dosage form, the risk of dose dumping due to e.g. rupturing of a coating is reduced because the amount of active ingredient in each coated unit is negligible.

The compositions according to the present invention are intended to reduce or essentially eliminate problems identified with other kind of compositions intended for administration once daily. Thus, a major disadvantage of the once-a-day treatment in the art may be a low plasma concentration at the end of the dosing period and thereby the lack of therapeutic response. As the treatment of pain and/or inflammatory conditions and/or related conditions, is a balance of therapeutic effect on the one hand and the risk of side effects on the other hand, e.g. due to accumulation of drug, the dosage interval is generally calculated so that the drug concentration is substantially decreased at the time of intake of the next dosage. Accordingly, the patient will very often suffer from disease symptoms before the drug concentration subsequent to the next dosage has reached the therapeutic level. In addition, it should be noted that in the treatment of pain and/or inflammatory conditions and/or related conditions, relatively higher dosages, corresponding to a relatively higher peak concentration, are often needed in case the symptoms break through. Accordingly, a relatively higher initial plasma concentration of an NSAID substance may be necessary compared to the plasma concentration at steady state.

However, to the best of our knowledge no oral non-steroid anti-inflammatory modified release pharmaceutical composition has been disclosed which at the same time can be produced in an easy, cheap and reliable manner and which provides a suitable profile for release of active substance (under acidic, neutral and basic conditions) resulting in an extended period of action so that the inflammatory condition is both rapidly alleviated after administration and avoided for a period of about 12 to 24 hours.

Therefore, there is a need for developing a composition comprising a non-steroid anti-inflammatory drug substance permitting the administration of dosages only once or twice a day in a safe and reliable manner, and which is easy to produce, preferably involving conventional production methods and as few production steps as possible. It is also important that an NSAID composition for daily administration comprises the active ingredient in such a way that the composition has a reliable dissolution rate since a

change in the dissolution pattern of the NSAID substance could be disadvantageous for the patient.

BRIEF DISCLOSURE OF THE INVENTION

The purpose of the present invention is to provide an oral modified release multiple-units composition for administration of a daily dosage of an NSAID substance in a dosage form which only requires administration at the most twice daily, preferably once daily, and which overcomes the drawbacks of hitherto suggested formulations of modified release compositions containing an NSAID substance in that the dosage form both provides a substantially fast release from a first fraction comprising multiple units and a delayed and extended release from a second fraction of multiple units of the NSAID substance whereby alleviation of symptoms is achieved shortly after administration and is maintained for at least 12 hours, preferably 24 hours after administration.

A further aspect of the invention is to provide a process for the preparation of a composition of an oral pharmaceutical modified release multiple-units composition containing an NSAID substance, and in addition, a method for treating patients with a composition according to the invention whereby the interval between each administration is increased to about 12-24 hours.

Accordingly, the present invention relates to an oral pharmaceutical modified release multiple-units composition in unit dosage form for administration of a therapeutically and/or prophylactically effective amount of a non-steroid anti-inflammatory drug substance (an NSAID substance), a unit dosage form comprising two NSAID-containing fractions,

i) a first NSAID-containing fraction of multiple-units for quick release of the NSAID substance, and

ii) a second NSAID-containing fraction of multiple-units for extended release of the NSAID substance,

the first fraction which – when subjected to dissolution method II as defined herein employing 0.07 N HCl as dissolution medium – releases at least 50% w/w of the NSAID substance present in the fraction within the first 20 min of the test,

the second fraction being in the form of coated delayed release multiple-units for extended release of the NSAID substance.

The present invention also relates to a composition for the administration of a therapeutically and/or prophylactically effective amount of an NSAID substance to obtain both a relatively fast onset of the therapeutic effect and the maintenance of a therapeutically active plasma concentration for a relatively long period of time, a unit dosage of the composition comprising at least two fractions as follows:

a first fraction of quick release multiple-units for relatively quick release *in vivo* of an NSAID substance to obtain a therapeutically and/or prophylactically active plasma concentration within a relatively short period of time, and

a second fraction of coated modified release multiple-units for extended release *in vivo* of an NSAID substance to maintain a therapeutically and/or prophylactically active plasma concentration in order to enable dosing once or twice daily,

the formulation of the first and the second fractions, with respect to release therefrom and with respect to the ratio between the first and the second fraction in the unit dosage, being adapted so as to obtain:

a relative fast *in vitro* release of the NSAID substance from the first fraction of quick release multiple-units, as measured by the dissolution method II as defined herein,

an extended *in vitro* release of the NSAID substance from the second fraction of extended release multiple-units relative to the *in vitro* release of the first fraction of the NSAID substance, as measured by the dissolution method III as defined herein,

the quick release and the extended *in vitro* release being adapted so that the first fraction is substantially released when the release from the second fraction is initiated corresponding to at least 50% w/w release of the NSAID substance contained in the

first fraction at the time when at the most about 15% w/w such as, e.g., at the most about 10% w/w or at the most about 5% w/w of the NSAID substance contained in the second fraction is released as measured by the dissolution method III as defined herein.

It should be noted that the dissolution methods mentioned above and throughout the specification of course may be adjusted to specific drug substances and in some cases replaced with other dissolution methods. However, the requirements claimed herein should still be fulfilled.

The modified release multiple-units dosage forms of the present invention achieve and maintain therapeutic plasma concentrations for a prolonged period of time. In order to achieve the relatively fast absorption for the first fraction it requires that NSAID substances dissolve in the stomach (cf. the discussion above). Since the solubility of an NSAID substance such as, e.g., lornoxicam is < 1 mg /100 ml in 0.1 N HCl (aqueous solution of 0.1 N hydrochloric acid) the present inventors have found that incorporation such an NSAID substance in free form or in the form of a traditional formulation does not give the desired quick release under acidic conditions to enable a fast onset of the therapeutic effect *in vivo*. However, and as it will be discussed in detail below, a quick release of an NSAID substance (which is a weak acid or has a very low solubility under acidic conditions) takes place under acidic conditions provided that the drug substance is presented in a formulation wherein specific means has been used in order to manipulate the release rate so that the release becomes much faster than from a traditional composition. Thus, in contrast to the prior art composition in which focus only has been on the extended release rate part of the compositions and on the possibility of changing the release from this part, the present inventors have found it necessary to adjust the release rate from both the fast and the slow release part of a composition when the NSAID substance either has a very low solubility in 0.1 N hydrochloric acid or has a pK_a below about 5.5 such as, e.g., about 4-5. Thus, both the fast release fraction and the delayed release fraction must be manipulated with respect to release in order to achieve a suitable overall release rate.

The first fraction of the composition constitutes the quick releasing part of the composition whereas the second fraction of the composition constitutes the delayed and extended release part of the composition. In the first fraction, the release rate is primarily governed by the formulation of the fraction, i.e. the ingredients employed and

the processing of the ingredients to obtain the first fraction (cf. Danish Patent Application filed on 10 September 1998 in the name of Nycomed Danmark). In those cases, where a coating is present on the units of the first fraction, the coating may of course also contribute to the control of the release of the active drug substance from the first fraction. In the second fraction, the release rate is primarily governed by the constitution and thickness of a controlled release membrane which are applied on pellet cores (also denoted "pellets").

The delayed and extended fraction is based on the application of a release controlling membrane. The release is being controlled by the membrane which makes the formulation much more robust and easier to manipulate and manufacture. Ideally there is no release controlling effect from the uncoated units of the second fraction, i.e. the uncoated multiple-units of the second fraction do not significantly contribute to any control of the extended release of the active drug substance but the uncoated multiple-units merely release the active drug substance freely without any significant retardation.

The modified release multiple-units dosage forms of the present invention achieve and maintain therapeutic levels and, at the same time, reduces the risks for any side effect, which are believed to be associated with high blood levels of NSAID substances. Furthermore, the delayed or extended release properties of the coating applied on the second fraction of the multiple-units dosage forms of the present invention are unaffected by the pH in the gastro-intestinal tract.

The first fraction of the multiple-units dosage form of the invention may also be in the form of coated multiple-units provided that the release rate of such a fraction is so fast in the dissolution medium employed in dissolution method II described herein that at least 50% w/w of the total dose of the first fraction is released within the first 20 min.

When a coating is present on the multiple-units of the first fraction then it could advantageous be of the same kind as an outer coating on the multiple-units of the second fraction. The employment of the same kind of coating for each fraction may be performed with substantially identical procedures and materials and the production cost can be kept at a low level.

DETAILED DISCLOSURE OF THE INVENTION

Accordingly, the present invention relates to an oral pharmaceutical modified release multiple-units composition in unit dosage form for administration of a therapeutically and/or prophylactically effective amount of a non-steroid anti-inflammatory drug substance (an NSAID substance), a unit dosage form comprising two NSAID-containing fractions,

i) a first NSAID-containing fraction of multiple-units for quick release of the NSAID substance, and

ii) a second NSAID-containing fraction of multiple-units for extended release of the NSAID substance,

the first fraction which - when subjected to dissolution method II as defined herein employing 0.07 N HCl as dissolution medium - releases at least 50% w/w of the NSAID substance present in the fraction within the first 20 min of the test,

the second fraction being in the form of coated delayed release multiple units for extended release of the NSAID substance.

As discussed above it is very important to secure that the release pattern of the active drug substance contained in the composition is suitable for a composition for administration once or twice daily. The employment of at least two different fractions of multiple-units gives very flexible formulation parameters. Thus, it is possible to vary i) the percentage of the total dose of the NSAID substance contained in each fraction and ii) the weight ratio between the different fractions. The system (i.e. formulation concept) is therefore very suitable to not only one specific drug substance but can within certain limits be applied on a class or many classes of active drug substances once the target release profile has been determined. Of course, a change from one active drug substance to another active drug substance may give rise to certain adjustments of the constitution of the individual fractions to the specific substance. In the following is given a discussion of how to determine a target profile for an active drug substance and the release requirements generally applicable for the group of active drug substances belonging to the non-steroid anti-inflammatory drug substances.

Dissolution requirements

As described in the following, a target release profile can be designed for any NSAID substance. In the following the target release profile for a selected NSAID substance is described, namely lornoxicam.

Based on the knowledge of the pharmacokinetics of lornoxicam and a study performed by us employing a plain tablet and a solution (Hitzenberger G, Radhofer-Welte S, Takacs F, Rosenow D.: Pharmacokinetics of lornoxicam in man, Postgrad. Med. J. 1990, 66, pp S22-S26), a target in vivo profile for a once daily product has been estimated (Figure 1).

The presumptions made in estimating this target profile were:

i) a double peak and an effective concentration for 24 hours are desired from a therapeutic point of view (i.e. plasma lornoxicam concentrations at 24 hours should be similar to the plasma concentration obtained 8-12 hours after administration of half the dose in the form of a plain tablet),

ii) that the first fraction of the composition should have an absorption rate similar to or faster than that of plain tablets

iii) that the peak concentration should not be higher than the peak concentration observed after administration of half the dose in the form of a plain tablet, and

iv) that the second peak should appear about 5-6 hours after dosing.

A person skilled in the art is capable of determining the actual values with respect to the above-mentioned provisions and based on such values perform any necessary correction to the estimated profile (target profile).

The estimated target plasma profile as well as the profile from plain tablets have been deconvoluted with plasma concentrations from an oral solution to give an estimated *in vivo* dissolution profile (Figure 2). All data were normalised to a dose of 16 mg. In the deconvolution a time interval of 0.5 hours was employed (cf. Langenbucher F., and H.

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Möller: Correlation of *in vitro* drug release with in vivo response kinetics. Part I: Mathematical treatment of time functions. Pharm. Ind. 1983, 45, pp 623-8 and Langenbucher F. and H. Möller: Correlation of in vitro drug release with in vivo response kinetics. Part II: Use of function parameters. Pharm. Ind. 1983, 45, pp 629-33).

The presumptions in making this deconvolution were that the daily dose of lornoxicam is the same irrespective of whether a once daily composition or a plain tablet or a solution were administered,

The estimated *in vivo* dissolution profile for a once daily product can be used as the target *in vitro* profile for the combination of a fast or quick release fraction (i.e. the first fraction) and an extended or slow release fraction (i.e. the second fraction, coated pellets). The estimated *in vivo* dissolution profile for the once daily composition can be used as the target *in vitro* profile, when performing the dissolution tests *in vitro* with 1 hour in 0.1 N HCl and then shift to phosphate buffer pH 7.3 or 7.4 (dissolution methods III or IV described herein). This knowledge has been utilized in order to arrive at the dissolution requirements described in the following.

The presumptions made in using the estimated *in vivo* profile as target for *in vitro* profile were:

i) that a plain tablet will remain in the stomach for about 1 hour before a passage into the intestine takes place (estimated from the difference in T_{max} between the solution (0.5 hours) and the plain tablet (1.5 hour),

ii) that the correlation between the *in vitro* dissolution and the *in vivo* dissolution is a 1:1 correlation, and

iii) that lornoxicam is absorbed through the whole gastrointestinal tract (including colon) in order not to loose any amount of active drug substance ready for absorption into the circulatory system.

Before going into detail with respect to the release requirement to the first fraction, the second fraction and the composition in its final form, in the following is given details

with respect to the target release profile for a once daily lornoxicam composition. The target profile has been estimated as described above.

Target release *in vivo* profile (corresponds to target release profile *in vitro* employing dissolution methods III or IV as described herein):

Time (hours)	% w/w released lornoxicam
0.5	21 (range: 10-25%)
1	29 (range: 15-35%)
2	37 (range: 25-45%)
3	42 (range: 30-55%)
4	52 (range: 40-65%)
5	62 (range: 45-70%)
6	69 (range: 50-75%)
7	75 (range: 55-80%)
8	79 (range: 60-85%)
9	83 (range: 60-90%)
10	86 (range: 60-95%)
12	89 (range: 65-99%)
16	94 (range: at least about 85%)
20	97 (range: at least about 90%)
24	100 (range: at least about 90%)

As apparent from the above, the first fraction must release the active drug substance very quickly in 0.1 N HCl or in the dissolution medium employed in dissolution method II described herein, i.e. under conditions simulating the conditions in the stomach and under these conditions the second fraction does not release any significant amount of the active drug substance. In this connection it is important to note that even if the second fractions does not release any significant amount of the active substance within the first 20 min or 1 hours under acidic conditions, then the controlled release coating is not necessarily designed as an enteric coating, i.e. a coating which is insoluble at acidic pH and soluble at neutral/basic pH. The compositions according to the invention exemplified in the experimental section are examples on compositions wherein the controlled release coating of the second fractions is not an enteric coating. Furthermore, application of an enteric coating on e.g. pellets would not lead to an extended release of

an active drug substance. The release will of course be delayed (no release under acidic conditions) but as the pH becomes neutral and alkaline, then the enteric coating dissolves, i.e. there is no membrane left to control the release.

Notably, the release of the active drug substance from the first fraction is at least 55% w/w such as, e.g., at least about 60% w/w, at least about 65% w/w, at least about 70% w/w, at least about 75% w/w or at least about 80% w/w of the total NSAID substance present in the first fraction within the first 20 min of the test, i.e. the dissolution method II (pH corresponding to 0.07 N HCl) as defined in the experimental section.

In one embodiment the composition may comprise modified release multiple units wherein the *in vitro* dissolution characteristics of the first fraction of quick release multiple-units within 0.5 hour provides a release as defined by the dissolution methods II as described herein of at least about 50% w/w, at least about 60% w/w, at least about 70% w/w, at least about 80% w/w, at least about 85% w/w, at least about 90% w/w or at least about 95% w/w calculated on the total amount of active drug substance contained in the first fraction.

In addition, the composition may comprise modified release multiple units wherein the *in vitro* dissolution characteristics of the first fraction of quick release multiple units within 1 hour provides a release as defined by the dissolution methods II described herein of at least about 50% w/w, such as, e.g., at least about 60% w/w, at least about 70% w/w, at least about 80% w/w, at least about 85%, at least about 90% w/w or at least about 95% w/w calculated on the total amount of active drug substance in the first fraction.

As apparent from the discussion above, the overall release characteristics with respect to release of the active drug substance from the final composition are composed of the release characteristics of the first and the second fraction of multiple-units, respectively. With regard to compositions containing an NSAID substance intended for administration once or twice daily, the present inventors have found that the release characteristics of the second fractions most suitably should have the following order of magnitude provided that the release characteristics of the first fraction are as discussed above.

Accordingly, the *in vitro* dissolution characteristics of the second fraction of extended release multiple units may in one embodiment within 1 hour provide a release as defined by the dissolution method III described herein in the range of 0%- about 30% w/w, such as, e.g., in the range of 0%- about 20% w/w, in the range of 0%-about 10%w/w such as about 5% w/w calculated on the total amount of active drug substance in the second fraction.

Furthermore, the *in vitro* dissolution characteristics of the second fraction of extended release multiple units may within 3 hours provide a release as defined by the dissolution method III described herein in the range of about 10%-70% w/w, such as, e.g., in the range of about 10%-60% w/w, in the range of about 12%-50% w/w, in the range of 14%-45% w/w, in the range of about 15%-30% w/w, in the range of about 15%-20% w/w such as, e.g., about 17% w/w of the NSAID substance.

Within 6 hours, the *in vitro* dissolution characteristics of the second fraction of extended release multiple units may provide a release as defined by the dissolution method III described herein in the range of about 35%-95% w/w, such as, e.g., in the range of about 50%-90% w/w, in the range of about 50%-80% w/w, in the range of 50%-75% w/w, in the range of about 50%-60% w/w, in the range of about 53%-59% w/w such as, e.g. about 56% w/w of the NSAID substance.

In addition, within 9 hours the *in vitro* dissolution characteristics of the second fraction of extended release multiple units may provide a release as defined by the dissolution method III described herein in the range of about 50%-100% w/w, such as, e.g., in the range of about 60%-98% w/w, in the range of about 65%-95% w/w, in the range of about 70%-90% w/w, in the range of about 70%-80% w/w such as, e.g., about 76% w/w of the NSAID substance.

To ensure that the final composition has a proper constitution with respect to the weight amount of first fraction relative to the amount of second fraction, the *in vitro* dissolution characteristics of the first and second fractions are in one embodiment adapted so that the first fraction is substantially released when the release from the second fraction is initiated, corresponding to at least 50% w/w release of the first fraction at the time at the most about 15% w/w such as, e.g., at the most about 10% or at the most about 5% w/w of the second fraction is released, as measured by

the dissolution method III described herein. In addition, the *in vitro* dissolution characteristics of the first and second fractions in the same or a second embodiment as mentioned above are adapted so that the first fraction is substantially released when the release from the second fraction is initiated, corresponding to at least 70% w/w release of the first fraction at the time at the most about 20% w/w such as, e.g., at the most 15% w/w or at the most about 10% w/w of the second fraction is released, as measured by the dissolution method III described herein.

Apart from the requirements to the individual fractions contained in the composition it is of course of utmost importance to ensure that the composition in its final form has *in vitro* dissolution characteristics which give evidence for a suitable *in vivo* behaviour, i.e. a fast onset of the effect together with an extended release of the active drug substance to ensure a therapeutic and/or prophylactic effect upon administration once or twice daily.

The two fractions of multiple units may be selected, with respect to the release from each fraction and the ratio between the two fractions, so that the *in vitro* dissolution characteristics of the composition within 1 hour provide a release of the NSAID substance in the first and second fractions in the range of from about 5% w/w to about 50% w/w, such as, e.g., in the range of from about 5% w/w to about 45% w/w, in the range of from about 15% w/w to about 40% w/w, in the range of from about 20% w/w to about 35% w/w such as about 29% w/w, as defined by the dissolution method III described herein.

In addition, the two fractions of multiple units may be selected, with respect to the release from each fraction and the ratio between the two fractions, so that the *in vitro* dissolution characteristics of the composition within 3 hours provide a release as defined by the dissolution method III described herein in the range of from about 20% w/w to about 80% w/w, such as, e.g., in the range of from about 25% w/w to about 70% w/w, the range of from about 30% w/w to about 60% w/w, in the range of from 35% w/w to about 55% w/w such as about 42% w/w.

In an additional aspect, the two fractions of multiple units may be selected, with respect to the release from each fraction and the ratio between the two fractions, so that the *in vitro* dissolution characteristics of the composition within 6 hours provide a release as

defined by the dissolution method III described herein in the range of from about 40% w/w to about 98% w/w, such as, e.g., in the range of from about 50% w/w to about 95% w/w, in the range of from about 60% w/w to about 90% w/w, in the range of from about 60% w/w to about 85% w/w, in the range of from about 60% to about 83% such as about 69-70% w/w.

Furthermore, the two fractions of multiple units may be selected, with respect to the release from each fraction and the ratio between the two fractions, so that the *in vitro* dissolution characteristics of the composition within 9 hours provide a release as defined by the dissolution method III described herein in the range of from about 50% w/w to about 100% w/w, such as, e.g., in the range of from about 60% w/w to about 99% w/w, in the range of from about 70% w/w to about 98% w/w, in the range of from about 70% w/w to about 97% w/w, in the range of from about 75% w/w to about 96% w/w, such as in the range of from about 80% w/w to about 96%, such as about 80-85% w/w.

In a preferred embodiment, the composition fulfils the above criteria with respect to the dissolution characteristics of the composition in the full time span mentioned.

The percentage of NSAID substance in the first fraction is in the range of about 5%-50% w/w such as, e.g., in the range of about 10%-45% w/w, in the range of about 15%-45% w/w, in the range of about 20%-40% w/w, in the range of about 25%-40% w/w, in the range of about 25%-35% w/w such as, e.g., about 30% w/w, calculated on the total amount of NSAID substance in the composition.

The percentage of NSAID substance in the second fraction is in the range of about 30%-99% w/w such as, e.g. in the range of about 40%-98% w/w, in the range of about 45%-95% w/w, in the range of about 50%-95% w/w, in the range of about 55%-85% w/w, in the range of about 60%-80% w/w, in the range of about 60%-75% w/w, in the range of abut 65%-75% w/w such as, e.g., about 70% w/w, calculated on the total amount of NSAID substance in the composition.

In a preferred embodiment, the multiple units of the second and, when appropriate, the first fraction are coated, cross-sectionally substantially homogeneous pellets.

It is preferred that the multiple units of the first fraction result in a peak plasma concentration of the NSAID substance which is substantially the same as the peak concentration resulting from the second fraction. As the peak plasma concentration of the second fraction is adapted so that plasma concentration has a prolonged character due to the dissolution characteristics of the fraction described herein, the peak of this second fraction should preferably substantially represent the upper level of the therapeutic plasma concentration. In a preferred embodiment, the plasma concentration level is of such a size that no NSAID substance is in excess.

Since the total amount of NSAID substance contained in the first fraction is balanced compared to the total amount of NSAID substance in the composition, a peak plasma concentration of NSAID substance derived from the first fraction which is higher than the peak concentration resulting from the second fraction does not necessarily represent a substantial waste of the NSAID substance.

However, unless the patient suffers from heavy breakthrough symptoms wherein a higher plasma concentration than the plasma concentration for maintaining symptom alleviation often seems to be needed, the concentrations obtained from the first fraction should not exceed the peak from the second fraction.

Even in the circumstances wherein the peak of the first fraction is preferably higher than the peak from the second fraction, unsuitable high plasma concentrations (within the toxic level) derived from the first fraction may easily be avoided by adjusting the amount of active drug substance contained in the first fraction.

In another embodiment, e.g. in the circumstances wherein the patient is well treated by administration once or twice a day with a composition according to the invention, the first fraction may be adapted so that it results in a peak plasma concentration of the NSAID substance which is lower than the peak concentration resulting from the second fraction. This would not necessarily result in breakthrough symptoms as the NSAID substance remaining in the plasma from the previous dosage administered may contribute to maintaining the plasma concentration sufficiently high until the second fraction of the composition is released. In other cases, the daily dosage may be administered at a suitable time of the day when the patient has experienced less need for the NSAID, e.g. before bedtime.

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Accordingly, an important aspect of the invention is an embodiment wherein the first fraction results in a therapeutically active plasma concentration of the NSAID substance until the delayed release of an NSAID substance from the second fraction of modified release multiple units contributes to the maintenance of a therapeutically active plasma concentration of the NSAID substance.

As discussed above, the multiple-units of the first fraction may be in the form of uncoated pellet cores, coated pellet cores, granules, a granulate or small plain tablets provided that the requirements with respect to release of active drug substance in 0.1 N HCl and under conditions as those described under dissolution method II herein are fulfilled. In those cases, where the first fraction is in the form of coated pellets, the time lag of the release from the second fraction relative to the first fraction may be obtained by a modified release coating of the second fraction which is present in a range of about 2%-80% such as, e.g., about 2%-70%, about 2-60%, about 3-50%, about 3-40%, about 4-30%, about 5-20% or about 2-5%, relative to the uncoated unit.

It is also preferred that the modified release coating of the fraction(s) is substantially water-insoluble, but water-diffusible and substantially pH-independent which will facilitate an absorption independent of the presence of food in the stomach.

Dosage

In general, the dosage of the active drug substance present in a composition according to the invention depends *inter alia* on the specific drug substance, the age and condition of the patient and of the disease to be treated.

Compositions according to the invention intended for once daily administration will generally contain a daily dose of the active drug substance whereas compositions according to the invention intended for twice daily administrations will generally contain half the daily dose of the active drug substance. However, the daily dose may be divided into several dosage forms.

In the following is listed the recommended daily doses for selected NSAID substances.

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Aceclofenac: 200 mg
Diclofenac: 100 mg
Etodolac: 400 mg
Fenbufen: 900 mg
Fenoprofen: 1.5 g
Flurbiprofen: 200 mg
Ibuprofen: 1.6 g
Indometacin: 100 mg
Ketoprofen: 200 mg
Meloxicam: 15 mg
Nabumeton: 1 g
Naproxen: 750 mg
Piroxicam: 20 mg
Sulindac: 300 mg
Tenoxicam: 20 mg
Tiaprofenic acid: 600 mg
Tolfenamic acid: 400 mg
Tolmetin: 800 mg

The amount of an NSAID substance of the modified release multiple-units composition according to the invention may be selected so that is corresponds to about 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 8 mg, 10 mg, 12 mg, 16 mg, 20 mg, 24 mg, 25 mg, 30 mg, 32 mg, 50 mg, 60 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1 g, 1.1 g, 1.2 g, 1.3 g or 1.6 g of NSAID substance which are dosages generally known in the art. However, the composition according to the invention preferably comprises an amount of an NSAID substance which is a daily therapeutically effective amount of the NSAID substance.

Generally, with conventional dosage forms such as plain tablets comprising an NSAID substance, it is not always possible to obtain identical release profiles when different dosages are administered together as the load of active ingredient may differ depending on the size of the tablet. The release profile for 100 mg given in a single dosage may thus differ from 100 mg given as 5 dosages comprising 20 mg each. Not even with the commercially available modified release dosage forms, a substantially identical release profile within the different dosages is always observed.

With a composition according to the present invention, it is now possible to administer different dosages with identical release profiles (cf. results reported in the experimental section). For example, if each modified release multiple-units composition according to the invention is prepared with the same type of multiple units of the first and second fractions and in the same ratios, each of the dosage forms may be administered together to obtain any desired total dosage without altering the overall release profile from the total dosage. Accordingly, reliable and predictable plasma concentrations during the complete time span between administration may be obtained independently of the total dosage.

Therefore, a further advantage of the composition according to the invention is that the composition may be produced in different series of dosage forms of e.g. 4 mg, 8 mg, 12 mg, 16 mg, 24 mg, 32 mg etc., each of the series having individual properties resulting from the design of modified release of the first and second fractions as well as from the ratio between the fractions. Any desired total dosage can then be selected from the relevant dosage forms within each of the series.

The preferred dosage form according to the invention is in the form of a capsule, tablet, sachet etc. The size of the dosage form is adapted to the amount of the NSAID substance of the composition.

The above suggested dosage amounts should not be regarded as a limitation of the scope of the invention as it is obvious for the skilled person that any desired amount of the NSAID substance may be applied and is only limited by the size of the composition and the type of the NSAID substance.

The overall goal of the present invention is to provide a composition in unit dosage form for the administration of a therapeutically effective amount of an NSAID substance once a day. However, as some patients may still need to, or prefer to, receive administration twice a day, the invention should not be limited to a once-a-day composition as long as each of the unit dosage forms fulfils the criteria with respect to the dissolution mentioned above.

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In a further aspect, the invention relates to a process for the preparation of an oral pharmaceutical modified release composition, the process comprising incorporating into the unit dosage at least two fractions as follows:

a first fraction of quick release multiple-units for relatively quick release *in vivo* of an NSAID substance to obtain a therapeutically or prophylactically active plasma concentration within a relatively short period of time, and a second fraction of coated extended release multiple-units for extended release *in vivo* of an NSAID substance to maintain a therapeutically active plasma concentration in order to enable dosing once or twice daily,

the formulation of the first and the second fractions, with respect to release therefrom and with respect to the ratio between the first and the second fraction in the unit dosage, being adapted so as to obtain:

a relative quick *in vitro* release of the NSAID substance from the first fraction of quick release multiple-units, as measured by the dissolution method II defined herein,

an extended *in vitro* release of the NSAID substance from the second fraction of extended release multiple-units relative to the *in vitro* release of the first fraction of the NSAID substance, as measured by the dissolution method III as defined herein, the quick release and the extended *in vitro* release being adapted so that the first fraction is substantially released when the release from the second fraction is initiated corresponding to at least about 50% w/w release of the NSAID substance contained in the first fraction at the time when about 5% w/w of the NSAID substance contained in the second fraction is released as measured by the dissolution method III as defined herein.

Definitions of selected terms used herein

The term "modified release multiple-units composition" used in the present context is defined as the release of the drug differs from that of a traditional composition. The release rate is in other words controlled and it is possible to manipulate the release rate by means of e.g. changing the formulation parameters. The rate is often controlled in such a manner that the plasma concentration levels are maintained for the longest

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possible period above the therapeutic (the therapeutically active) level, but below the toxic level. However, the term "modified" is not restricted to an extended or prolonged effect, the term "modified" may as well cover the situation where the release rate is manipulated in such a manner that a quicker release than normally expected is obtained. Thus, in the present context the terms "quick" , "fast" and "enhanced" release as well as "controlled", "delayed", "sustained", prolonged", "extended" and other synonyms well known to a person skilled in the art are covered by the term "modified".

The term modified release in the present context refers to a composition which can be coated or uncoated and prepared by using pharmaceutically acceptable excipients and/or specific procedures which separately or together are designed to modify the rate or the place at which the active ingredient or ingredients are released (Ph. Eur. 97).

The term "extended release" in the present context refers to a modified release composition of which the release of the active ingredient and its subsequent absorption are prolonged in comparison with a conventional non-modified form (Commision of the European Communities).

The terms "quick release", "fast release" or "enhanced release" in the present context refer to a modified release composition of which the release of the active ingredient and its subsequent absorption are fast. More specifically, the terms "quick release", "fast release" or "enhanced release" mean that for a composition – when subjected to a dissolution method II described herein – at least about 50% w/w of the active substance is dissolved within the first 20 min of the test.

The term "fraction" of multiple units in the present context refers to a part of the multiple units of a dosage unit. One fraction will generally differ from another fraction of multiple units of the dosage unit. Even though only two fractions have been defined, it is within the scope of the invention to have more than two fractions in one dosage unit. Accordingly, the dosage unit according to the invention comprises at least two fractions.

The term "dosage unit" in the present context refers to one single unit, e.g. a capsule, tablet, a sachet or any other relevant dosage form known within the art. A dosage unit

represents a plurality of individual units which in accordance with the general state of the art may be in the form of a capsule, a tablet, a sachet, etc.

The term "bioavailability" designates the rate and extent to which the drug is absorbed from the modified multiple-units composition.

In the present context the term "therapeutically active plasma concentration which enables dosing once or twice daily" includes the situation wherein the NSAID substance administered has been metabolised to active metabolites resulting in a therapeutic effect for the stated period. It also includes the situation wherein the NSAID substance administered is present in a periferal compartment resulting in a therapeutic effect for the stated period.

The terms "NSAIDs" or "NSAID substances" are used herein to designate a group of drugs that belongs to non-steroid anti-inflammatory drug substances and pharmaceutically acceptable salts, prodrugs and/or complexes thereof as well as mixtures thereof.

The therapeutic classes mentioned herein are in accordance with the ATC (Anatomical Therapeutic Chemical) classification system.

Active drug substances

In the following are given examples of active drug substances which may be incorporated in a composition according to the invention. A majority of the active drug substances mentioned are weak acids, i.e. substances which have a pK_a value below about 5.5 such as, e.g., in a range of from about 3.0 to about 5.5 or in a range of from about 4.0 to about 5.0. In this connection it can be mentioned that the pK_a value for lornoxicam is about 4.7, for naproxen about 4.2, for indometacin about 4.5 and for acetylsalicylic acid about 3.5. When such substances which have a pK_a value of between about 3.0 to about 5.5 is employed in the composition, the present inventors have found that the first fraction should be in the form of uncoated multiple-units as the coating or the manufacture of the units to a form suitable for application of a coating seem to have a retarding effect on the release rate of the active drug substance from the first fraction (see the experimental section). Moreover, active drug substances like

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those mentioned above (i.e. weak acids having a pK_a value of at the most about 5.5 or about 5.0) generally have a poor solubility in media having a pH below the pK_a value; as an example the solubility of lornoxicam at a pH corresponding to 0.1 N HCl is less than about 1 mg/100 ml at room temperature and active drug substances like acetylsalicylic acid, indometacin and naproxen are regarded as substances which are practically insoluble in water and 0.1 N HCl at room temperature. From the discussion relating to solubility and availability of the active drug substance in order to get access to the circulatory system it is should be appreciated that the release (dissolution) of the active drug substance from the first fraction should be quick under acidic conditions, e.g., in 0.1 N HCl even if the active drug substance has a very low solubility in this medium. First fractions containing such active drug substances are generally not in the form of coated multiple-units in compositions according to the invention (cf. the discussion above).

However, when the active drug substance incorporated in a composition according to the invention has a pK_a value of at least about 5.0 such as at least about 5.5 the multiple-units of the invention may as well be in the form of coated multiple-units such as, e.g., coated pellet cores.

The first fraction is normally uncoated when the NSAID substance has a solubility in 0.1 N hydrochloric acid at room temperature of at the most about 0.5% w/v such as, e.g. at the most about 0.1% w/v, at the most about 0.05% w/v, at the most about 0.03% w/v, at the most about 0.01% w/w, at the most about 0.007% w/v, at the most about 0.005% w/v, at the most about 0.003% w/v, at the most about 0.002% w/v or at the most about 0.001% w/v.

The first fraction may be coated when the NSAID substance has a solubility in 0.1 N hydrochloric acid at room temperature of at least about 0.1% w/v such as e.g. at least about 0.5% w/v or at least about 1% w/v.

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Relevant examples of NSAID substances suitable for use in compositions according to the invention are:

- aminoarylcarboxylic acid derivatives like e. g. enfenamic acid, flufenamic acid, isonixin, meclofenamic acid, mefenamic acid, morniflumate, niflumic acid, and tolfenamic acid,
- arylacetic acid derivatives like e.g. aceclofenac, acemetacin, amfenac, bromfenac, cimmetacin, diclofenac, etodolac, fentiazac, glucametacin, indomethacin, lonazolac, metiavinic acid, oxametacine, pirazolac, proglumetacin, sulindac, tiaramide, tolmetin, and zomepirac,
- arylcarboxylic acids like e.g. ketorolac and tinoridine,
- arylpropionic acid derivatives like e. g. alminoprofen, bermoprofen, carprofen, dexibuprofen, fenbufen, fenoprofen, flunoxaprofen, flurbiprofen, ibuprofen, ibuproxam, ketoprofen, loxoprofen, naproxen, oxaprozin, pranoprofen, protizinic acid, and tiaprofenic acid,
- pyrazoles like e.g. epirizole,
- pyrazolones like e.g. benzpiperylon, mofebutazone, oxyphenbutazone, phenylbutazone, and ramifenazone,
- salicylic acid derivatives like e.g. acetaminosalol, acetylsalicylic acid, benorylate, eterisalate, fendosal, imidazole salicylate, lysine acetylsalicylate, morpholine salicylate, parsalmide, salamidacetic acid and salsalate,
- thiazinecarboxamides like a.o. ampiroxicam, droxicam, lornoxicam, meloxicam, piroxicam, and tenoxicam,
- others like bucillamine, bucolome, bumadizon, diferenpiramide, ditazol, emorfazone, nabumetone, nimesulide, proquazone and piroxicam (e.g. in the form of a betacyclodextrin complex).

From a market point especially the following NSAIDs are interesting: lornoxicam, diclofenac, nimesulide, ibuprofen, piroxicam, piroxicam (betacyclodextrin), naproxen, ketoprofen, tenoxicam, aceclofenac, indometacin, nabumetone, acemetacin, morniflumate, meloxicam, flurbiprofen, tiaprofenic acid, proglumetacin, mefenamic acid, fenbufen, etodolac, tolfenamic acid, sulindac, phenylbutazone, fenoprofen, tolmetin, acetylsalicylic acid, dexibuprofen and pharmaceutically acceptable salts, complexes and/or prodrugs and mixtures thereof.

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Other relevant active drug substances are COX-2 (COX is an abbreviation for cyclooxygenase) inhibitors like e.g. celecosib and flosulide.

At present, the most preferred drug substance is lornoxicam and pharmaceutically acceptable salts, complexes and prodrugs thereof. Lornoxicam may be present in a composition according to the invention as the sole drug substance or in combination with other drug substances.

The modified release oral dosage form of the present invention preferably includes an NSAID substance as the therapeutically active ingredient in an amount corresponding to from 1 to about 1600 mg of by weight. Alternatively, the dosage form may contain molar equivalent amounts of pharmaceutically acceptable salts thereof. The dosage form contains an appropriate amount to provide a substantially equivalent therapeutic effect.

A composition according to the invention may contain a further active drug substance. Relevant substances in this context are e.g. antidepressants, opioids, prostaglandine analogs (e.g. misoprostol), glucocorticosteroids, cytostatics (e.g. methotrexate), H_2 receptor antagonists (e.g. cimetidine, ranitidine), proton pump inhibitors (e.g. pantoprazole, omeprazole, lansoprazole), antacids, acetaminophen (paracetamol), penicillamine, sulfasalazine and/or auranorfin.

The term "antidepressant" used in the present context includes tricyclic antidepressants as well as other antidepressants and mixtures thereof. Pharmaceutically acceptable salts and/or complexes of antidepressant are also within the definition of antidepressant. Thus, the term "antidepressant" is used here to designate a group of drugs that have, to varying degrees, antidepressive properties and/or suitable properties with respect to alleviation or treatment of neurogenic pain and/or phantom pain. In the present context the term "antidepressant" encompasses drug substances mainly from the therapeutic class N06 or from the following drug classification: Psychoanaleptics excluding anti-obesity preparations; anti-depressants/thymoanaleptics including substances used in the treatment of endogenous and exogenous depression such as, e.g., imipramine, nortriptyline, amitriptyline, oxipramol and MAO-inhibiting substances; lithium; combinations of drugs with ataractics; psychostimulants including drugs which increase the psychic and physical performance and which have a fatigue depressing, stimulating effect such as, e.g., fentyllines, fencamfamine, methylphenidate, amphetamines;

pyscholeptic-psychoanaleptic combinations; nootropics [which are a class of psychoactive drugs which are claimed to have a selective action on integrative functions of the CNS. Their action is alleged to be particularly associated with intellectual function, learning and memory. Nootropics include preparations containing substances such as piracetam, pyritinol, pyrisuccideanol maleate, meclofenoxate, cyprodenate and their combinations with other substances, excluding those products with a vasodilatory action (see the therapeutic class C04A). Combinations with cardiac glycosides are classified in the therapeutic class C01A.]; and neurotonics and other miscellaneous products including products which are not classified above such as single or combination products containing bisibutiamin, deanol and derivatives, GABA, GABOB, N-acetyl asparaginic acid glutaminic acid and salts, kavain, phospholipid, succinodinitrate.

The presently most interesting drug substances belong to the tricyclic antidepressants. Relevant examples of antidepressants are: tricyclic antidepressants such as, e.g. dibenzazepine derivatives like carpipramine, clomipramine, desipramine, imipramine, imipraminoxide, imipramine pamoate, lofepramine, metapramine, opipramol, quinupramine, trimipramine; dibenzocycloheptene derivatives like amitriptyline, amitriptyline and chlordiazepoxide, amitriptyline and medazepram, amitriptyline and pridinol, amitriptyline and perphenazine, amitriptylinoxide, butriptyline, cyclobenzaprine, demexiptiline, nortriptyline, nortriptyline and diazepam, nortriptyline and perphenazine, nortriptyline and fluphenazine, nortriptyline and flupentixol, noxiptilin, protriptyline; dibenzoxepine derivatives like doxepin; and other tricyclic anti-depressants like adinazolam, amoxapine, dibenzepin, dimetacrine, dosulepin, dosulepin and diazepam, dothiepin, fluacizine (fluoracyzine, toracizin), iprindole, maprotiline, melitracen, melitracene and flupentixol, pizotyline, propizepine, and tianeptine; other antidepressants like 5-hydroxytryptophan, ademetionine, amfebutamone, amfebutamone hydrochloride, amineptine, amineptine hydrochloride, amisulpride, fluoxetine hydrochloride, fluoxetine, hypericin, lithium carbonate, sertraline hydrochloride, sertraline, St John's wort dry extract, trimipramine maleate, citalopram, citalopram hydrobromide, clomipramine chloride, clomipramine hydrochloride, d-phenylalanine, demexiptiline, demexiptiline hydrochloride, dimethacrine tartrate, dothiepin, dothiepin hydrochloride, doxepin, fluphenazine hydrochloride, fluvoxamine, fluvoxamine hydrogen maleate, fluvoxamine maleate, ginkgo biloba, indalpine, isocarboxazide, johanniskrauttrockenestrakt, 1-tryptophan, lithium citrate, lithium sulfate, lofepramine,

maprotiline, maprotiline hydrochloride, maprotiline mesilate, medifoxamine, metaprimine fumarate, mianserin, moclobemide, nitroxazepine hydrochloride, nomifensine, nomifensine maleate, nomifensin hydrogenmaleat, oxitriptan, paroxetine, paraoxetine hydrochloride, phenelzine, phenelzine sulfate, piracetam, pirlindole, pivagabine, prolintane hydrochloride, propizepine hydrochloride, protriptyline hydrochloride, quinupramine, remoxipride hydrochloride, rubidium chloride, setiptiline maleate, tianeptine sodium, trazodone hydrochloride, venlafaxine hydrochloride, maprotiline, toloxatone, tranylcypromine, trazodone, trazodone hydrochloride, viloxazine, viloxazine hydrochloride,zimelidine, zimelidine dihydrochloride.

At present, the most interesting drug substances for use in a composition according to the invention are amitriptyline and/or imipramine and pharmaceutically acceptable salts, complexes and prodrugs thereof. Amitriptyline and/or imipramine may be present in a composition according to the present invention either as the sole drug substance or in combination with other drug substances. Amitriptyline is a very interesting drug candidate with respect to preventing and/or treating neurogenic pains and phantom pains.

The term "opioid" is used here to designate a group of drugs that are, to varying degrees, opium- or morphine-like in their properties. The term includes natural and synthetic opioids as well as active metabolites such as morphine-6-glucuronide and morphine-3-glucuronide, and mixtures of opioids. Pharmaceutically acceptable salts and/or complexes of opioids are also within the definition of opioids.

Further relevant examples of opioids for use in compositions according to the invention include alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine butorphanol, clonitazene, codeine, cyclazocine, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene fentanyl, heroin, hydrocondone, hydromorphone, hydroxypethidine, isomethadone, dextropropoxyphene, ketobemidone, levallorphan, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicormorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum,

pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tilidine, tramadol, salts thereof, mixtures of any of the foregoing, mixed μ-agonists/ antagonists, μ- and/or κ-agonists, combinations of the above, and the like.

Within the scope of the invention is of course that more than one active drug substance may be present in a composition, e.g. more than one NSAID substance and/or drug substances within the same or different therapeutic classes. Specific relevant therapeutic classes are M01A (NSAIDs), RO5D, N02 (analgesics), N2A (opioids) and N2B (non-narcotic analgesics).

Dose

In one embodiment of the present invention, the first fraction of multiple units comprises an amount of an NSAID substance corresponding to from about 50% to about 5% (between 1/2 and 1/20) of the daily dosage. In patients which are satisfactorily treated on 2-3 daily dosages of a conventional non-sustained formulation, the first fraction may in one example contain an amount of the NSAID substance corresponding to 40% of the daily dosage. The second fraction may then contain the remaining 60% of the daily dosage.

However, a preferred amount of the first fraction may comprise 30% of the daily dosage and the second fraction 70% of the daily dosage.

In another embodiment of the present invention, the first fraction of multiple units comprises an amount of an NSAID substance corresponding to the amount of the NSAID substance necessary for obtaining a therapeutic effect upon a first single oral dose of a conventional non-sustained formulation of the NSAID substance.

Formulation details

First fraction

As described above, the formulation of the first fraction depends on the specific active drug substance to be incorporated. If the solubility at room temperature in 0.1 N HCl is

low and the pK_a value is below about 5.5. or 5.0, then the first fraction is in the form of uncoated multiple-units. A very suitable formulation of the first fraction has under such conditions been found to be in the form of a granulate wherein special means have been employed in order to ensure a quick release of the poor soluble active drug substance. The granulate is typically prepared by wet-granulation (a process well known for a person skilled in the art) employing as little organic solvent as possible in order to reduce any environmental and personal risk. Furthermore, the present inventors have found that incorporation of an antacid-like substance like, e.g., sodium bicarbonate (sodium hydrogencarbonate), magnesium carbonate, magnesium hydroxide, magnesium metasilicate aluminate and other alkaline substance, has a pronounced increasing effect on the release rate.

In one embodiment, the individual units of the relatively fast release fraction according to the invention will normally be a granulate having a size (average diameter) of at the most about 250 µm such as, e.g. at the most about 240 µm, at the most about 230 µm, at the most about 220 µm, at the most abut 210 µm, at the most about 200 µm, at the most about 190 µm, at the most about 180 µm, at the most about 175 µm, at the most about 150 µm, at the most about 125 µm, at the most about 100 µm, at the most about 90 µm or at the most about 80 µm.

As described above, the first fraction may also be in the form of coated multiple-units such as coated pellets provided that the pK_a of the active drug substance is at least about 5.0 or 5.5. From the experimental section *inter alia* it appears that such coated cores may have the same coating as the coating of the second fraction, but the thickness of the coating differs in such a manner that the coating of the first fraction is much thinner than that of the second fraction. For further details with respect to coating see below.

Second fraction

The individual units of the extended release fraction according to the invention will normally be pellets or beads having a size (average diameter) of from about 0.1 to 2 mm. The most preferred pellet size is from 0.5 to 0.8 mm. The pellets or beads comprise a combination of active substance, the NSAID substance and excipients.

When the pellets or beads are not coated, the combination of the active substance and the excipients is referred to as a core.

In the present context, the term "cores which are cross-sectionally substantially homogeneous" designates cores in which the active substance is not confined to an exterior layer on the core body, in other words normally cores which, through the cross-section of the core body, contain substantially the same type of composition comprising minor particles containing active substance, in contrast to the non-pareil type of cores which each consists of an excipient body with active substance applied to its surface. From this definition, it will be understood that the cores which are cross-sectionally substantially homogeneous will normally consist of a mixture of active substance with excipient(s), this mixture will not necessarily be qualitatively or quantitatively homogeneous through the total cross-sectional area of the core but may show, e.g., a concentration gradient of the NSAID substance or they may consist substantially solely of NSAID substance. In the following specification and claims, such cores which are cross-sectionally substantially homogeneous will, for the sake of brevity, often simply be designated "cores".

It is contemplated that the core comprising the NSAID substance in a substantially homogeneous form provides a more reproducible release of the active ingredient than compared to e.g. particles in which the active ingredient forms part of the coating.

It should, however, be understood that the invention is not limited to pellet formulation containing the above-mentioned cores; in principle, the type of cores can be any kind such as, e.g. matrices, non-pareil cores as well.

It is preferred that the release profile of the core of the individual unit is substantially non-limiting with respect to the desired release of the coated pellet, e.g. that the core itself provides at least about 90% w/w such as, e.g., at least about 95% w/w, at least about 97% w/w, at least about 98% such as about 100% release within 1 hour, measured in the *in vitro* dissolution test described in the Examples. However, pellet cores showing a slower release of the active substance are still within the scope of the invention.

Dosage forms

The oral pharmaceutical modified release multiple-units formulation according to the invention will typically be a capsule containing a multiplicity of the units, typically more than 100, a sachet containing a multiplicity of the units, typically more than 1000, or a tablet made from a multiplicity of the units, typically more than 100, in such a manner that the tablet will disintegrate substantially immediately upon ingestion in the stomach into a multiplicity of individual units which are distributed freely throughout the gastro-intestinal tract.

In the present context the term "once daily"/"once-a-day" is intended to mean that it is only necessary to administer the pharmaceutical formulation once a day in order to obtain a suitable therapeutic and/or prophylactic response; however, any administration may comprise co-administration of more than one dosage unit, such as, e.g., 2-4 dosage units if the amount of active substance required may not be formulated in only one composition unit or if a composition unit of a minor size is preferred.

In agreement with the above-mentioned definition of "once daily"/"once-a-day", "twice daily"/"twice-a-day" is supposed to mean that it is only necessary to administer the pharmaceutical formulation at the most twice a day in order to obtain a suitable therapeutic and/or prophylactic response in the patient.

Irrespective of the above-mentioned definitions of "once" and "twice" daily, a dosage unit constructed to deliver the active ingredient after only one daily administration is preferred. However, due to individual circumstances some patients may need a new dosage after e.g. 12 or 18 hours if the patient e.g. has an abnormal absorption or bowel transit time. If the individual has a relatively fast bowel transit time, some of the active ingredient may be excreted before the full dosage is released, or may be released in the colon from which the absorption may be decreased.

A multiple unit pharmaceutical composition according to the present invention is preferably formed as a unit dosage form which upon oral administration disintegrates into a multiplicity of individual units. The dosage unit form is preferably a solid dosage unit form such as, e.g., a tablet, a capsule, or a sachet, especially in the form of capsules.

The actual load of the NSAID substance in a pharmaceutical composition according to the invention, i.e. the concentration in % w/w of the NSAID substance calculated on the total weight of the multiple units, may depend on the particular NSAID substance employed in the formulation. The formulation principle employed in the present invention is very flexible. As an example it can be mentioned that compositions can be designed so that the load of the NSAID substance in the individual multiple units of the two fractions and the content of the two fractions for one dosage unit comprising e.g. 10 mg of NSAID substance is identical with another dosage unit comprising e.g. 100 mg, the release profile for each of the dosages will be identical. Consequently, an individual total dosage can be administered to the patient by combining the relevant dosage units e.g. selected from a series of 4, 8, 12, 16, 24 and 32 mg of the NSAID substance without altering the overall release profile of the total amount of the NSAID substance administered.

The compositions mentioned above may be prepared by conventional methods known in the art. The invention also relates to a method for preparing an oral pharmaceutical modified release multiple-units composition.

Coating

In a further embodiment, the invention relates to a method for preparing an oral pharmaceutical modified release multiple-units formulation in which

a) individual units containing an active substance are coated with an inner film-coating mixture ("the inner coat") comprising a film-forming substance,
b) the thus coated units are optionally provided with a first outer film layer comprising e.g. a stabilizing agent ("the middle coat"),
c) the thus coated units of the second fraction are optionally provided with a second outer film layer comprising a film-forming agent ("the outer coat"),
d) a mixture of individual units of the first and second fraction are formulated in a dosage form in the desired ratio of the two fractions.

In general, the inner coating is applied in an amount corrsponding to 2-20% w/w. The middle coating, if present, is applied in an amount corresponding to about 4% w/w of

the uncoated units and the outer coat is applied in an amount corresponding to about 1-2% w/w of the uncoated units.

The film-forming agent of step c) may be so selected that adhesion between the units is prevented at elevated temperatures, the coated units are then subsequently heated to a temperature above 40 °C, preferably not above 65-75 °C, and thereby a continuous phase is formed in the inner film layer in homogeneous admixture with the film-forming substance. In some cases, this curing process may also take place before the outer coating layer may be applied.

The modified release coating is applied on the multiple units from a solution and/or suspension preferably in an aqueous solvent, but an organic coating composition may also be applied.

Examples of film-forming agents which are suitable for use in accordance with the present invention are agents selected from the group consisting of cellulose derivatives such as, e.g., ethylcellulose, cellulose acetate, cellulose propionate, cellulose butyrate, cellulose valerate, cellulose acetate propionate; acrylic polymers such as, e.g., polymethyl methacrylate; vinyl polymers such as, e.g., polyvinyl acetate, polyvinyl formal, polyvinyl butyryl, vinyl chloride-vinyl acetate copolymer, ethylene-vinyl acetate copolymer, vinyl chloride-propylene-vinyl acetate copolymer; silicon polymers such as, e.g., ladder polymer of sesquiphenyl siloxane, and colloidal silica; polycarbonate; polystyrene; polyester; coumarone-indene polymer; polybutadiene; and other high molecular synthetic polymers.

In certain preferred embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers are well known in the art, and are described in NF XVII as fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups.

In one preferred embodiment, the acrylic coating is an acrylic resin lacquer used in the form of an aqueous dispersion, such as that which is commercially available from Rohm Pharma under the tradename Eudragit®. In further preferred embodiments, the acrylic coating comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the tradenames Eudragit® RL 30 D and Eudragit® RS 30 D, re-

spectively. Eudragit® RL 30 D and Eudragit® RS 30 D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit® RL 30 D and 1:40 in Eudragit® RS 30 D. Eudragit® RL/RS mixtures are insoluble in water and in digestive fluids. However, coatings formed from the same are swellable and permeable in aqueous solutions and digestive fluids. The Eudragit® RL/RS dispersions may be mixed together in any desired ratio in order to ultimately obtain a modified release formulation having a desirable dissolution profile. The most desirable modified release formulations may be obtained from a retardant coating based on Eudragit® NE 30D, which is a neutral resin having a molecular weight of 800,000.

The amount of coating applied is adapted so as to obtain a predetermined dissolution characteristic of the fraction of the composition. The percentage by weight of the modified release coating on the individual pellet will, for the fraction providing the extended duration of effect of the NSAID substance, be at the most about 20% w/w on an average, such as, e.g. about 15% w/w, about 12% w/w, preferably at the most about 10% w/w on an average, more preferred in the range of about 3% to 6 % w/w on an average, based on the weight of the uncoated individual pellet. The amount of coating applied depends on the predetermined dissolution characteristics of the particular core composition and the desired release profile of the fraction.

However, the amount of coating applied should also be adapted so that there will be no rupturing problems.

The coating may be admixed with various excipients such as plasticizers, anti-adhesives such as, e.g., colloidal silicium dioxide, inert fillers, and pigments in a manner known *per se*.

Tackiness of the water-dispersible film-forming substances may be overcome by simply incorporating an anti-adhesive in the coating. The anti-adhesive is preferably a finely divided, substantially insoluble, pharmaceutically acceptable non-wetting powder having anti-adhesive properties in the coating. Examples of anti-adhesives are metallic stearates such as magnesium stearate or calcium stearate, microcrystalline cellulose, or mineral substances such as calcite, substantially water-insoluble calcium phosphates or substantially water-insoluble calcium sulphates, colloidal silica, titanium dioxide, barium

sulphates, hydrogenated aluminium silicates, hydrous aluminium potassium silicates and talc. The preferred anti-adhesive is talc. The anti-adhesive or mixture of anti-adhesives is preferably incorporated in the coating in an amount of about 0.1-70% by weight, in particular about 1-60% by weight, and preferably about 8-50% by weight of the inner film layer. By selecting a small particle size of the talc, a larger surface area is obtained; the consequent higher anti-adhesive effect makes it possible to incorporate smaller amounts of specific anti-adhesives.

The individual modified release coated multiple-units may further comprise a middle coating between the "inner coat" and the "outer coat". Such coating may be adapted to stabilize the controlled release coated multiple-units and to prevent undesired changes of the release profile of each coated unit. Accordingly, the middle lacquer or coating may contribute to stability of the release profile of the dosage unit. Accordingly, the multiple units may further comprise an outer film layer.

In one aspect, the outer second layer comprises a water-based film-forming agent which prevents adhesion between the units at elevated temperatures and imparts flowability to the units, the water-based film-forming agent being anti-adhesive at temperatures above about 40 °C, especially temperatures above about 50 °C, such as a temperature between about 60 °C and about 120 °C, and being selected from diffusion coating materials such as ethylcellulose or enteric coating materials such as anionic poly(meth)acrylic acid esters, hydroxypropylmethylcellulosephthalate, cellulose-acetatephthalate, polyvinylacetatephthalate, polyvinylacetatephthalate-crotonic acid copolymerisates, or mixtures thereof, or water-soluble coating materials such as water-soluble cellulose derivatives, e.g. hydroxypropylcellulose, carboxymethylcellulose, methylcellulose, propylcellulose, hydroxyethylcellulose, carboxyethylcellulose, carboxymethylhydroxyethylcellulose, hydroxymethylcellulose, carboxymethylethylcellulose, methylhydroxypropylcellulose or hydroxypropylmethylcellulose.

Examples of plasticizers for use in accordance with the present invention include triacetin, acetylated monoglyceride, rape oil, olive oil, sesame oil, acetyl tributyl citrate, acetyl triethyl citrate, glycerin, sorbitol, diethyloxalate, diethylmalate, diethylmaleate, diethylfumarate, diethylsuccinate, diethylmalonate, dioctylphthalate, dibutylsebacetate, triethylcitrate, tributylcitrate, glyceroltributyrate, polyethyleneglycol, propyleneglycol,

1,2-propyleneglycol, dibutylsebacate, diethylsebacate and mixtures thereof. The plasticizer is normally incorporated in an amount of less than 10% by weight, calculated on the dry matter content of the coating composition.

Pharmaceutically acceptable excipients

Apart from the active drug substance in the multiple units, the pharmaceutical composition according to the invention may further comprise pharmaceutically acceptable excipients.

In the present context, the term "pharmaceutically acceptable excipient" is intended to denote any material which is inert in the sense that it substantially does not have any therapeutic and/or prophylactic effect *per se.* A pharmaceutically acceptable excipient may be added to the active drug substance with the purpose of making it possible to obtain a pharmaceutical formulation which has acceptable technical properties. Although a pharmaceutically acceptable excipient may have some influence on the release of the active drug substance, materials useful for obtaining modified release are not included in this definition.

Fillers/diluents/binders may be incorporated such as sucrose, sorbitol, mannitol, lactose (e.g., spray-dried lactose, α-lactose, β-lactose, Tablettose®, various grades of Pharmatose®, Microtose or Fast-Floc®), microcrystalline cellulose (e.g., various grades of Avicel®, such as Avicel® PH101, Avicel® PH102 or Avicel® PH105, Elcema® P100, Emcocel®, Vivacel®, Ming Tai® and Solka-Floc®), hydroxypropylcellulose, L-hydroxypropylcellulose (low-substituted) (e.g. L-HPC-CH31, L-HPC-LH11, LH 22, LH 21, LH 20, LH 32, LH 31, LH30), dextrins, maltodextrins (e.g. Lodex® 5 and Lodex® 10), starches or modified starches (including potato starch, maize starch and rice starch), sodium chloride, sodium phosphate, calcium phosphate (e.g. basic calcium phosphate, calcium hydrogen phosphate), calcium sulfate, calcium carbonate. In pharmaceutical formulations according to the present invention, especially microcrystalline cellulose, L-hydroxypropylcellulose, dextrins, maltodextrins, starches and modified starches have proved to be well suited.

Disintegrants may be used such as cellulose derivatives, including microcrystalline cellulose, low-substituted hydroxypropyl cellulose (e.g. LH 22, LH 21, LH 20, LH 32, LH 31,

LH30); starches, including potato starch; croscarmellose sodium (i.e. cross-linked carboxymethylcellulose sodium salt; e.g. Ac-Di-Sol®); alginic acid or alginates; insoluble polyvinylpyrrolidone (e.g. Polyvidon® CL, Polyvidon® CL-M, Kollidon® CL, Polyplasdone® XL, Polyplasdone® XL-10); sodium carboxymethyl starch (e.g. Primogel® and Explotab®).

Surfactants may be employed such as nonionic (e.g., polysorbate 20, polysorbate 21, polysorbate 40, polysorbate 60, polysorbate 61, polysorbate 65, polysorbate 80, polysorbate 81, polysorbate 85, polysorbate 120, sorbitane monoisostearate, sorbitanmonolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan monooleate, sorbitan sesquioleate, sorbitan tri oleate, glyceryl monooleate and polyvinylalkohol), anionic (e.g., docusate sodium and sodium lauryl sulphate) and cationic (e.g, benzalkonium chloride, benzethonium chloride and cetrimide) or mixtures thereof.

Other appropriate pharmaceutically acceptable excipients may include colorants, flavouring agents, and buffering agents.

In the following examples, the invention is further disclosed.

BRIEF DESCRIPTION OF THE DRAWING

Figure 1 shows a target plasma profile for lornoxicam together with a profile for plain tablets and solutions used to estimate the target profile,

figure 2 shows target *in vivo* dissolution profile for lornoxicam once daily and plain tablets,

figure 3 shows dissolution profiles of lornoxicam compositions containing 8 mg of lornoxicam; further details are given in Examples 14 and 15 herein,

figure 4 shows dissolution profiles of compositions according to Example 15,

figure 5 shows dissolution profiles of compositions according to Example 17.

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MATERIALS AND METHODS

Materials employed in the compositions which were investigated in the course of development of the present invention were as given in the following. In those cases where reference is given to an official pharmacopoeia, the reference is to the current edition of the stated pharmacopoeia.

The following abbreviations are used:

Ph. Eur.:	European Pharmacopoeia
USP/NF:	United States Pharmacopoeia National Formulary
DLS:	Dansk Lægemiddelstandard

Materials	Quality	Manufacturer
Cellulosum microcristallinum (Avicel PH 101)	Ph.Eur.	FMC
Polysorbate 20	Ph.Eur.	Henkel
Lactose monohydrate	Ph.Eur.	DMV
Carmellose sodium (Blanose 7 LFD)	Ph.Eur.	Aqualon
Maltodextrin (Glucidex 2)	USPNF	Roquette
Pregelatinised Starch (Starch 1500)	USPNF	Colorcon
Hypromellose (Methocel E 5 Premium)	Ph. Eur.	Dow
Magnesii stearas	Ph.Eur.	Akcros Chemicals
Talcum	Ph.Eur.	Whittaker, Clark and Daniels
Eudragit NE 30 D	Ph.Eur.	Röhm Pharma GmbH
Croscarmellose sodium (Ac-Di-Sol)	Ph.Eur.	FMC
Dibasic Calcium Phosphate, Anhydrous (Calcium hydrogen phosphate, mean particle size approx. 30 µm)	USPNF	Kyowa
Sodium bicarbonate (sodium hydrogencarbonate, mean particle size approx. 120 µm)	USPNF	Kirsch
Hydroxypropylcellulose (HPC L fine)	Ph. Eur.	Nippon Soda
Low-substituted Hydroxy Propyl Cellulose (LH21)	USPNF	Shin-Etsu
Ethanol, 96 %	DLS	Danisco

Aqua Purificata	Ph. Eur.	
Naproxen	Ph. Eur.	Syntex Pharm.
Polyvidone 30	Ph. Eur.	BASF
Isopropanol	Ph. Eur.	Sveda Kemi

Whenever relevant, the mean particle size was determined by employment of a Malvern laser particle size analyser.

In the following five different dissolution methods I-V are described. In the table below is given an overview of the important differences between the five methods:

Dissolution method	Dissolution medium	
	pH	volume
I	7.4	900 ml
II	0.07 N HCl	900 ml
III	0.1 N HCl/7.3[a]	750 ml of medium 1 and 250 ml of medium 2
IV	0.1 N HCl/7.4[b]	750 ml of medium 1; after 1 hour this medium is changed to 900 ml of medium 2
V	7.3	1000 ml

[a] 750 ml 0.1 N HCl is employed in the first 1 hour of the test and then 250 ml of a medium 2 is added leading to a resulting pH of the dissolution medium of 7.3

[b] 750 ml 0.1 N HCl is employed in the first 1 hour of the test and is then replaced by 900 ml of a medium 2 having a pH of 7.4

The various dissolution methods have been employed to show that the method chosen for determining the dissolution profile of various compositions has an influence on the result obtained, i.e. different dissolution profiles are obtained when employing different dissolution methods.

The dissolution methods given below give details partly with respect to the test method and partly with respect to the analysis method. The following methods are directed to

compositions containing lornoxicam as an example of an NSAID substance; however, in the case of compositions containing other drug substances than lornoxicam the test methods and details with respect to procedure and preparation of reagents are the same apart from an adjustment of the analysis method and the drug substance included in the standard solutions to conditions which are suitable for the drug substance in question. A person skilled in the art will have no difficulties in selecting a suitable method of analysis for a specific drug substance.

DISSOLUTION METHOD I

pH 7.4 (lornoxicam)

Test method

Apparatus: Ph. Eur. Dissolution test for solid dosage forms and USP XXIII <711> apparatus 2, equipped with Sotax AT7 and Perkin Elmer UV/VIS Spectrometer Lambda 2. The measurement was performed continuously using Perkin-Elmer Dissolution Software for Lambda Series UV/VIS Spectrometers Version 3.0/ JAN 94. The calculations were performed using the same software.

Glass fibre filter: Whatman GF/F

Dissolution medium: 900.0 ml dissolution medium pH 7.4

Number of revolutions: 50 rpm

Stirrer: Paddle

Temperature of dissolution medium: 37 °C ± 0.5 °C

Measuring times: Every 5 minutes after the start of the test (details appear from the following examples)

Analysis method

Detection wavelength: λ = 378 nm

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Measuring equipment: UV/VIS – spectrophotometer, 1 cm cuvette

Preparation of reagents

Dissolution medium: An aqueous solution containing 10.1 mg/ml of sodium hydrogenphosphate dihydrate (Na_2HPO_4 $2H_2O$) and 1.6 mg/ml and sodium dihydrogenphosphate monohydrate (NaH_2PO_4 H_2O); the pH of the dissolution medium is 7.4.

Standards

Stock solutions: 2 stock solutions (S_1 and S_2) with a concentration of 200 µg/ml lornoxicam are prepared. Lornoxicam is dissolved in solvent for standards given below.

Standards: 20.00 ml of each of the stock solutions are added to the reference vessel (cf. below).
Solvent for standards:1.5% w/w aqueous sodium acetate solution : methanol (1:1 v/v)

Test procedure

900 ml of the dissolution medium are filled to each of the vessels (typically three or six vessels for the product and one vessel for reference solution). The medium is heated to 37 °C ± 0.5 °C. The product to be tested (e.g. a granulate, pellets, a final composition) is placed in the vessels, and the spindel is started. In the last vessel, 20.0 ml of each of the stock solutions are added. The absorbance of the samples and standards is measured at 378 nm with a zero setting towards the dissolution medium.

The percentage dissolved is measured over a suitable time interval.

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DISSOLUTION METHOD II

0.07 HCl (lornoxicam)

Lornoxicam has a very low solubility in 0.1 N HCl *inter alia* in order to show that the relatively fast release fraction indeed releases lornoxicam at acidic pH (simulating the pH conditions in the stomach), dissolution method II is employed.

Test method

Apparatus: Ph. Eur. Dissolution test for solid dosage forms and USP XXIII <711> apparatus 2, equipped with Sotax AT7 and Perkin Elmer UV/VIS Spectrometer Lambda 2. The measurement was performed continuously using Perkin-Elmer Dissolution Software for Lambda Series UV/VIS Spectrometers Version 3.0/ JAN 94. The calculations were performed using the same software.

Glass fibre filter: Whatman GF/F

Dissolution medium: 900.0 ml dissolution medium

Number of revolutions: 50 rpm

Stirrer: Paddle

Temperature of dissolution medium: 37 °C ± 0.5 °C

Measuring time: Every 5 minutes after the start of the test (details appear from the following examples)

Analysis method

Detection wavelength: λ = 378 nm

Measuring equipment: UV/VIS – spectrophotometer, 1 cm cuvette

Preparation of reagents

Dissolution medium: Weigh out 50.0 g of sodium chloride and measure out 141.6 ml of concentrated hydrochloric acid. Dissolve the chemical with distilled water and dilute to 25 l with distilled water.

Standards

Stock solutions: 2 stock solutions (S_1 and S_2) with a concentration of 200 μg/ml lornoxicam were prepared. Lornoxicam is dissolved in solvent for standards (cf. below).

Standards: 20.00 ml of each of the stock solutions is added to the reference vessel (cf. below).

Solvent for standards: 1.5% w/w aqueous sodium acetate solution : methanol (1:1 v/v)

Test procedure

900 ml of dissolution medium are filled to each of the vessels (typically three or six vessels for the product and one vessel for reference solution). The medium is heated to 37 °C $\pm$ 0.5 °C. The product to be tested (e.g. a granulate, pellets or a final composition) is placed in the vessel. In the last vessel, 20.0 ml of each of the stock solutions are added. The spindel is started, and the absorbance of the samples and standards is measured at 378 nm with zero setting towards the dissolution medium.

The percentage dissolved is measured over a suitable time interval.

DISSOLUTION METHOD III

0.1 N HCl / pH 7.3 (lornoxicam)

This dissolution method includes a change in pH to simulate the *in vivo* situation.

Test method

Apparatus: Ph. Eur. Dissolution test for solid dosage forms and USP XXIII <711> apparatus 2, equipped with Sotax AT7 and Perkin Elmer UV/VIS Spectrometer Lambda 2. The measurement was performed continuously using Perkin-Elmer Dissolution Software for Lambda Series UV/VIS Spectrometers Version 3.0/ JAN 94. The calculations were performed using the same software.

Glass fibre filter: Whatman GF/F

Dissolution medium: 750 ml of dissolution medium 1, after 1 hour 250 ml of dissolution medium 2 are added

Number of revolutions: 50 rpm

Stirrer: Paddle

Temperature of dissolution medium: 37 °C ± 0.5 °C

Measuring times: Every 5 minutes after the start of the test (details appear from the following examples)

Analysis method

Detection wavelength: λ = 378 nm

Measuring equipment: UV/VIS - spectrophotometer, 1 cm cuvette

Preparation of reagents

Dissolution media
Dissolution medium 1: 0.1 N HCl

Dissolution medium 2: Weigh out 73,6 g trisodium phosphate, dodecahydrate (Na_3PO_4, $12H_2O$) and measure out 31,8 ml 0,1 N sodium hydroxide. Dissolve the chemicals in distilled water and dilute to 1000,0 ml with distilled water.

Standards

Stock solutions: 2 stock solutions (S_1 and S_2) with a concentration of 200 µg/ml lornoxicam were prepared. Lornoxicam is dissolved in solvent for standards (cf. below).

Standards: 20.00 ml of each of the stock solutions are added to the reference vessel (cf. below).

Solvent for standards:1.5% w/w aqeous sodium acetate solution : methanol (1:1 v/v)

Test procedure

750 ml of dissolution medium 1 are filled to each of the vessels (typically three or six vessels for the product and one vessel for reference solution). The medium is heated to 37 °C ± 0.5 °C. The product to be tested (e.g. a granulate, pellets or a final composition) is placed in the vessel. In the last vessel, 20.0 ml of each of the stock solutions are added. The spindel is started. After 1 hour 250 ml of dissolution medium 2 (37 C° ± 0.5 °C) are added.

The absorbance of the samples and standards is measured at 378 nm with zero setting towards the dissolution medium.

The percentage dissolved is measured over a suitable time interval.

DISSOLUTION METHOD IV

0.1 N HCl / pH 7.4 (lornoxicam)

This dissolution method includes a change in pH to simulate the *in vivo* situation. Furthermore, this dissolution method has been employed in experiments performed in order to clarify whether a pre-treatment of the product in 0.1 N hydrochloric acid has

any influence on the results obtained afterwards in a dissolution medium having a pH of 7.4.

Test method

Apparatus: Ph. Eur. Dissolution test for solid dosage forms and USP XXIII <711> apparatus 2, equipped with Sotax AT7 and Perkin Elmer UV/VIS Spectrometer Lambda 2. The measurement was performed continuously using Perkin-Elmer Dissolution Software for Lambda Series UV/VIS Spectrometers Version 3.0/ JAN 94. The calculations were performed using the same software.

Glass fibre filter: Whatman GF/F

Dissolution medium: 750 ml of dissolution medium 1, after 1 hour the medium is changed to 900 ml of dissolution medium 2.

Number of revolutions: 50 rpm

Stirrer: Paddle

Temperature of dissolution medium: 37 °C ± 0.5 °C

Measuring times: Every 5 minutes after the start of the test (details appear from the following examples)

Analysis method

Detection wavelength: λ = 378 nm

Measuring equipment: UV/VIS - spectrophotometer, 1 cm cuvette

Preparation of reagents

Dissolution media:

Dissolution medium 1: 0.1 N HCl

Dissolution medium 2: Distilled water containing 10.1 mg/ml of sodium hydrogenphosphate dihydrate (Na_2HPO_4 $2H_2O$) and 1.6 mg/ml of sodium dihydrogenphosphate monohydrate (NaH_2PO_4 H_2O)

Standards

Stock solutions: 2 stock solutions (S_1 and S_2) with a concentration of 200 µg/ml lornoxicam were prepared. Lornoxicam is dissolved in solvent for standards (cf. below).

Standards: 20.00 ml of each of the stock solutions is added to the reference vessel (cf. below)

Solvent for standards: 1.5% w/w aqueous sodium acetate solution : methanol (1:1 v/v)

Test procedure

750 ml of dissolution medium 1 are filled to each of the vessels (typically three or six vessels for the product and one vessel for reference solution). The medium is heated to 37 °C ± 0.5 °C. The product to be tested (e.g. a granulate, pellets or a final composition) is placed in the vessel. In the last vessel, 20.0 ml of each of the stock solutions are added. The spindel is started. After 1 hour the medium is decanted carefully and the medium is discarded. To the remaining product in the vessel 900 ml of dissolution medium 2 (37 °C ± 0.5 °C) are added. The absorbance of the samples and standards is measured at 378 nm with zero setting towards the dissolution medium employed.

The percentage dissolved is measured over a suitable time interval.

DISSOLUTION METHOD V

pH 7.3 (lornoxicam)

This dissolution method was used to *inter alia* clarify the influence of pH and/or the specific dissolution medium on the release rate and also to clarify, if the results obtained at pH 7.3 - without any pre-treatment in 0.1 N hydrochloric acid – were different from those obtained with pre-treatment in 0.1 N hydrochloric acid.

The buffer capacity of the dissolution medium employed was investigated to ensure a sufficient capacity. pH in the medium was measured before a product was added and after the end of the test. Both measurements revealed the same pH value (7.28), i.e. the buffer capacity is sufficient.

Test method

Apparatus: Ph. Eur. Dissolution test for solid dosage forms and USP XXIII <711> apparatus 2, equipped with Sotax AT7 and Perkin Elmer UV/VIS Spectrometer Lambda 2. The measurement was performed continuously using Perkin-Elmer Dissolution Software for Lambda Series UV/VIS Spectrometers Version 3.0/ JAN 94. The calculations were performed using the same software.

Glass fibre filter: Whatman GF/F

Dissolution medium: 750 ml of the dissolution medium 1 and 250 ml of dissolution medium 2, the resulting pH is 7.3

Number of revolutions: 50 rpm

Stirrer: Paddle

Temperature of dissolution medium: 37 °C ± 0.5 °C

Measuring times: Every 5 minutes after the start of the test (details appear from the following examples)

Detection wavelength: λ = 378 nm

Measuring equipment: UV/VIS - spectrophotometer, 1 cm cuvette

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Preparation of reagents

Dissolution media:

Dissolution medium 1: 0.1 N HCl

Dissolution medium 2: Weigh out 73,6 g trisodium phosphate dodecahydrate (Na_3PO_4 $12H_2O$) and measure out 31,8 ml 0,1 N sodium hydroxide. Dissolve the chemicals in distilled water and dilute to 1000,0 ml with distilled water.

Standards

Stock solutions: 2 stock solutions (S_1 and S_2) with a concentration of 200 µg/ml lornoxicam were prepared. Lornoxicam is dissolved in solvent for standards (cf. below).

Standards: 20.00 ml of each of the stock solutions is added to the reference vessel (cf. below).

Solvent for standards: 1,5 % sodium acetate solution : methanol (1:1)

Test procedure

750 ml of the dissolution medium 1 and 250 ml of dissolution medium 2 are filled to each of the vessels (typically three or six vessels for the product and one vessel for reference solution). The medium is heated to 37 °C $\pm$ 0.5 °C. The product to be tested (e.g. a granulate, pellets or a final composition) is placed in the vessel. In the last vessel, 20.0 ml of each of the stock solutions are added. The spindel is started. The absorbance of the samples and standards is measured at 378 nm with zero setting towards the dissolution medium.

The percentage dissolved is measured over a suitable time interval.

Calculation for all methods

Percentage dissolved was calculated with reference to an external standard in the reference vessel.

The concentration of the standard in the reference vessel is calculated by the formula below:

$$\text{mg lornoxicam per 1000 ml} = \left(\frac{q_1 \bullet 20}{V} + \frac{q_2 \bullet 20}{V}\right) \bullet \frac{1000}{940}$$

Where:

q_1	=	amount of standard weighed out for S_1 (mg)
q_2	=	amount of standard weighed out for S_2 (mg)
20	=	added volume of S_1 and S_2 to the reference vessel (ml)
V	=	dilution volume of the standard (ml)
940	=	volume in the reference vessel after addition of the standards (S_1 and S_2) to the vessel (ml)
1000	=	conversion factor to 1000 ml

The content of lornoxicam as percentage dissolved was calculated from the formula below:

$$\frac{abs_{sample} \bullet StA \bullet V \bullet 100}{abs_{StA}\ 1000 \bullet u} \bullet \frac{n}{100}$$

Where

abs_{sample}	=	absorbance measured in each vessel containing samples
StA	=	mg lornoxicam pr 1000 ml in the vessel containing standard
V	=	volume of the medium (ml)
100	=	factor converting to percent
abs_{StA}	=	absorbance measured in vessel containing the standard
u	=	declared content (mg)
n	=	potency of the standard (%)

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100	=	factor converting to percent
1000	=	factor converting the concentration of the standard to mg/ml

The following examples are intended to illustrate specific embodiments of the present inventions but are not intended in any way to limit the invention.

EXAMPLES

The following Examples 1 – 8 relate to the preparation of various cores containing lornoxicam as an example of an NSAID substance. Example 9 relates to the preparation of a quick release granulate, Examples 10-17 illustrate *inter alia* the influence of the composition of the pellets or the coat on the release rate and Example 18 relates to an immediate release composition disclosed in EP-A-0 438 249.

EXAMPLE 1

Preparation of cores containing lornoxicam and coating of the cores with a CR coating

Batch Nos. 04029831 (uncoated pellet cores) and 05029833 (coated pellet cores) were prepared.

Lornoxicam pellet cores were prepared by manufacturing of pellet cores and subsequent coating with an inner and an outer coat.

The pellet cores were prepared by the use of an extrusion/spheronization technique.

The ingredients are listed in Table 1. The ingredients I and II were mixed in a beaker by stirring, wetted with 150 g water and then mixed to a homogenous mass. The ingredients III to VII were filled into a Moulinex laboratory size mixer and mixed for 5 min, whereafter the homogenous mass was added and mixed. The beaker was rinsed with the remaining water and added to the mixer.

Table 1

	Ingredients	Amount (g):
I	Lornoxicam	54
II	Polysorbate 20	54
III	Cellulose, microcrystalline	102
IV	Lactose	315
V	Carmellose sodium	3
VI	Maltodextrin	12
VII	Pregelatinized starch	60
VIII	Purified water	150 + 18

The resulting mass was extruded in a Nica E 140 extruder with a screen size of 0.6 mm. The extrudate was spheronized in a laboratory size spheronizer at a rotation speed of 700 rpm for 4 min. The pellet cores thus produced were dried in a laboratory size fluid bed dryer with an inlet temperature of approximately 40° C, and the drying process was continued until the outlet temperature has reached approximately 30° C. The total drying time was approximately 25 min.

The dried pellet cores were fractionated in a Retsch sieving apparatus with a lower screen of 0.5 mm and an upper screen of 0.8 mm.

The release of lornoxicam from the pellet cores obtained was determined by dissolution method I (pH 7.4) and is as follows:

Time	Release (%)
10 min.	52.1
1 h	97.6

Thus, the relase of lornoxicam from the uncoated pellets is rapid and is almost accomplished within about 1 hour.

100 g of these pellet cores were coated with an inner coat and an outer coat in a laboratory size bottom spray fluid bed coater with a spray pressure of 1 bar for both the

inner coat and the outer coat. The temperature of the coating process was maintained at an inlet temperature of approximately 35° C to 40° C.

The composition of the coating is shown in Table 2:

Table 2

Ingredient	Amount (g)
Inner coat	
Hypromellose (Methocel E prem)	3.25
Magnesium stearate	0.68
Talc	6.07
Eudragit NE 30 D	216
Purified water	274
Outer coat	
Hypromellose (Methocel E5 prem)	4.0
Talc	4.0
Purified water	96.0

In the coating process the following amount of inner and outer coat was applied. The amount of dry matter applied calculated in percentage of the pellet core weight also appears from the below:

Inner coat: 35.9 g coating solution (corresponding to a dry matter content of approximately 5.5% w/w of the pellet core weight)
Outer coat: 12.5 g coating solution (corresponding to a dry matter content of approximately 1% w/w of the pellet core weight)

After the application of the coatings, the coated pellet cores were cured at a bed temperature of approximately 70° C for 30 min, whereafter the coated pellet cores were cooled to a bed temperature below 35° C.

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After the coating, the coated pellet cores are screened through a 1.2 mm screen. Oversized material is discarded.

EXAMPLE 2

Preparation of pellet cores according to the invention leaving out a surface active substance from the cores

Batch No. 09029831 (uncoated pellet cores) was prepared.

Lornoxicam pellet cores were prepared by using the ingredients listed in Table 3.

Table 3

	Ingredients	Amount (g)
I	Lornoxicam	27
II	Cellulose,microcrystalline	54
III	Lactosemonohydrate	216
IV	Carmellosesodium	3
V	Purified water	84

The pellet cores were prepared by the use of the extrusion/spheronization technique as described in Example 1, wherein the ingredients I to IV were mixed for 5 min in a Moulinex laboratory size mixer, whereafter the ingredients V was added.

The release of lornoxicam from pellet cores was determined by dissolution method I (pH 7,4) and is as follows:

Time	Release (% w/w)
10 min	19.1
1 h	69.8

From the dissolution data given above it is seen that the release is not accomplished after 1 hour and compared with the result obtained with the uncoated pellet cores in Example 1 it seems as if the inclusion of a surface active agent like e.g. polysorbate 20 has a significant influence on the dissolution rate.

EXAMPLE 3

Preparation of pellet cores corresponding to the pellets in Example 1 but in a smaller batch size

Batch No. 09029832 (uncoated pellet cores) was prepared.

This Example is intended to illustrate any relevant variation which may turn up as a dependency of the batch size.

Lornoxicam pellet cores were prepared as described in Example 1 with the exception that in Example 3, the amounts of the ingredients listed in Table 4 were used.

Table 4

	Ingredients	Amount (g)
I	Lornoxicam	27
II	Polysorbate 20	27
III	Cellulose, microcrystalline	51
IV	Lactose	157.5
V	Carmellose sodium	1.5
VI	Maltodextrin	6
VII	Pregelatinized starch	30
VIII	Purified water	60 + 15

The release of lornoxicam from these pellets cores was determined by dissolution method I (pH 7.4) and is as follows:

Time	Release (% w/w)
10 min	61.2
1 h	98.0

Thus, the pellet cores prepared have the same dissolution behaviour as the pellet cores prepared in Example 1, i.e. the batch size seems to be without any significant influence on the release rate.

EXAMPLE 4

Preparation of coated pellet cores having a thinner inner coating than the coated pellet cores of Example 1

Batches Nos. 11029831 (uncoated pellet cores) and 20029832 (coated pellet cores) were prepared.

Lornoxicam pellet cores were prepared as described in Example 1 with the exception that in Example 4, the amounts of the ingredients listed in Table 5 were used.

Table 5

	Ingredients	Amount (g)
I	Lornoxicam	27
II	Polysorbate 20	27
III	Cellulose, microcrystalline	51
IV	Lactose	157.5
V	Carmellose sodium	1.5
VI	Maltodextrin	6
VII	Pregelatinized starch	30
VIII	Purified water	51 + 15

The release of lornoxicam from these pellets cores was determined by dissolution method I (pH 7.4) and is as follows:

Time	Release (% w/w)
10 min	63.8
1h	100.7

Accordingly, the release of lornoxicam from the pellet cores is accomplished within 1 hour.

The pellet cores were coated as described in Example 1 with the exception that in Example 4, 100 g pellet cores were coated with an amount of inner and outer coat as follows:

Inner coat: 20.0 g coating solution (corresponding to a dry matter content of approximately 3% w/w of the pellet core weight).
Outer coat: 12.5 g coating solution (corresponding to a dry matter content of approximately 1% w/w of the pellet core weight).

As appears from the above, the amount of dry matter of the inner coat is smaller than in Example 1, whereas the amount of dry matter of the outer coat is the same as in Example 1. Accordingly, it is expected that the release of lornoxicam from the coated pellets of Example 4 is faster than that of lornoxicam from the coated pellets of Example 1.

EXAMPLE 5

Preparation of pellet cores corresponding to those of Example 3 with the exception that the surface active agent is replaced by lactose

Batch No. 11029834 (uncoated pellet cores) was prepared.

Lornoxicam pellet cores were prepared as described in Example 2 with the exception that in Example 5, the ingredients listed in Table 6 were used. Compared with the above Example 3 it is seen that the composition of pellet cores of Example 5 is very similar to those of Example 3, the only differences are that in the pellet cores of Example 3 a

surface active agent (polysorbate 20) is included and the amount of water employed differs a little.

Table 6

	Ingredients	Amount (g)
I	Lornoxicam	27
II	Cellulose, microcrystalline	51
III	Lactose	184.5
IV	Carmellose sodium	1.5
V	Maltodextrin	6.0
VI	Pregelatinized starch	30.0
VII	Purified water	84.0

The release of lornoxicam from these pellets cores were determined by dissolution method I (pH 7.4) and is as follows:

Time	Release (% w/w)
10 min	20.5
1h	62.4

In conclusion the same pattern is observed as in Example 2, namely that the exclusion of a surface active agent has a decreasing effect on the release rate of lornoxicam from the pellet cores.

EXAMPLE 6

Preparation of pellet cores having a content of a disintegrant

Batch No. 19029834 (uncoated pellet cores) was prepared.

Lornoxicam pellet cores were prepared by using the extrusion/spheronization technique as described in Example 1. However, the ingredients used in Example 6 are listed in Table 7:

Table 7

	Ingredients	Amount (g)
I	Lornoxicam	27
II	Polysorbate 20	27
III	Cellulose, microcrystalline	51
IV	Lactose	142.5
V	Carmellose sodium	1.5
VI	Maltodextrin	6
VII	Pregelatinized starch	30
VIII	Croscarmellose sodium	15
IX	Purified water	51 + 15 + 15

The ingredients I and II were mixed in a beaker, wetted with 51 g water and then mixed to a homogeneous mass. The ingredients III to VIII were added to a Moulinex laboratory size mixer and mixed for 5 min, whereto the homogeneous mass was added and mixed. The beaker was rinsed with 2 x 15 g water and added to the mixer.

The extrudation and spheronizing procedure were performed as described in Example 1.

The release of lornoxicam from the pellet cores was determined by dissolution method II (0.07 N HCl) and is as follows:

Time	Release (% w/w)
1h	5.7

Thus, only a very small amount of the lornoxicam present in the pellets is released at a pH corresponding to that of 0.07 N HCl. The inclusion of an disintegrant such as, e.g., croscarmellose sodium does not seem to have any increasing effect on the release rate of lornoxicam from the pellet cores. Furthermore, uncoated cores containing lornoxicam do not seem to be a suitable choice in order to obtain a relatively fast release of lornoxicam at low pH like the conditions in the stomach.

EXAMPLE 7

Preparation of pellet cores – modification of the composition of the pellets in order to influence the release rate of lornoxicam

Batch No. 19029836 (uncoated pellet cores) was prepared.

Lornoxicam pellet cores were prepared. The ingredients used are listed in Table 8.

Table 8

	Ingredients	Amount (g)
I	Lornoxicam	7.5
II	Sodium bicarbonate	37.7
III	Cellulose, microcrystalline	90.4
IV	Dibasic Calcium Phosphate, Anhydrous	104.1
V	Low-substituted Hydroxypropyl Cellulose	45.3
VI	Hydroxypropylcellulose	15
VII	Purified water	115.8
VIII	Ethanol 99.9 %	38.7

The ingredients II to IV were mixed in a Moulinex laboratory size mixer and mixed for 5 min. To 100 g of this mixture ingredient I was added and mixed in a cubus mixer for 5 min. The resulting mass was screened through a 0.5 mm screen and returned to the Moulinex mixer and mixed for further 6 min. A premixed mixture of ingredient VII and VIII was added to the powder mixture and massed for 6 min.

The resulting mass was then extruded and spheronized according to the method described in Example 1.

The release of lornoxicam from the pellet cores was determined by dissolution method II (0.07 N HCl) and is as follows:

Time	Release (% w/w)
After 1h	37.8

The release of lornoxicam from the pellets is significantly increased compared with the pellets of Example 6, but still not quite satisfactory.

EXAMPLE 8

Preparation of pellets coated with a coating having varying amounts of a hydroxypropylmethylcellulose (HPMC)

Batch No. 23029833 (uncoated pellets) was prepared

Lornoxicam pellet cores were prepared as described in Example 4 and with the same composition.

The release of lornoxicam from the pellet cores was determined by dissolution method III (0.1 N HCl followed by pH 7.3) for 3 hours (i.e. 1 hour at a pH corresponding to the pH of 0.1 N HCl and 2 hours at pH 7.3) and is as follows:

Time	Release (% w/w)
10 min	36.9
1h	37.2
1 + 1 h:	86.4
1 + 2h:	95.7

Thus, the release in 0.1 N HCl is not very high (most of the lornoxicam which releases in 0.1 N HCl is released within the first 10 min) and the release rate is certainly not fast enough to anticipate that lornoxicam is released *in vivo* sufficiently fast to lead to a therapeutic effect.

In the following, two different batches of coated pellets of 100 g each were prepared.

Batch 1 (Batch No. 24029832 – coated pellet cores) :

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100 g pellet cores were coated according to the procedure described in Example 1. The composition of the coating is as follows:

Ingredients	Amount (g)
Inner coat	
Hypromellose (Methocel E5 prem)	11.3
Magnesium stearate	0.6
Talc	5.4
Eudragit NE 30 D	191.7
Purified water	291
Outer coat	
Hypromellose (method E% prem)	4.0
Talc	4.0
Purified water	96.0

The following amount of inner and outer coat was used:

Inner coat: 20.1 g coating solution (corresponding to a dry matter content of approximately 3% w/w of the pellet core weight; the HPMC content corresponds to 15.1% w/w).
Outer coat: 12.5 g coating solution (corresponding to a dry matter content of approximately 1% w/w of the pellet core weight).

Batch 2 (Batch No.. 26029832 – coated pellet cores):

100 g pellet cores were coated as described in Example 1. The composition of the coating is as follows:

Ingredients	Amount (g)
Inner coat	
Hypromelose (Methocel E5 prem.)	3.74
Magnesium stearate	0.17
Talc	1.48

Eudragit NE 30 D	31.9
Purified water	62.7

Outer coat

Hypromellose (method E% prem)	4.0
Talc	4.0
Purified water	96.0

The following amount of inner and outer coat was used:

Inner coat: 20.1 g coating solution (corresponding to a dry matter content of approximately 3% w/w of the pellet core weight; the HPMC content corresponds to 25% w/w).

Outer coat: 12.5 g coating solution (corresponding to a dry matter content of approximately 1% w/w of the pellet core weight).

EXAMPLE 9

Preparation of a quick release granulate containing lornoxicam

Batch No. 972510 (granulate) was prepared.

A granulate containing lornoxicam were prepared by using the ingredients listed in Table 9. The composition of the granulate is essentially the same as that of the pellet cores of Example 7. The granulate was prepared in order to investigate whether it is possible to achieve a faster release of lornoxicam from a granulate than from pellet cores. From the results given below it is seen that the step of preparing pellets from a particulate composition containing lornoxicam has a dramatically decrease on the release rate of lornoxicam from the composition.

Table 9

	Ingredients	Amount (kg)
I	Lornoxicam	2.00
II	Sodium hydrogencarbonate	10.00
III	Cellulose microcristalline	24.00
IV	Calcium hydrogen phosphate anhydrous	27.60
V	Hydroxy Propyl Cellulose	4.00
VI	Low-Substituted Hydroxy Propyl Cellulose	12.00
VII	Purified water	27.00
VIII	Ethanol 96 %	9.00
IX	Calcium stearate	0.40

Ingredients II, III IV, V and VI were added to a Diosna intensive mixer and mixed for 1 min with the impeller speed I and chopper speed I. Out of this mixture, 10 kg was added the ingredient I by sieving through a Quadro Comil U20 with the sieve 062R in the following way: A part of the 10 kg mixture was sieved followed by ingredient I, whereafter the remaining of the 10 kg mixture was sieved. Ingredient I was not added to the mixture and mixed in the Diosna mixer for approximately 1 min.

A mixture of ingredient VII and VIII was added to the Diosna mixer, whereafter the granulation was started for 6 min with impeller speed I and with no use of the chopper.

After the granulation, the granulate was dried in a fluid bed until the outlet temperature had reached approximately 50°C and water content was below 1.0%, determined as LOD (Loss on Drying) when a sample of approximately 10 g was heated to a temperature of 70°C in 30 min. The granulate was sieved through a 0.71 sieve using a Frewitt siever. Oversized material was discarded.

Ingredient IX was sieved in the Quadro Comil with a sieve 062R and an equal amount of the granulate described above was added and mixed. This mixture was mixed with the remaining of the granulate in the Diosna mixer for 25 sec with an impeller speed of I and without using the chopper.

This mixture was compressed into a 9,5 mm concave tablets with a hardness of 80 to 100 N (the compression of the granulate was performed in order to avoid any of the problems which could arise during dissolution testing of a granulate and which are related to such bad wetting properties of a granulate that the granulate would float on the top of the dissolution medium giving rise to a *in vitro* unsatisfactory release of lornoxicam. However, later results have shown that granulates prepared in accordance with the above have suitable wetting properties, i.e. the final step of compression before dissolution testing is not necessary.

The dissolution of tablet cores was determined by the dissolution method II (0.07 N HCl) and is as follows:

Time	Release (% w/w)
20 min	100.6

The disintegration time of the tablets tested was at the most about 5 min. Thus, the dissolution rate of the granulate is expected to be of the same or quicker order of magnitude.

The release data given above are most surprising and give evidence that a fast release fraction containing a drug substance which is almost insoluble under acidic conditions can only be obtained if the composition is designed to a very fast release. In other words, application of traditionally prepared granulates and/or compositions made from such traditional granulates or particulate formulations do not seem to release the drug substance sufficiently fast under acidic conditions as those prevailing in the stomach. Accordingly, such traditional compositions are expected to release only a minor amount of the drug substance in the stomach and to release the remaining amount of lornoxicam in the intestines, i.e. after the composition reaches the intestines 1-3 hours after intake.

Compared with the dissolution data given in Example 7 a dramatically increase in dissolution rate is observed for the granulate compared with the pellet cores. Thus, in order to achieve a very fast release of lornoxicam from a composition it seems as if the fast fraction advantageously may be constituted by a granulate rather than uncoated pellet cores or film-coated pellet cores.

Conclusion with respect to Examples 1-9

In the preceding examples it has been shown that pellets cores cannot release lornoxicam very quickly at pH 7,4 unless a surfactant is added (Examples 2 and 5), even though lornoxicam is soluble at pH 7,4. When a surfactant, e.g. polysorbate 20, was added the release at pH 7,4 was acceptable from the point of view that the core can enter an once daily formulations without significantly controlling the dissolution rate (Examples 1, 3 and 4). This control should ideally be taken care of by the applied lacquer.

When these pellet cores were analyzed with respect to dissolution behaviour under acidic conditions in which lornoxicam is only slightly soluble a satisfactory release was not obtained even if a surfactant was used (Examples 6 and 8). Therefore, another kind of subunits have to be used for the relatively fast releasing fraction. Subunits in the form of a granulate and with the composition as described in Example 9 seem to give a satisfactory fast release. However, subunits with the same formulation as in Example 9, but in the form of pellet cores, will not give a satisfactory release rate in acidic conditions as shown in Example 7.

EXAMPLE 10

Preparation of a composition containing a mixture of uncoated and coated pellet cores

The following example illustrate the dissolution behaviour of a composition containing a mixture of uncoated and coated pellet cores. The uncoated pellets are intended to simulate a fast release fraction and the coated pellets are intended to simulate a delayed release fraction.

Coated pellets obtained according to Example 1 were mixed with pellet cores obtained according to Example 4 and the final composition contained 40% of uncoated pellet cores and 60% coated pellets (the percentage is given as % w/w of the total dose of lornoxicam in the composition, i.e. the uncoated fraction accounts for 40% w/w of the total content of lornoxicam whereas the coated fraction accounts for 60% w/w of the

total content of lornoxicam. A unit dosage form of the composition contains 8 mg of lornoxicam.

The dissolution test was carried out according to dissolution method III. The following dissolution data were obtained:

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Time (h)	11029831 (uncoated fraction) + 05029833 (coated fraction) (5.5/4.3)* Release (% w/w)
0	0
0.5	1.4
1	2.9
2	38.4
3	46.1
4	49.6
5	53.5
6	55.9
7	59
8	61.4
9	64.6
10	67.2
11	69.2
13	74
14	75.6
15	77.9
16	79.3
17	80.7
18	82.5
19	83.6
20	85.3
21	86.4
22	87
23	88.1
24	89

* (5.5/4.3) relates to the fact that the content of dry matter in the coat is 5.5% w/w and the HPML content is 4.3% w/w.

From the data given above it is seen that only 2.9% w/w lornoxicam is released after 1 hour. Thus, the "fast release fraction", i.e. the uncoated pellets, is not able to release all its content of lornoxicam under acidic conditions and during the first hour of the test. If this was the case, a release of about 40% is to be expected after 1 hour.

A dramatically increase in dissolution is observed after 2 hours reflecting the pH change of the dissolution medium 1 hour after the start of the test. Furthermore, a retardation of the release of lornoxicam is observed at pH 7.4 compared with the uncoated pellets cores, i.e. the coating is in control of the release rate. However, a composition containing a mixture of uncoated and coated pellets does not seem to enable a fast release of lornoxicam. Therefore, the fast release fraction has to been manipulated in some way in order to release the active substance (lornoxicam) faster).

EXAMPLE 11

Preparation of a composition containing a mixture of a quick release granulate and a delayed release fraction of coated pellet cores

The composition described below was prepared in order to investigate the influence on the overall release rate of the granulate prepared in Example 9 which seems to have favourable properties with respect to a quick and very fast release of lornoxicam even under acidic conditions.

Coated pellets obtained according to Example 4 were mixed with a granulate obtained according to Example 9, where the mixture contained 40% w/w of the total dose of lornoxicam in the form of the granulate and the remaining 60% w/w of the total dose of lornoxicam was in the form of coated pellets (the concentration of lornoxicam in the granulate is about 2-3 % w/w and about 9% w/w in the uncoated pellets). The dissolution test was carried out according to dissolution method III. The following dissolution data was obtained:

Time (h)	972510 (granulate) +20029832 (coated pellets) (3/4.3) Release (% w/w)
0	0
1	37.2
2	41.3
3	44.6
4	48.2
5	51.3
6	53.9
7	57
8	59.6
9	61.8
10	64.7
11	66.9
12	69.4
13	71.6
14	73.6
15	75.7
16	77.6
17	79.5
18	81.2
19	82.9
20	84.4
21	86
22	87.4
23	88.5
24	89.8

From the dissolution data given above, a fast release of lornoxicam is observed which is ascribed to the influence of the lornoxicam granulate.

In contrast to the results obtained in Example 10 a release of about 40% w/w of lornoxicam is observed after 1 hours. Thus, the above example gives evidence that a manipulation of the composition of the fast release fraction is necessary in order to achieve a suitable release even at a low pH. Furthermore, a delayed release is observed with respect to the coated pellets fraction.

EXAMPLE 12

Investigation of the controlled release lacquer composition on the overall dissolution rate

Coated pellets obtained according to Example 8 (batch 1, 15% w/w HPMC in the coat was mixed with granulate obtained according to Example 9. The mixture contained 40% w/w of the total dose of lornoxicam in the form of the granulate, whereas the remaining 60% w/w of lornoxicam was in the form of coated pellets. The dissolution test was carried out according to dissolution method III. The following dissolution data was obtained:

Time (h)	972510 (granulate) + 24029832 (coated pellets) (3/15.1) Release (% w/w)
0	0
0.5	35.7
1	35.7
2	43.2
3	50.0
4	55.8
5	60.9
6	66.2
7	70.7
8	74.4
9	78.3
10	81.5
11	84.8
12	87.3
13	89.3
14	91.1
15	92.6
16	93.8
17	95.0
18	95.9
19	96.6
20	97.2
21	97.5
22	97.8
23	98.0
24	97.5

From the dissolution data given above a much faster release of the delayed release fraction is observed compared with the results obtained in Example 11. Thus, the

composition of the coat can be adjusted to a suitable release rate. In this example the content of HPMC in the coat is 15.1% w/w.

EXAMPLE 13

Investigation of the influence of the composition of the controlled release coat on the release rate

Coated pellets obtained according to Example 8 (batch 2) were mixed with a granulate obtained according to Example 9. The mixture contained 40% w/w of the lornoxicam content in the form of the granulate and the remaining 60% w/w in the form of coated pellets. The dissolution test was carried out according to dissolution method III.

The following dissolution data was obtained:

Time (h)	972510 (granulate) + 26029832 (coated pellets) (3/25.0) Release (% w/w)
0	0
0.5	37.3
1	37.3
2	58
3	69.1
4	79.9
5	87.6
6	92.6
7	95.9
8	97.8
9	98.9
10	99.3
11	99.4
12	99.4
13	99.4
14	99.4
15	99.5

After 6 hours 92.6% w/w is released whereas only 69.4% w/w was released in Example 12. Thus, the increase of the concentration of HPMC in the coat (25% in the present example in contrast to 15% in Example 12) has an increasing effect on the release rate of lornoxicam from the composition.

EXAMPLE 14

Determination of release rate of lornoxicam from controlled release pellets

Dissolution data from coated pellets from Examples 1, 4 and 8 (batches 1 and 2) were determined by dissolution method I (pH 7.4). The following data have been obtained.

Time (h)	05029833 (coated pellets) (5.5/4.3) Example 1	20029832 (coated pellets) (3.0/4.3) Example 4	24029832 (coated pellets) (3.0/15.1) Example 8, batch 1	26029832 (coated pellets) (3.0/25.0) Example 8, batch 2
0	0	0	0	0
0.5	6.9	10.1	17.3	32.7
1	12.1	16.9	29	52.6
2	20.3	28.5	49.5	82.1
3	28.1	39.7	67.2	96.9
4	35.4	50	81.6	101.9
5	42	58.9	91.5	102.9
6	49.1	69.1	98.5	103
7	55.2	76.2	102.1	103.2
8	60.7	82.2	103.9	102.9
9	65.6	86.9	104.8	102.9
10	69.9	90.5	105.2	103.1
11	73.7	93.4	105.5	102.9
12	77.2	93.4	105.5	
13	80.3	95.2	105.8	
14	82.6	97.7	105.5	
15	85	97.9	105.8	
16	87.1	98	105.8	
17	88.6	98.7	105.9	
18	89.9	98.8	105.9	
19	91.2	99	105.8	

The data are also presented in Figure 3. Comparison of the results obtained from the composition of Example 1 with that of Example 4 illustrates that the thickness of the CR (controlled release) coat influences the release rate in such a manner that a thinner coat leads to a more rapid release. The influence of HPMC as an example of a substance which is capable of forming pores in the coat on the release rate is illustrated by the release rate of the two different batches of Example 8 and the results reveal an increasing release rate when the concentration of HPMC increases.

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Conclusion with respect to Examples 10-14

In Examples 10-14, the preparation of a composition containing two fractions of subunits has been presented. One fraction representing a quick release part and the other fraction representing a controlled and delayed release part. Furthermore, the Examples illustrate the influence on the release rate of i) the composition of the quick release fraction and ii) composition and amount of lacquer applied on the controlled release fraction.

EXAMPLE 15

Investigation of the influence of the dissolution medium on the release rate

Dissolution data from coated pellets from Examples 4 and 8 (batch 2) were obtained using dissolution method V (pH 7.3), and are as follows:

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Time (h)	20029832 (coated pellets) (3.0/4.3)[7.3] Example 4	26029832 (coated pellets) (3.0/25.0)[7.3] Example 8, batch 2
0	0	0
0.5	6.2	22
1	10.1	36.1
2	17.3	60.7
3	24.3	79.2
4	30.9	90.7
5	36.9	96.9
6	42.9	100.1
7	48.2	101.4
8	53.1	101.9
9	57.6	102
10	61.8	102
11	65.7	102
12	69.3	102
13	72.4	102
14	75.4	102
15	78	102
16	80.3	102
18	84.3	
20	87.3	

The data are compared with the data from Example 14 in Figure 3. An influence of the dissolution medium on the dissolution rate is observed, i.e. the choice of dissolution method is important (not only with respect to pH but also with respect to factors like, e.g., ionic strength, osmotic pressure etc.).

EXAMPLE 16

Investigation of the influence of a pre-treatment in 0.1 N hydrochloric acid on the dissolution rate at pH 7.4

Dissolution data from coated pellets from Example 4 and Example 8 (batch 2) was determined by dissolution method I (pH 7.4) and method IV (1hour at a pH corresponding to 0.1 N HCl and then at pH 7.4) and are as follows:

Time (h) in pH 7.4	26029832 (3,0/25)(HCl/7,4) Example 8, batch 2 Dissolution method IV	20029832 (3,0/4,3)(HCl/7,4) Example 4, Dissolution method IV	20029832 (3,0/4,3) Example 8 batch 2 Dissolution method I	26029832 (3,0/25,0) Example 4, Dissolution method I
0	0	0	0	0
0.5			10.1	32.7
1	47.6	16.9	16.9	52.6
2	77.5	29.1	28.5	82.1
3	92.4	39.6	39.7	96.9
4	98.1	48.3	50	101.9
5	100.2	56.9	58.9	102.9
6	100.6	64.8	69.1	103
7	100.6	71.6	76.2	103.2
8	100.7	77	82.2	102.9
9			86.9	102.9
10		85.7	90.5	103.1
11		88.8	93.4	102.9
12		91.3	93.4	
13		93.4	95.2	
14		94.8	97.7	
15		96	97.9	
16		97	98	
17		97.6	98.7	
18		98.3	98.8	
19		98.6	99	

The dissolution results from Example 16 reveal that a pre-treatment with acid does not have any significantly influence on the rate of release from the delayed release fraction, i.e. the coated pellets fraction.

In Figure 4 the data are presented and in order to make a proper comparison possible, the release data obtained by dissolution method IV have been displaced by 1 hour corresponding to the time period for treatment in 0.1 N HCl. Thus, in Figure 4, the zero setting for all compositions is when the dissolution medium has a pH of 7.4. The observed differences with respect to the dissolution of lornoxicam from Example 1 and 4, respectively, are not significant and are within the standard deviation observed.

Conclusion with respect to Examples 15 and 16

The results from Examples 15 and 16 have shown that coated pellets have the same release rate independent on whether a pre-treatment in acid has been included or not whereas a change in the dissolution method (from method I to method V) has a significant influence on the release rate.

EXAMPLE 17

Investigation on the influence of dose on the dissolution rate

In this Example the dissolution profiles of a dose of 16 mg of lornoxicam are compared to a dose of 8 mg of lornoxicam. Dissolution profiles are obtained according to dissolution method III.

Time (h)	972510+24029832 8 mg Example 12 8 mg lornoxicam pr. capsule	972510+24029832 Reanalysis of Example 12 (new sample) 8 mg lornoxicam pr. capsule	972510+24029832 Reanalysis of Example 12 (new sample) 16 mg lornoxicam pr. capsule
0	0	0	0
1	35.7	36.2	35.3
2	43.2	47	46.3
3	50.0	55.9	55
4	55.8	63.9	61.7
5	60.9	70.6	67.1
6	66.2	77.4	73.1
7	70.7	83	77.1
8	74.4	87.1	81.4
9	78.3	91.3	85.5
10	81.5	94.2	90.5
11	84.8	95.9	91.9
12	87.3	97.8	93.9
13	89.3	98.7	95.7
14	91.1	99	96.7
15	92.6	99.9	97.7
16	93.8	99.9	98.1
17	95.0	99.7	99
18	95.9	100.1	99.1
19	96.6		
20	97.2		
21	97.5		
22	97.8		
23	98.0		
24	97.5		

Data are presented in Figure 5 and the curves show that the dose is without any significant influence on the release rate. In Figure 5 a target profile calculated for

lornoxicam has been included and it is seen that the compositions tested have profiles very close to the target profile.

EXAMPLE 18

Investigation on whether a plain granulate quickly releases an NSAID substance

A granulate containing naproxen was prepared using the ingredients listed in Table 10. The granulate was prepared in order to investigate whether a plain granulate like the one disclosed in EP-A-0 438 249A1 (ELAN Corporation P.L.C.) releases naproxen quickly (as defined herein) when the dissolution testing is done according to dissolution method II (n = 2) described herein. No standards were used and, accordingly, a literature value for E (1%, 1 cm) = 63 was used to calculate the content in the samples. The composition of the granulate corresponds to the one disclosed in Example 1 of EP-A-0 438 249A1 (ELAN Corporation P.L.C.).

Table 10

Ingredients	Amount (g)
Naproxen	232.0
Polyvidone 30	7.2
Isopropanol	65.7

Naproxen and polyvidone 30 were mixed in a lab scale Kenwood mixer for 3 min. The mixture was granulated by slowly adding the isopropanol over a period of 2 min and the mixing was continued for 1 min. Then the granulate was dried on trays at 50 °C for 12 hours. Thereafter half of the granulate was sieved through a 500 µm sieve and the other half of the granulate was sieved through a 1000 µm sieve. Oversized material was discarded in both cases. The thus obtained two granulates were tested according to dissolution method II described herein.

Batch No. 26089831: 500 µm sieved granulate in an amount corresponding to a 150 mg tablet. In the following is given the results from the dissolution test.

Time (h)	Release (dissolved naproxen) % w/w
0	0
0.5	15
1	16.1
1.5	16.5
2	17.6

Batch No. 26089831: 1000 µm sieved granulate in an amount corresponding to a 150 mg tablet. In the following is given the results from the dissolution test.

Time (h)	Release (dissolved naproxen) % w/w
0	0
0.5	11.4
1	13.4
1.5	14.2
2	15.7

From the results given above, it is clear that such plain formulations do not release the NSAID substance very fast and, accordingly, such formulations or compositions do not fall under the definition of quick release defined herein (i.e. that at least about 50% of the NSAID substance is released within the first 20 min of the dissolution test).

CLAIMS

1. An oral pharmaceutical modified release multiple-units composition in unit dosage form for administration of a therapeutically and/or prophylactically effective amount of a non-steroid anti-inflammatory drug substance (an NSAID substance), a unit dosage form comprising at least two NSAID-containing fractions,

i) a first NSAID-containing fraction of multiple-units for quick release of the NSAID substance, and

ii) a second NSAID-containing fraction of multiple-units for extended release of the NSAID substance,

the first fraction which - when subjected to dissolution method II as defined herein employing 0.07 N HCl as dissolution medium - releases at least 50% w/w of the NSAID substance present in the fraction within the first 20 min of the test,

the second fraction being in the form of coated delayed release multiple units for extended release of the NSAID substance.

2. A composition according to claim 1, wherein the first fraction – when subjected to dissolution method II as defined herein employing 0.07 N HCl as dissolution medium – releases at least 55% w/w such as, e.g., at least about 60% w/w, at least about 65% w/w, at least about 70% w/w, at least about 75% w/w or at least about 80% w/w of the total NSAID substance present in the first fraction within the first 20 min of the test.

3. A composition according to claim 1 or 2, wherein the quick *in vitro* release and the extended *in vitro* release being adapted so that the first fraction is substantially released when the release from the second fraction is initiated corresponding to at least 50% w/w release of the NSAID substance contained in the first fraction at the time when at the most 15% w/w such as at the most 10% w/w or at the most 5% w/w of the NSAID substance contained in the second fraction is released as measured by the dissolution method III defined herein.

4. A composition according to any one of the preceding claims, wherein the NSAID substance contained in the first fraction has a pK_a value between from about 3.0 to about 5.5 and the first fraction is in the form of uncoated units.

5. A composition according to any one of the preceding claims, wherein the NSAID substance has a solubility in 0.1 N hydrochloric acid at room temperature of at the most about 0.5% w/v such as, e.g. at the most about 0.1% w/v, at the most about 0.05% w/v, at the most about 0.03% w/v, at the most about 0.01% w/w, at the most about 0.007% w/v, at the most about 0.005% w/v, at the most about 0.003% w/v, at the most about 0.002% w/v or at the most about 0.001% w/v.

6. A composition according to any one of claims 1-3, wherein the NSAID substance contained in the first fraction has a pK_a value of at least 5.0 such as at least about 5.5.

7. A composition according to claim 6, wherein the first fraction is present in the form of coated units.

8. A composition according to any one of claims 1-3 or 6-7, wherein the NSAID substance has a solubility in 0.1 N hydrochloric acid at room temperature of at least about 0.1% w/v such as e.g. at least about 0.5% w/v or at least about 1% w/v.

9. A composition according to any one of the preceding claims intended for administration once or twice daily.

10. A composition according to any one of the preceding claims for the administration of a therapeutically and/or prophylactically effective amount of an NSAID substance to obtain both a relatively fast onset of the therapeutic effect and the maintenance of therapeutically active plasma concentration for a relatively long period of time, a unit dosage of the composition comprising at least two fractions as follows:

a first fraction of quick release multiple-units for relatively quick release *in vivo* of an NSAID substance to obtain a therapeutically and/or prophylactically active plasma concentration within a relatively short period of time, and

a second fraction of coated modified release multiple-units for extended release *in vivo* of an NSAID substance to maintain a therapeutically and/or prophylactically active plasma concentration in order to enable dosing once or twice daily,

the formulation of the first and the second fractions, with respect to release therefrom and with respect to the ratio between the first and the second fraction in the unit dosage, being adapted so as to obtain:

a relative quick *in vitro* release of the NSAID substance from the first fraction of quick release multiple-units, as measured by the dissolution method II as defined herein,

an extended *in vitro* release of the NSAID substance from the second fraction of extended release multiple-units relative to the *in vitro* release of the first fraction of the NSAID substance, as measured by e.g. the dissolution method III as defined herein,

the quick release and the extended *in vitro* release being adapted so that the first fraction is substantially released when the release from the second fraction is initiated corresponding to at least 50% w/w release of the NSAID substance contained in the first fraction at the time when at least about 15% w/w such as, e.g., at least about 10% w/w or at least about 5% w/w of the NSAID substance contained in the second fraction is released as measured by the dissolution method III defined herein.

11. A composition according to any one of the preceding claims, wherein the NSAID substance is selected from the group consisting of lornoxicam, diclofenac, nimesulide, ibuprofen, piroxicam, piroxicam (betacyclodextrin), naproxen, ketoprofen, tenoxicam, aceclofenac, indometacin, nabumetone, acemetacin, morniflumate, meloxicam, flurbiprofen, tiaprofenic acid, proglumetacin, mefenamic acid, fenbufen, etodolac, tolfenamic acid, sulindac, phenylbutazone, fenoprofen, tolmetin, acetylsalicylic acid, dexibuprofen, and pharmaceutically acceptable salts, complexes and/or prodrugs thereof and mixtures thereof.

12. A composition according to any one of the preceding claims, wherein the NSAID substance in the first fraction is the same as the NSAID substance contained in the second fraction.

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13. A composition according to any one claims 1-11, wherein the NSAID substance in the first fraction is different from the NSAID substance contained in the second fraction.

14. A composition according to any one of the preceding claims, wherein the NSAID substance in the first fraction is lornoxicam.

15. A composition according to any one of the preceding claims, wherein the NSAID substance in the second fraction is lornoxicam.

16. A composition according to any one of the preceding claims comprising a further active drug substance.

17. A composition according to any one of the preceding claims, wherein a further active drug substance is included in at least one of the first and second fraction.

18. A composition according to claim 16 or 17, wherein the further active drug substance is an antidepressant, an opioid, a prostaglandine analog (e.g. misoprostol), a glucocorticosteroid, a cytostaticum (e.g. methotrexate), a H_2 receptor antagonist (e.g. cimetidine, ranitidine), a proton pump inhibitor (e.g. pantoprazole, omeprazole, lansoprazole) and/or an antacidum.

19. A composition according to claim 16 or 17, wherein the further active drug substance is paracetamol, penicillamine, sulfasalazine and/or auranorfin.

20. A composition according to any one of the preceding claims, wherein the NSAID substance is lornoxicam.

21. A composition according to any one of the preceding claims, wherein the quick release multiple-units of the first fraction have a mean particle size of at the most about 250 µm such as, e.g. at the most about 240 µm, at the most about 230 µm, at the most about 220 µm, at the most abut 210 µm, at the most about 200 µm, at the most about 190 µm, at the most about 180 µm, at the most about 175 µm, at the most about 150 µm, at the most about 125 µm, at the most about 100 µm, at the most about 90 µm or at the most about 80 µm.

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22. A composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the first fraction of quick release multiple-units provides within 1 hour a release as defined by the dissolution method II defined herein of at least 50% w/w, such as, e.g., at least about 60% w/w, at least about 70% w/w, at at least about 80% w/w, at least about 85% w/w at least about 90% w/w or at least about 95% w/w of the NSAID substance.

23. A composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the second fraction of extended release multiple-units provides within 1 hour a release as defined by the dissolution method III defined herein in the range of 0%-30% w/w, such as in the range of 0%-20% w/w, in the range of 0%-10% w/w, such as at the most about 5% w/w of the NSAID substance.

24. A composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the second fraction of extended release multiple-units provides within 3 hours a release as defined by the dissolution method III defined herein in the range of about 10%-70% w/w, such as, e.g., in the range of about 10%-60% w/w, in the range of about 12%-50% w/w, in the range of 14%-45% w/w, in the range of about 15%-30% w/w, in the range of about 15%-20% w/w such as, e.g., about 17% w/w of the NSAID substance.

25. A composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the second fraction of extended release multiple-units provides within 6 hours a release as defined by the dissolution method III defined herein in the range of about 35%-95% w/w, such as, e.g., in the range of about 50%-90% w/w, in the range of about 50%-80% w/w, in the range of 50%-75% w/w, in the range of about 50%-60% w/w, in the range of about 53%-59% w/w such as, e.g. about 56% w/w of the NSAID substance.

26. A composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the second fraction of modified release multiple-units provides within 9 hours a release as defined by the dissolution method III defined herein in the range of about 50%-100% w/w, such as, e.g., in the range of about 60%-98% w/w, in the range of about 65%-95% w/w, in the range of about 70%-90% w/w, in the range of about 70%-80% w/w such as, e.g., about 76% w/w of the NSAID substance.

27. A composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the first and second fractions are adapted so that the first fraction is substantially released when the release from the second fraction is initiated corresponding to at least 50% w/w of the first fraction at the time at the most about 15% w/w such as, e.g., at the most about 10% w/w or at the most about 5% w/w of the second fraction is released as measured by the dissolution method III defined herein.

28. A composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the first and second fractions are adapted so that the first fraction is substantially released when the release from the second fraction is initiated corresponding to at least 70% w/w release of the first fraction at the time at the most about 20% w/w such as, e.g. at the most about 15% or at the most about 10% w/w of the second fraction is released as measured by the dissolution method III as defined herein.

29. A composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the composition provides within 1 hour a release of the NSAID substance from the composition in the range of about 5-50% w/w, such as, e.g., in the range of about 5-45% w/w, in the range of about 15-40% w/w, in the range of about 20-35% w/w such as about 29% w/w, as defined by the dissolution method III as defined herein.

30. A composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the composition provides within 3 hours a release as defined by the dissolution method III as defined herein in the range of about 20-80% w/w, such as, e.g., in the range of about 25-70% w/w, in the range of about 30-60% w/w, in the range of about 35-55% w/w such as about 42% w/w.

31. A composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the composition provides within 6 hours a release as defined by the dissolution method III defined herein in the range of about 40-98% w/w, such as, e.g., in the range of about 50-95% w/w, in the range of about 60-90% w/w, in the range of about 60-85% w/w, most preferred in the range of about 60-83% w/w such as about 69% w/w.

32. A composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the composition provides within 9 hours a release as defined by the dissolution method III as defined herein in the range of about 50-100% w/w, such as, e.g., in the range of about 60-99% w/w, in the range of about 70-98% w/w, in the range of about 70-97% w/w, in the range of about 75-96% w/w, in the range of about 80-96% w/w, about 80-85% w/w such as about 83% w/w.

33. A composition according to any one of the preceding claims, wherein the percentage of NSAID substance in the first fraction is in the range of about 5%-50% w/w such as, e.g., in the range of about 10%-45% w/w, in the range of about 15%-45% w/w, in the range of about 20%-40% w/w, in the range of about 25%-40% w/w, in the range of about 25%-35% w/w such as, e.g., about 30% w/w, calculated on the total amount of NSAID substance in the composition.

34. A composition according to any one of the preceding claims, wherein the percentage of NSAID substance in the second fraction is in the range of about 30%-99% w/w such as, e.g. in the range of about 40%-98% w/w, in the range of about 45%-95% w/w, in the range of about 50%-95% w/w, in the range of about 55%-85% w/w, in the range of about 60%-80% w/w, in the range of about 60%-75% w/w, in the range of abut 65%-75% w/w such as, e.g., about 70% w/w, calculated on the total amount of NSAID substance in the composition.

35. A composition according to any one of the preceding claims, wherein the multiple-units of the second fraction are coated cross-sectionally substantially homogeneous pellets.

36. A composition according to any one of the preceding claims, wherein the multiple-units of the first fraction are cross-sectionally substantially homogeneous pellets.

37. A composition according to any one of the preceding claims, wherein the first fraction results in a peak plasma concentration of NSAID substance which is substantially the same as the peak plasma concentration resulting from the second fraction.

38. A composition according to any one of claims 1-36, wherein the first fraction results in a peak plasma concentration of the NSAID substance which is higher than the peak plasma concentration resulting from the second fraction.

39. A composition according to any one of claims 1-36, wherein the first fraction results in a peak plasma concentration of the NSAID substance which is lower than the peak plasma concentration resulting from the second fraction.

40. A composition according to any one of the preceding claims, wherein the first fraction results in a therapeutically active plasma concentration of the NSAID substance until the extended release of an NSAID substance from the second fraction of modified release multiple-units contributes to the maintenance of a therapeutically active plasma concentration of the NSAID substance.

41. A composition according to any one of the preceding claims, wherein the extended release coating of the second fraction is substantially water-insoluble, but water-diffusible and substantially pH-independent.

42. A composition according to any one of the preceding claims, wherein the first fraction is coated units and the coating is a substantially water-insoluble, but water-diffusible and substantially pH-independent coating.

43. A composition according to any one of the preceding claims, wherein a unit dosage of the composition comprises from about 1 to about 32 mg of the NSAID substance.

44. A composition according to any one of claims 1-42, wherein a unit dosage comprises from about 1 mg to about 1.6 g such as from about 1 mg to about 1.2 g of the NSAID substance.

45. A composition according to any one of claims 1-42, wherein a unit dosage comprises from about 50 mg to about 1.1 g of the NSAID substance.

46. A composition according to any one of claims 1-42, wherein a unit dosage comprises from about 100 mg to about 1.0 g of the NSAID substance.

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47. A composition according to any one of claims 1-42, wherein a unit dosage comprises from about 200 mg to about 900 mg of the NSAID substance.

48. A composition according to any one of claims 1-42, wherein a unit dosage comprises from about 300 mg to about 800 mg of the NSAID substance.

49. A composition according to any one of the preceding claims comprising a unit dosage for the administration of the therapeutically effective amount of the NSAID substance twice daily.

50. A composition according to any one of claims 1-48 comprising a unit dosage for the administration of the therapeutically effective amount of the NSAID substance once daily.

51. A composition according to any one of the preceding claims wherein the unit dosage of the composition is in the form of a capsule, tablet or sachet.

52. A composition according to any one of the preceding claims, wherein the NSAID substance is lornoxicam and the unit dosage of the composition contains 4, 8, 12, 16, 20, 24, 28, 32 or 36 mg of lornoxicam.

53. A process for the preparation of a unit dosage form of an oral pharmaceutical modified release composition according to any one of the preceding claims, the process comprising incorporating into the unit dosage form at least two fractions as follows: a first fraction of quick release multiple-units for relatively quick release *in vivo* of an NSAID substance to obtain a therapeutically or prophylactically active plasma concentration within a relatively short period of time, and a second fraction of coated extended release multiple-units for extended release *in vivo* of an NSAID substance to maintain a therapeutically active plasma concentration in order to enable dosing once or twice daily,

the formulation of the first and the second fractions, with respect to release therefrom and with respect to the ratio between the first and the second fraction in the unit dosage, being adapted so as to obtain:

a relative quick *in vitro* release of the NSAID substance from the first fraction of quick release multiple-units, as measured by the dissolution method II defined herein,

an extended *in vitro* release of the NSAID substance from the second fraction of extended release multiple-units relative to the *in vitro* release of the first fraction of the NSAID substance, as measured by the dissolution method III as defined herein, the quick release and the extended *in vitro* release being adapted so that the first fraction is substantially released when the release from the second fraction is initiated corresponding to at least about 50% w/w release of the NSAID substance contained in the first fraction at the time when at the most about 15% w/w such as, e.g., at the most about 10% w/w or at the most about 5% w/w of the NSAID substance contained in the second fraction is released as measured by the dissolution method III as defined herein.

54. A method for treating a patient suffering from pain and/or inflammatory conditions and/or the like comprising administering to the patient an effective amount of an NSAID substance in the form of a composition according to any one of claims 1-52 once or twice daily.

55. A method for administering a therapeutically and/or prophylactically effective amount of an NSAID substance to a patient in need thereof to obtain both a relatively fast onset of the therapeutic effect and the maintenance of therapeutically active plasma concentration for a relatively long period of time, the method comprising administering once or twice daily a unit dosage of a composition comprising at least two fractions as follows:

a first fraction of quick release multiple-units for relatively quick release *in vivo* of an NSAID substance to obtain a therapeutically and/or prophylactically active plasma concentration within a relatively short period of time, and

a second fraction of coated modified release multiple-units for extended release *in vivo* of an NSAID substance to maintain a therapeutically and/or prophylactically active plasma concentration.

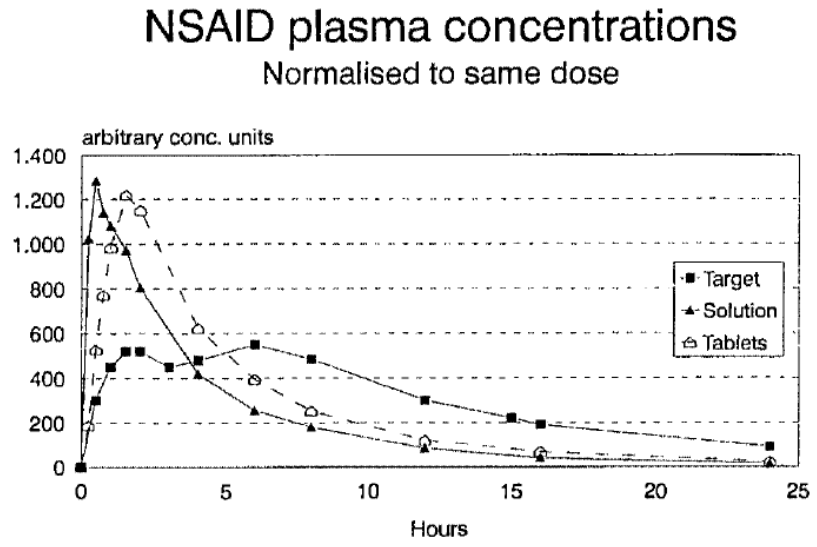

NSAID plasma concentrations
Normalised to same dose
arbitrary conc. units
1.400
1.200
1.000
800
600
400
200
0
0
5
10
15
20
25
Hours
Target
Solution
Tablets

Fig. 1

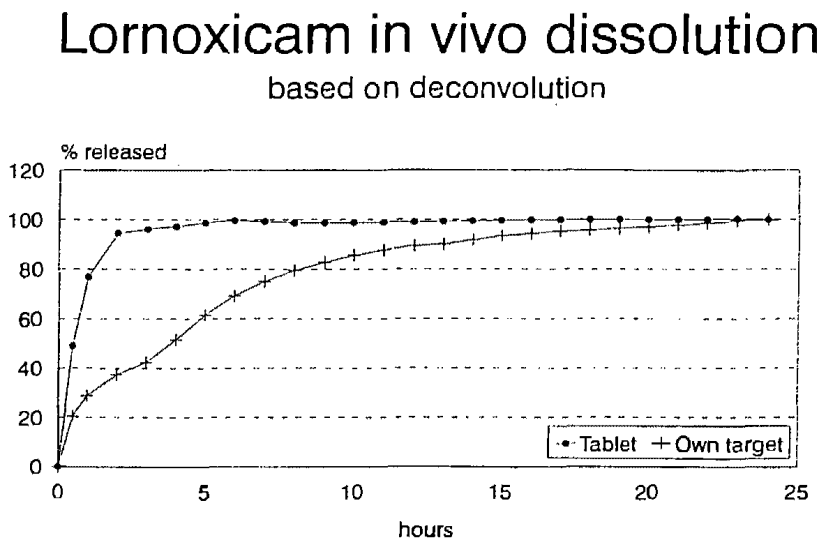

Lornoxicam in vivo dissolution
based on deconvolution
% released
120
100
80
60
40
20
0
0
5
10
15
20
25
hours
Tablet
Own target

Fig. 2

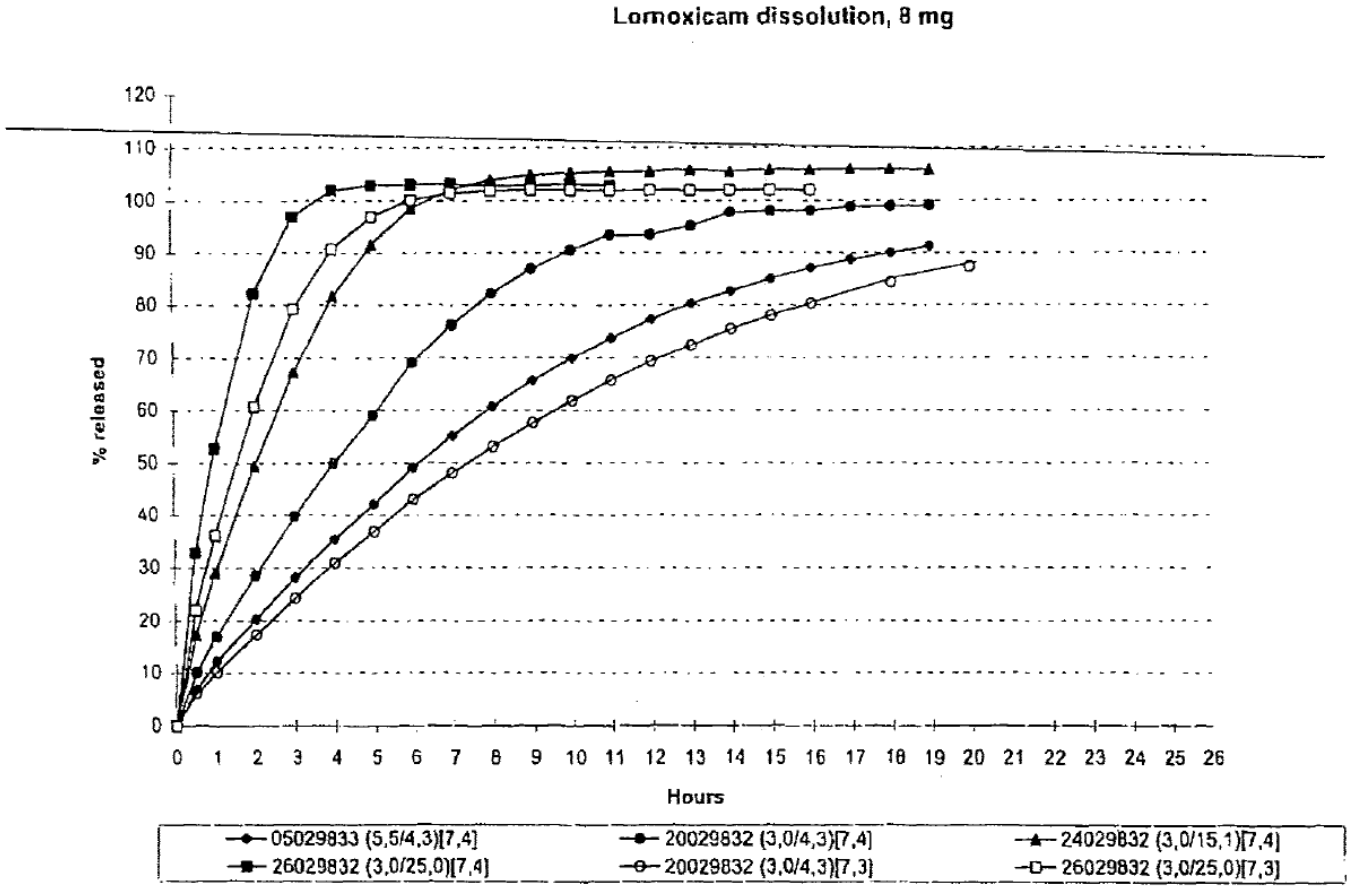

Lornoxicam dissolution, 8 mg
% released
Hours
05029833 (5,5/4,3)[7,4]
20029832 (3,0/4,3)[7,4]
24029832 (3,0/15,1)[7,4]
26029832 (3,0/25,0)[7,4]
20029832 (3,0/4,3)[7,3]
26029832 (3,0/25,0)[7,3]

Fig. 3

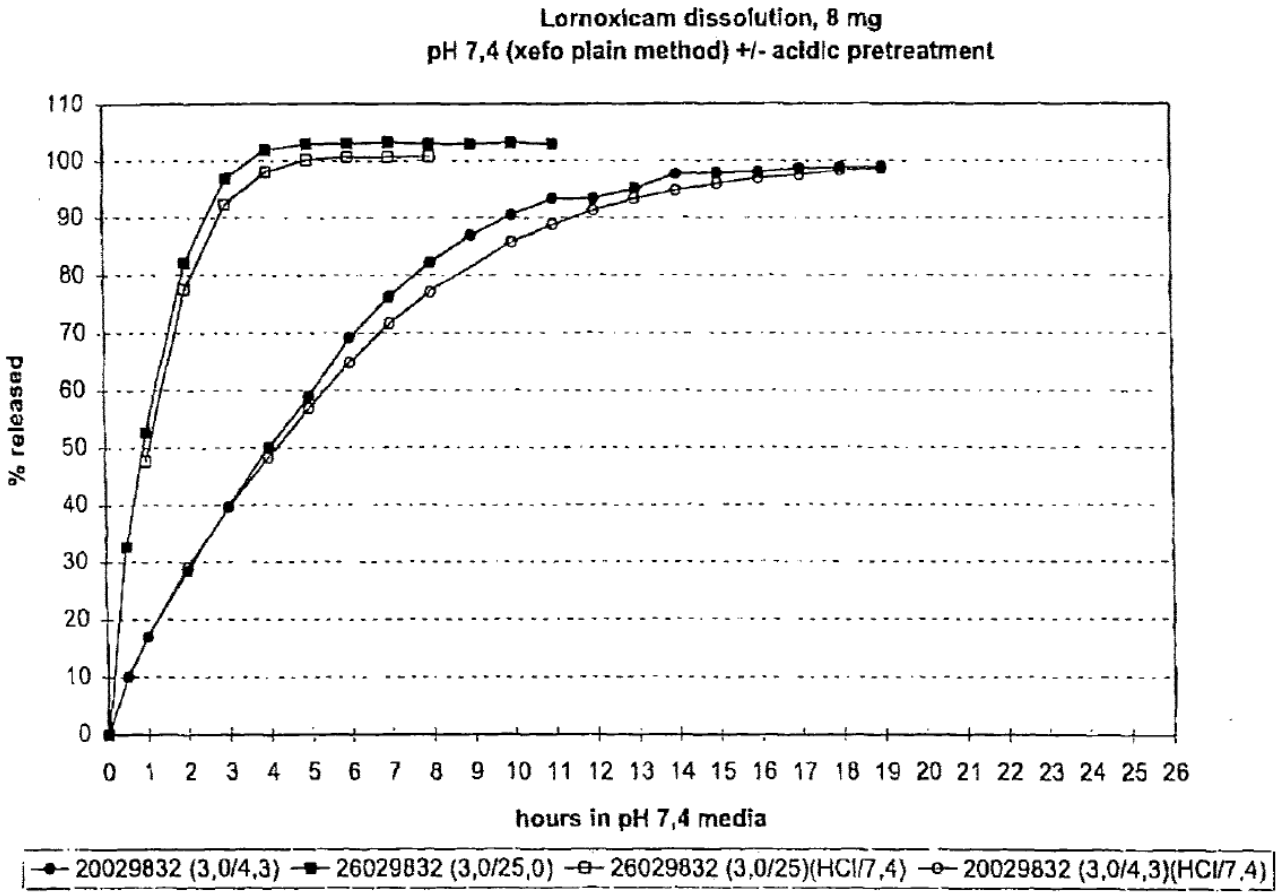


Fig. 4

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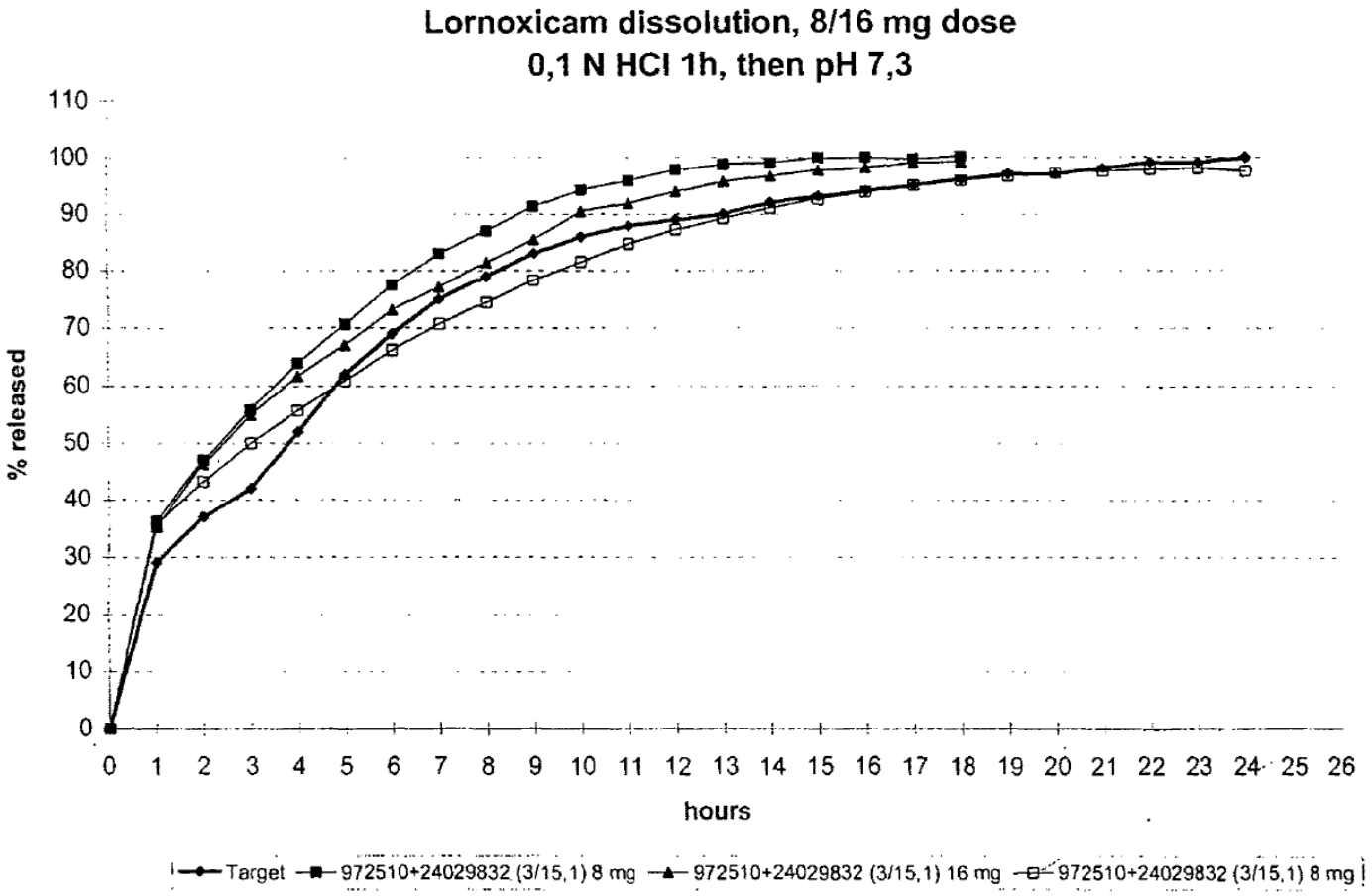

Lornoxicam dissolution, 8/16 mg dose
0,1 N HCl 1h, then pH 7,3
% released
hours
Target
972510+24029832 (3/15,1) 8 mg
972510+24029832 (3/15,1) 16 mg
972510+24029832 (3/15,1) 8 mg

Fig. 5

INTERNATIONAL SEARCH REPORT

Interr ıal Application No
PCT/DK 98/00388

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/20 A61K9/50 A61K31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	US 5 043 167 A (ROTINI LEONE G ET AL) 27 August 1991	1-13, 16-19, 21-51, 53,54
Y	see the whole document	14,15, 20,52

X,Y	EP 0 438 249 A (ELAN CORP PLC) 24 July 1991	1-13, 16-19, 21-51, 53,54
	see the whole document	

Y	US 5 478 577 A (SACKLER RICHARD ET AL) 26 December 1995 see the whole document	1-13

	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 December 1998	21/12/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fischer, W

Form PCT/ISA/210 (second sheet) (July 1992)

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INTERNATIONAL SEARCH REPORT

Interi nal Application No
PCT/DK 98/00388

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 06787 A (DYER ALISON MARGARET ;CSIR (ZA); ROLFES HEIDI (ZA); MERWE THILO LO) 27 February 1997 see abstract see page 5, line 25-29 see page 14, line 1 - line 4	14,15, 20,52
P,X, Y	WO 97 32573 A (NYCOMED DANMARK A S ;SKINHOEJ ANETTE (DK)) 12 September 1997	1-13, 16-19, 21-51, 53,54
L	"L": DOCUMEMENT SO QUOTED SINCE IT CASTS DOUBT ON THE VALIDITY OF THE CONVENTION-PRIORITY CLAIMED see the whole document	

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

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INTERNATIONAL SEARCH REPORT

In..tional application No.
PCT/DK 98/00388

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 54
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 54
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Although claims 54 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Claims Nos.: 54

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. nal Application No
PCT/DK 98/00388

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification: **A61K 31/44, A61P 1/04**	A1	(11) International Publication Number:	**WO 00/71122**
		(43) International Publication Date:	30 November 2000 (30.11.2000)

(21) International Application Number: PCT/US99/11389

(22) International Filing Date: 20 May 1999 (20.05.1999)

(60) Parent Application or Grant
PAR PHARMACEUTICAL, INC. [/]; (). MALCOLM, S., F., Ross [/]; (). MALCOLM, S., F., Ross [/]; (). WITTEKIND, Raymond, R. ; ().

Published

(54) Title: STABILIZED COMPOSITION BASED ON PYRIDINYL-SULFINYL-BENZIMIDAZOLES AND PROCESS
(54) Titre: COMPOSITION STABILISEE A BASE DE PYRIDINYL-SULFINYL-BENZIMIDAZOLE ET PROCEDE ASSOCIE

(57) Abstract

A novel composition comprising a compound of formula(I) wherein R1¿ and R2¿ are same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R6¿ is selected from the group consisting of hydrogen, methyl, and ethyl; and R3¿ and R5¿ are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, ethoxy, methoxyethoxy and ethoxyethoxy; and R4¿ is selected from the group consisting of methoxy, ethoxy, methoxyethoxy and ethoxyethoxy; or a pharmaceutically acceptable acid addition salt thereof, and a compound of formula (II) R7¿CO¿2M where in R7¿ is an organic radical and M is a cation, a pharmaceutical formulation containing the composition, methods of preventing or reducing ulceration of the gastrointestinal tract by anti-inflammatory agents using the composition, and methods of stabilizing the composition are described.

(57) Abrégé

L'invention concerne une nouvelle composition renfermant un composé, ou un sel d'addition acide pharmaceutiquement acceptable de ce dernier, de formule (I) dans laquelle R1¿ et R2¿ sont identiques ou différents, chacun étant sélectionné dans le groupe constitué par hydrogène, alkyle, halogène, carbométhoxy, carboéthoxy, alkoxy, et alcanoyle ; R6¿ est sélectionné dans le groupe constitué par hydrogène, méthyle et éthyle ; R3¿ et R5¿ sont identiques ou différents, chacun étant sélectionné dans le groupe constitué par hydrogène, méthyle, méthoxy, éthoxy, méthoxyéthoxy et éthoxyéthoxy ; R4¿ est sélectionné dans le groupe constitué par méthoxy, éthoxy, méthoxyéthoxy et éthoxyéthoxy. L'invention concerne également un composé de formule (II) R7¿CO¿2M dans laquelle R7¿ est un radical organique et M est un cation, une formulation pharmaceutique renfermant la composition, des méthodes de prévention et de réduction de l'ulcération du tractus gastro-intestinal par des agents anti-inflammatoires contenant la composition, et des méthodes de stabilisation de la composition.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
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PCT

(10) International Publication Number
WO 00/71122 A1

(51) International Patent Classification[7]: A61K 31/44, A61P 1/04

(21) International Application Number: PCT/US99/11389

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(25) Filing Language: English

(26) Publication Language: English

(71) Applicant *(for all designated States except US)*: PAR PHARMACEUTICAL, INC. [US/US]; One Ram Ridge Road, Spring Valley, NY 10577 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: MALCOLM, S., F., Ross [IL/IL]; 4 Pekc'in Street, 62286 Tel Aviv (IL).

(74) Agent: WITTEKIND, Raymond, R.; Frommer Lawrence & Haug LLP, 745 Fifth Avenue, New York, NY 10151 (US).

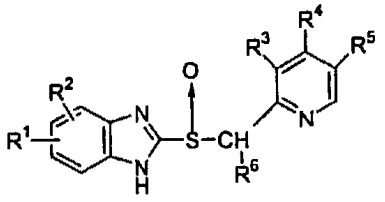
(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW.

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Published:
— *With international search report.*
— *With amended claims.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: STABILIZED COMPOSITION BASED ON PYRIDINYL-SULFINYL-BENZIMIDAZOLES AND PROCESS



(I)

(57) Abstract: A novel composition comprising a compound of formula(I) wherein R^1 and R^2 are same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl, and ethyl; and R^3 and R^5 are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, ethoxy, methoxyethoxy and ethoxyethoxy; and R^4 is selected from the group consisting of methoxy, ethoxy, methoxyethoxy and ethoxyethoxy; or a pharmaceutically acceptable acid addition salt thereof, and a compound of formula (II) R^7CO_2M where in R^7 is an organic radical and M is a cation, a pharmaceutical formulation containing the composition, methods of preventing or reducing ulceration of the gastrointestinal tract by anti-inflammatory agents using the composition, and methods of stabilizing the composition are described.

WO 00/71122 A1

Description

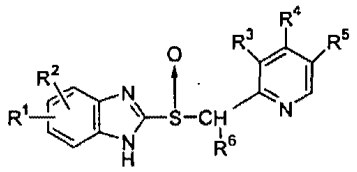
STABILIZED COMPOSITION BASED ON PYRIDINYL-SULFINYL-BENZIMIDAZOLES AND PROCESS

Anti-inflammatory agents, notably agents characterized by the presence of a carboxylic acid group, suffer from a serious side effect, namely, ulceration of the gastrointestinal tract, when administered orally. For example, naproxen, 2-(6-methoxy-2-naphthyl)propionic acid, which is marketed as Naprosyn® in the United States, causes severe ulceration of the stomach and duodenum. Substituted 2-(2-benzimidazolyl)pyridines are known to inhibit gastric acid secretion in mammals, including man. One such compound, 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, omeprazole, which is marketed under the brand name Losec®, is a potent inhibitor of gastric acid secretion and thereby useful for the treatment of peptic ulcer disease. Like the aforementioned anti-inflammatory agents, the 2-(2-benzimidazolyl)pyridines, particularly omeprazole, suffer from a serious defect, namely, instability under physiological conditions. It would thus be desirable to take advantage of the anti-inflammatory properties of the organic carboxylic acids, and at the same time, the gastric acid inhibiting properties of the 2-(2-benzimidazolyl)pyridines, while enhancing the stability of the gastric acid inhibitor. By so doing, a stabilized composition for the treatment of inflammatory disease conditions such as osteoarthritis and rheumatoid arthritis, without the attendant ulceration of the gastrointestinal tract would be available for treatment of inflammation. It has now been found that this goal is achieved when a composition of a 2-(2-benzimidazolyl)pyridines and a salt of an anti-inflammatory organic acid is administered to a patient suffering from inflammatory disease, the salt of the organic

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acid ameliorating the inflammation and stabilizing the antiulcerogenic 2(-2-benzimidazolyl)pyridine.

The present invention relates to a composition comprising a compound of



I

formula I

wherein R^1 and R^2 are same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl; and R^3 and R^5 are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, ethoxy, methoxyethoxy and ethoxyethoxy; and R^4 is selected from the group consisting of methoxy, ethoxy, methoxyethoxy and ethoxyethoxy; or a pharmaceutically acceptable acid addition salt thereof, and a compound of formula II

$$R^7CO_2M \quad II$$

wherein R^7 is an organic radical and M is a cation, useful for the treatment of inflammation with concomitant prevention or reduction of the ulceration of the gastrointestinal tract, and stabilization of the antiulceration compound of formula I. The present invention also relates to a pharmaceutical formulation containing the composition and a method of preparing the formulation.

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Subgeneric to the composition are compositions wherein:

(a) R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is hydrogen; and R^3, R^4 and R^5 are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy and ethoxy; or a pharmaceutically acceptable addition salt thereof;

(b) R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl; R^3 is methyl; R^4 is methoxy; and R^5 is methyl; or a pharmaceutically acceptable acid addition salt thereof;

(c) R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl; R^3 is hydrogen; R^4 is methoxy; and R^5 is methyl, or R^3 is methyl, R^4 is methoxy and R^5 is hydrogen; or a pharmaceutically acceptable acid addition salt thereof;

(d) R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl; $R^3$and R^5 are selected from the group consisting of hydrogen and methoxy; or a pharmaceutically acceptable acid addition salt thereof;

(e) R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and

alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl, and $R^3$and R^5 are methyl; and R^4 is hydrogen; or a pharmaceutically acceptable acid addition salt thereof;

(f) R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl; $R^3$and R^5 are hydrogen; and R^4 is ethoxy, methoxyethoxy or ethoxyethoxy; or a pharmaceutically acceptable acid addition salt thereof.

(g) R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl; R^3, R^4 and R^5 are methyl; or a pharmaceutically acceptable acid addition salt thereof; and

(h) A composition according to claim 1 wherein R^1 is hydrogen, chloro, methyl, ethyl, methoxy, acetyl, carboethoxy or carbomethoxy ; R^2 is hydrogen or methyl; R^6 is hydrogen, methyl or ethyl; $R^3$and R^5 are methyl; and R^4 is methoxy, or in which R^1 is hydrogen, chloro, methyl, ethyl, methoxy, acetyl, carboethoxy or carbomethyl; R^2 is hydrogen, methyl or ethyl; R^4 is methoxy ; and R^3 is methyl R^5 is hydrogen, or R^3 is hydrogen and R^5 is methyl, or a pharmaceutically acceptable acid addition salt thereof.

Preferred compositions are those wherein a compound of the formula I is selected from the group consisting of 2-[2-(4-methoxy)pyridinylmethysulfinyl]-5-acetyl-6-methyl)-benzimidazole, 2-[2-(4-methoxy)pyridinylmethysulfinyl]-4,6-dimethyl)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-

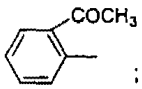
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acetyl-6-methyl)benzimidazole, 2-[2-(4-methoxy)pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)benzimidazole, 2-[2-(4-ethoxy)pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)benzimidazole, 2-[2-(3-methyl-4-methoxy)pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)benzimidazole, 2-[2-(4-methoxy-5-methyl)pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-carbomethoxy)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-acetyl)benzimidazole, 2-[2-(4-methoxy-5-methyl)pyridinylmethysulfinyl]-(5-methoxy)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-methoxy)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-methyl)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinylbenzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridylmethysulfinyl]-(5-chloro)benzimidazole, or a pharmaceutically acceptable addition salt thereof.

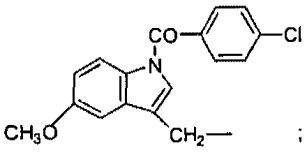
More preferred is one wherein R^1 is hydrogen; R^2 is methoxy; R^3 and R^5 are methyl; R^4 is methoxy; and R^6 is hydrogen which is 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

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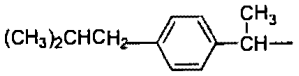
Also subgeneric thereto are compositions where the organic radical is selected from the group consisting of:

(a) 

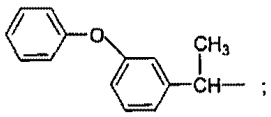
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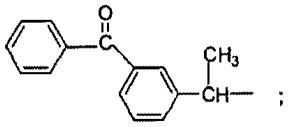
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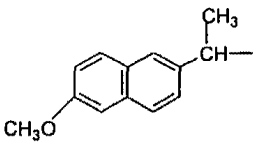
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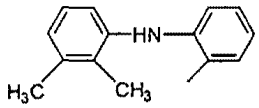
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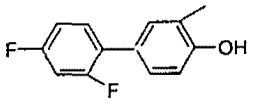
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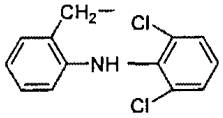
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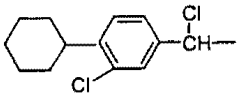
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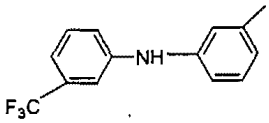
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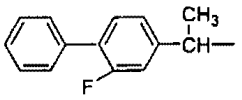
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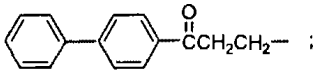
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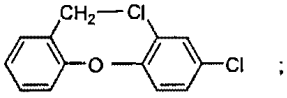
(i)  ;

(j)  ;

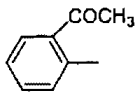
(k)  ;

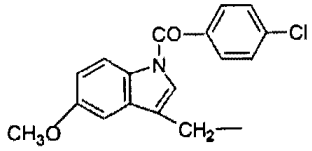
(l)  ;

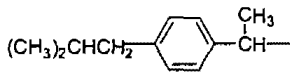
(m)  ;

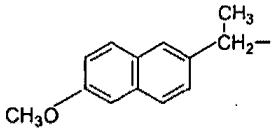
(n)  ;

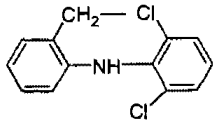
Compositions wherein the organic radical is selected from the group consisting of:

(o)  ;

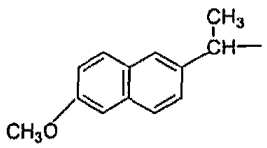
(p)  ;

(q)  ;

(r)  ; and

(s)  are more preferred.

A most preferred composition is one wherein the organic radical is

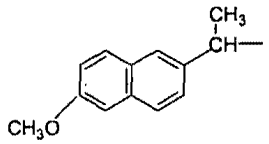


Also subgeneric thereto are:

(a) a composition wherein M is sodium, potassium, magnesium, calcium, or aluminum; and

(b) a composition wherein M is sodium.

A most preferred composition is one wherein R^1 is hydrogen; R^2 is methoxy; R^3 and R^5 are methyl; R^4 is methoxy; R^6 is hydrogen; R^7 is



and M is sodium.

As used through the specification and appended claims, the term "alkyl" refers to a straight or branched chain hydrocarbon radical containing no unsaturation and having 1 to 10 carbon atoms. Examples of alkyl groups are methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 1-pentyl, 3-hexyl, 4-heptyl, 2-octyl, 3-nonyl, 4-decyl and the like. The term "alkanol" refers to a compound formed by a combination of an alkyl group and hydroxy radical. Examples of alkanols are methanol, ethanol, 1- and 2-propanol, 2,2-dimethylethanol, hexanol, octanol, decanol and the like. The term "alkanoic acid" refers to a compound formed by combination of a carboxyl group with a hydrogen atom or alkyl group. Examples of alkanoic acids are formic acid, acetic acid, propanoic acid, 2,2-dimethylacetic acid, hexanoic acid, octanoic acid, decanoic acid and the like. The term "halogen" refers to a member of the family fluorine, chlorine, bromine, or iodine. The term "alkanoyl" refers to the radical formed by removal of the hydroxyl function from an alkanoic acid. Examples of alkanoyl groups are formyl, acetyl, propionyl, 2,2-dimethylacetyl, hexanoyl, octanoyl, decanoyl and the

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like. The term "lower" as applied to any of the aforementioned groups refers to a group having a carbon skeleton containing up to an including 8 carbon atoms.

The compounds of the present invention which lack an element of symmetry exist as optical antipodes may be prepared from the corresponding racemic forms by standard optical resolution techniques, involving, for example, the separation of diastereomeric salts of those instant compounds characterized by the presence of a carboxylic acid group and an optically active base, or by synthesis from optically active precursors.

The present invention comprehends all optical isomers and racemic forms thereof and all geometric isomers of the compounds disclosed and claimed herein. The formulas of the compounds shown herein are intended to encompass all possible geometric and optical isomers of the compounds so depicted.

The 2-(2-benzimidazolyl)pyridines and the methods of preparation thereof are described in U.S. Patent 4,255,431 granted March 10, 1981 to U.K. Junggren and S.E. Sjöstrand, as is their antisecretory inhibitory properties.

The organic carboxylic acids and their anti-inflammatory properties, as well as their ulcerogenic effects are described in U.K. Patent Application GB 2 105 193 A.

The salts of the organic carboxylic acids are known or are prepared by conventional methods, for example, treatment of a carboxylic acid with an alkali metal or alkaline earth metal in a suitable solvent such as alkanol, e.g., methanol, ethanol, 2-propanol, and the like, and aqueous combinations thereof.

The stabilization of a 2-(2-benzimidizolyl)pyridine by a salt of an organic carboxylic acid in an aqueous medium is demonstrated in a conventional assay. In the

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assay, the 2-(2-benzimidazolyl)pyridine is dissolved in water and the stability thereof is determined and compared to that of a solution of a 2-(2-benzimidazolyl)pyridine and a salt of an organic acid in water.

In a specific assay, omeprazole (10 mg) is dissolved in water (100 ml) at room temperature, and samples are removed periodically and assayed for omeprazole by high performance liquid chromatography on a column of Hypersil (250 x 4.6 mm) using 0.02 Mammonium acetate buffer: acetonitrile (65:35). The pressence of omeprazole is detected by ultraviolet spectroscopy at a wavelength of 235 nm.

The results are shown in the table:

Time, hr	Omeprazole in water, %	Omeprazole+Naproxen Na in water, %
0	100	100
2	95.8	97.7
19	69.8	94.9

Effective quantities of the compositions of the invention may be administered to a patient by any of the various methods, for example, orally as in capsule or tablets, parenterally in the form of sterile solutions or suspensions, and in some cases intravenously in the form of sterile solutions. The free base final products, while effective themselves, may be formulated and administered in the form of their pharmaceutically acceptable acid addition salts for purposes of stability, convenience of crystallization, increased solubility and the like.

The active compositions of the present invention may be orally administered, for example, with an inert diluent or with an edible carrier, or they may be enclosed in gelatin capsules, or they may be compressed into tablets. For the purpose of oral

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therapeutic administration, the active compounds of the invention may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, suppositories, chewing gum and the like. These preparations should contain at least 0.5% of active compositions, but may be varied depending upon the particular form and may conveniently be between 4% to about 70% of the weight of the unit. The amount of active compound in such compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present invention are prepared so that an oral dosage unit form contains between 1.0-300 milligrams of active compound.

The tablets, pills, capsules, troches, suppositories and the like may also contain the following ingredients: a binder such as microcystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, cornstarch and the like; a lubricant such as magnesium stearate or Sterotex; a glidant such as colloidal silicon dioxide; and a sweetening agent and certain preservatives, dyes, coloring and flavors. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

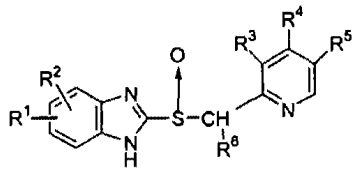
For the purpose of parenteral therapeutic administration, the active composition of the invention may be incorporated into a solution or suspension. These preparations should contain at least 0.1% of active compound, but may be varied between 0.5 and about 30% of the weight thereof. The amount of active compound in such compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present inventions are

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prepared so that a parenteral dosage unit contains between 0.5 to 100 milligrams of active compound.

The solutions or suspensions may also include the following components: a steril diluent such as water for injection, saline solution, fixed oils, polyethylene gylcols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in disposable syringes or multiple dose vials made of glass or plastic.

Included among pharmaceutical formulations are stabilized pharmaceutical unit dosage forms comprising a core (a) comprising a compound of formula I



I

wherein R^1 and R^2 are same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl, and R^3 and R^5 are the same or different and are each selected from the group consisting of

hydrogen, methyl, methoxy, ethoxy, methoxyethoxy and ethoxyethoxy; and R^4 is selected from the group consisting of methoxy, ethoxy, methoxyethoxy or ethoxyethoxy; or a pharmaceutically acceptable acid addition salt thereof, and a compound of formula II

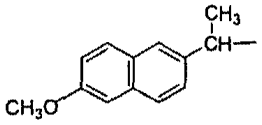
$$R^7CO_2M \quad II$$

wherein R^7 is an organic radical and M is a cation;

(b) a first coating of the core comprising at least one layer of a polymeric coating; and

(c) a second coating comprising an enteric coating.

Preferred stabilized pharmaceutical unit dosage forms are those wherein the compound of formula I comprises compounds wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, carbomethoxy, carbethoxy, alkoxy and alkanoyl; R^6 is hydrogen; and R^3, R^4, and R^5 are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy; and ethoxy; or a pharmaceutically acceptable acid addition salt thereof and the compound of formula II wherein the organic radical is selected from the group consisting of



wherein M is sodium, potassium, calcium, barium or aluminum.

More preferred stabilized pharmaceutical unit dosage forms are those wherein the compound of formula I is 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethylsulfinyl]-

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(5-methoxy)benzimidazole and the compound of formula II is sodium 2-(6-methoxy-2-napthyl)propionic acid.

The stabilized pharmaceutical dosage forms of the present invention are formulated by granulating a mixture of the compounds of formulas I and II. Pharmaceutically acceptable excipients, for example, fillers, binders and lubricants may be included in the granulation for the purpose of facilitating the granulation and improving the acceptance of the ultimate tablet. Among fillers there may be mentioned hydroxyalkylcellulose, particularly hydroxypropylcellulose. Among binders there may be mentioned polyvinylpyrolidine. Among lubricants there may be mentioned talc and magnesium.

The granulate is first coated with at least one layer of a polymeric coating, for example a hydroxyalkylalkylcellulose, polyethylene glycol and a pigment coating, particularly a coating containing hydroxypropylmethylcellulose. The coated granulate is then coated with an enteric coating comprising a methacrylic acid copolymer. Among methacrylic acid copolymers there may be mentioned methacrylic acid ethyl acrylate copolymer.

The granulation is carried out in conventional equipment using a solvent such as 2-propanol, and the granulate is dried prior to the next operation, i.e., coating the granulate. The first coating is applied by granulating the dried granulate with, for example, hydroxypropylmethylcellulose, polyethylene, pigment, preferably in aqueous suspension, also in conventional equipment, followed by drying, i.e., removing the solvent by evaporation under conventional conditions. The dried coated granulate is then coated with a methacrylic acid copolymer, particularly methacrylic

acid ethyl acrylate copolymer to yield the stabilized pharmaceutical dosage form in pellet form.

The granulation and coating steps are generally performed under conventional conditions. In one such granulation and coating procedure, 2-[2-(3,5-dimetyl-4-methoxy)-pyridinylmethylsulfinyl]-(5-methoxy)benzimidazole (omeprazole) (20 mg/tablet), sodium 2-(6-methoxy-2-naphthyl) propionic acid (naproxen sodium) (550 mg/tablet), hydroxypropylcellulose (30 mg), polyvinylpyrrolidone (30 mg/tablet), talc (5.0 mg/tablet), and magnesium stearate (5.0 mg/tablet)is granulated in 2-propanol, dried, and the dried granulate is first coated with hydroxypropylmethylcellulose, polyethylene glycol, pigment (9mg/tablet), the coated granulate dried and granulated with a methacrylic acid ethyl acrylate copolymer in aqueous suspension and dried to form the tablet.

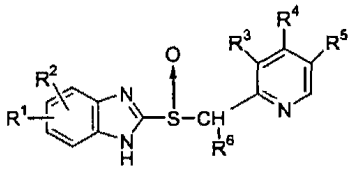
The tablets are stable in the solid form over a reasonably long period of time, showing no significant change in the omeprazole titer. At a temperature of 40°C and relative humidity of 75%, enteric coated tablets of omeprazole and naproxen sodium, prepared as described above, are stable over a period of three months. After three months, the omeprazole titer was determined to be 96.9%, relative to the initial amount, by high performance liquid chromatography.

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Claims

What is claimed:

1. A composition comprising a compound of formula I



I

wherein R^1 and R^2 are same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl, and R^3 and R^5 are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, ethoxy, methoxyethoxy and ethoxyethoxy; and R^4 is selected from the group consisting of methoxy, ethoxy, methoxyethoxy or ethoxyethoxy; or a pharmaceutically acceptable acid addition salt thereof, and a compound of formula II

$$R^7CO_2M \quad II$$

wherein R^7 is an organic radical and M is a cation.

2. A composition according to claim 1 wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, carbomethoxy, carboethoxy, alkoxy, and alkanoyl, R^6 is hydrogen; and R^3, R^4, and R^5 are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy and ethoxy; or a pharmaceutically acceptable addition salt thereof.

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3. A composition according to claim 1 wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl; R^3 is methyl; R^4 is methoxy; and R^5 is methyl; or a pharmaceutically acceptable acid addition salt thereof.

4. A composition according to claim 1 wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl; and R^3 is hydrogen; R^4 is methoxy; and R^5 is methyl or R^3 is methyl, R^4 is methoxy and R^5 is hydrogen; or a pharmaceutically acceptable acid addition salt thereof.

5. A composition according to claim 1 wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl, R^6 is selected from the group consisting of hydrogen, methyl, and ethyl, $R^3$and R^5 are hydrogen and methoxy; or a pharmaceutically acceptable acid addition salt thereof.

6. A composition according to claim 1 wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, and alkanoyl, R^6 is selected from the group consisting of hydrogen, methyl and ethyl; and $R^3$and R^5 are methyl; and R^4 is hydrogen; or a pharmaceutically acceptable acid addition salt thereof.

7. A composition according to claim 1 wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl,

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halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl; $R^3$and R^5 are hydrogen; and R^4 is ethoxy, methoxyethoxy or ethoxyethoxy; or a pharmaceutically acceptable acid addition salt thereof.

8. A composition according to claim 1 wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, alkoxy and alkanoyl, R^6 is selected from the group consisting of hydrogen, methyl and ethyl; R^3, R^4 and R^5 are methyl; or a pharmaceutically acceptable acid addition salt thereof.

9. A composition according to claim 1 wherein R^1 is hydrogen, chloro, methyl, ethyl, methoxy, acetyl, carbethoxy or carbomethoxy ; R^2 is hydrogen or methyl; R^6 is hydrogen, methyl or ethyl; $R^3$and R^5 are methyl; and R^4 is methoxy, or in which R^1 is hydrogen, chloro, methyl, ethyl, methoxy, acetyl, carboethoxy or carbomethyl; R^2 is hydrogen, methyl or ethyl; R^4 is methoxy ; and R^3 is methyl and R^5 is hydrogen or R^3 is hydrogen and R^5 is methyl, or a pharmaceutically acceptable acid addition salt thereof.

10. A composition according to claim 1 wherein a compound of the formula I is selected from the group consisting of 2-[2-(4-methoxy)pyridinylmethysulfinyl]-5-acetyl-6-methyl)benzimidazole, 2-[2-(4-methoxy)pyridinylmethysulfinyl]-4,6-dimethyl)-benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-acetyl-6-methyl)-benzimidazole, 2-[2-(4-methoxy)pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole, 2-[2-(4-ethoxy)pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole, 2-[2-

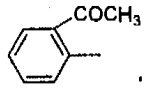
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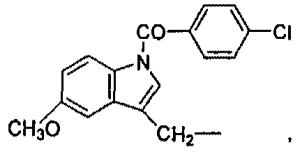
(3-methyl-4-methoxy)pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)benzimidazole, 2-[2-(4-methoxy-5-methyl)-pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-carbomethoxy)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-acetyl)benzimidazole, 2-[2-(4-methoxy-5-methyl)-pyridinylmethysulfinyl]-(5-methoxy)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)-pyridinylmethysulfinyl]-(5-methoxy)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)-pyridinylmethysulfinyl]-(5-methyl)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)-pyridinylmethysulfinylbenzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)-pyridinylmethysulfinyl]-(5-chloro)benzimidazole, or a pharmaceutically acceptable addition salt thereof.

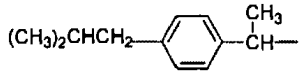
11. A composition according to claim 10 wherein R^1 is hydrogen; R^2 is methoxy; R^3 and R^5 are methyl; R^4 is methoxy; and R^6 is hydrogen which is 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

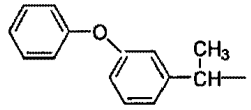
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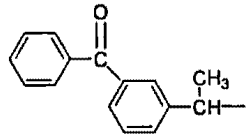
12. A composition according to claim 1 wherein the organic radical is selected from the group consisting of:

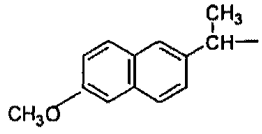


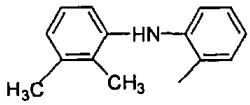


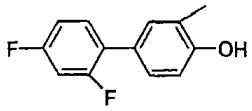


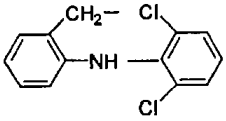


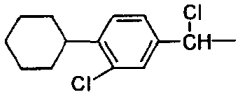


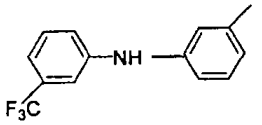


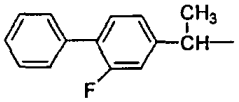


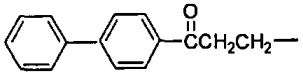


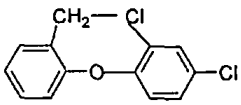




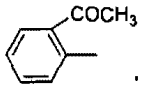


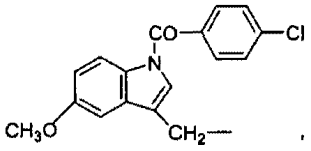


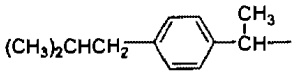


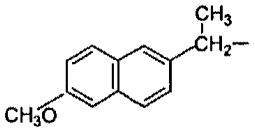


13. A composition according to claim 12 wherein the organic radical is selected from the group consisting of:

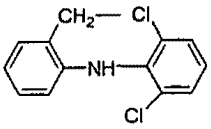




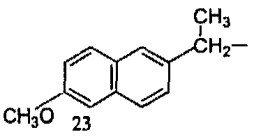




and



14. The composition according to claim 13 wherein the organic radical is



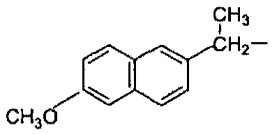
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15. A compound according to claim 1 wherein M is sodium, potassium, magnesium, calcium, barium or aluminum.

16. A composition according to claim 15 wherein M is sodium, potassium, calcium, barium or aluminum.

17. A composition according to claim 16 wherein M is sodium.

18. A composition according to claim 17 wherein R^1 is hydrogen, R^2 is methoxy; R^3 and R^5 are methyl; R^4 is methoxy; R^6 is hydrogen; R^7 is



and M is sodium.

19. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 1.

20. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 2.

21. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the

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gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 3.

22. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 4.

23. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 5.

24. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 6.

25. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 7.

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26. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 8.

27. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 9.

28. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 10.

29. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 11.

30. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an

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ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 12.

31. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 13.

32. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 14.

33. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 15.

34. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 16.

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35. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 17.

36. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 18.

37. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 1.

38. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 2.

39. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an

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ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 3.

40. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 4.

41. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 5.

42. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 6.

43. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 7.

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44. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 8.

45. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 9.

46. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 10.

47. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 11.

48. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an

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ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 12.

49. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 13.

50. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 14.

51. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 15.

52. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 16.

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53. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 17.

54. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 18.

55. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract hy an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 1 and a pharmaceutically acceptable carrier therefor.

56. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 2 and a pharmaceutically acceptable carrier therefor.

57. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 3 and a pharmaceutically acceptable carrier therefor.

58. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 4 and a pharmaceutically acceptable carrier therefor.

59. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 5 and a pharmaceutically acceptable carrier therefor.

60. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 6 and a pharmaceutically acceptable carrier therefor.

61. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 7 and a pharmaceutically acceptable carrier therefor.

62. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 8 and a pharmaceutically acceptable carrier therefor.

63. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the

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active ingredient a composition of claim 9 and a pharmaceutically acceptable carrier therefor.

64. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 10 and a pharmaceutically acceptable carrier therefor.

65. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract in a mammal by an anti-inflammatory agent, comprising as the active ingredient a composition of claim 11 and a pharmaceutically acceptable carrier therefor.

66. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 12 and a pharmaceutically acceptable carrier therefor.

67. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 13 and a pharmaceutically acceptable carrier therefor.

68. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 14 and a pharmaceutically acceptable carrier therefor.

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69. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 15 and a pharmaceutically acceptable carrier therefor.

70. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 16 and a pharmaceutically acceptable carrier therefor.

71. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 17 and a pharmaceutically acceptable carrier therefor.

72. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 18 and a pharmaceutically acceptable carrier therefor.

73. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 1 and a pharmaceutically acceptable carrier therefor.

74. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the

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active ingredient a composition of claim 2 and a pharmaceutically acceptable carrier therefor.

75. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 3 and a pharmaceutically acceptable carrier therefor.

76. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 4 and a pharmaceutically acceptable carrier therefor.

77. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 5 and a pharmaceutically acceptable carrier therefor.

78. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 6 and a pharmaceutically acceptable carrier therefor.

79. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 7 and a pharmaceutically acceptable carrier therefor.

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80. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 8 and a pharmaceutically acceptable carrier therefor.

81. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 9 and a pharmaceutically acceptable carrier therefor.

82. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 10 and a pharmaceutically acceptable carrier therefor.

83. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 11 and a pharmaceutically acceptable carrier therefor.

84. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 12 and a pharmaceutically acceptable carrier therefor.

85. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the

active ingredient a composition of claim 13 and a pharmaceutically acceptable carrier therefor.

86. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 14 and a pharmaceutically acceptable carrier therefor.

87. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 15 and a pharmaceutically acceptable carrier therefor.

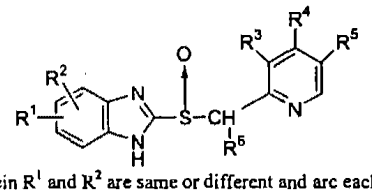
88. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 16 and a pharmaceutically acceptable carrier therefor.

89. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 17 and a pharmaceutically acceptable carrier therefor.

90. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 18 and a pharmaceutically acceptable carrier therefor.

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91. A method of stabilizing a compound of formula I



I

wherein R^1 and R^2 are same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl; and R^3 and R^5 are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, ethoxy, methoxyethoxy and ethoxyethoxy; and R^4 is selected from the group consisting of methoxy, ethoxy, methoxyethoxy or ethoxyethoxy; or a pharmaceutically acceptable acid addition salt thereof by combining the compound of formula I with a compound of formula II

$$R^7CO_2M \qquad II$$

wherein R7 is an organic radical and M is a cation to form a stabilized composition.

92. A method according to claim 91 wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, carbomethoxy, carboethoxy, alkoxy, and alkanoyl, R^6 is hydrogen; and R^3, R^4, and R^5 are the same or different and each selected from the group consisting of hydrogen, methyl, methoxy and ethoxy; or a pharmaceutically acceptable addition salt thereof.

93. A method according to claim 91 wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy and alkanoyl; R^6 is selected from the

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group consisting of hydrogen, methyl and ethyl; R^3 is methyl; R^4 is methoxy; and R^5 is methyl; or a pharmaceutically acceptable acid addition salt thereof.

94. A method according to claim 91 wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl; and R^3 is hydrogen, R^4 is methoxy; and R^5 is methyl, or R^3 is methyl; R^4 is methoxy and R^5 is hydrogen; or a pharmaceutically acceptable acid addition salt thereof.

95. A method according to claim 91 wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl; $R^3$and R^5 are hydrogen and methoxy; or a pharmaceutically acceptable acid addition salt thereof.

96. A method according to claim 91 wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl; and $R^3$and R^5 are methyl and R^4 is hydrogen; or a pharmaceutically acceptable acid addition salt thereof.

97. A method according to claim 91 wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl; $R^3$and R^5 are hydrogen; and R^4 is

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ethoxy, methoxyethoxy or ethoxyethoxy; or a pharmaceutically acceptable acid addition salt thereof.

98. A method according to claim 91 wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl; R^3, R^4 and R^5 are all methyl; or a pharmaceutically acceptable acid addition salt thereof.

99. A method according to claim 91 wherein R^1 is hydrogen, chloro, methyl, ethyl, methoxy, acetyl, carboethoxy or carbomethoxy ; R^2 is hydrogen or methyl; R^6 is hydrogen, methyl or ethyl; $R^3$and R^5 are methyl; and R^4 is methoxy, or in which R^1 is hydrogen, chloro, methyl, ethyl, methoxy, acetyl, carboethoxy or carbomethyl; R^2 is hydrogen, methyl or ethyl; R^4 is methoxy ; and R^3 is methyl and R^5 is hydrogen or R^3 is hydrogen and R^5 is methoyl, or a pharmaceutically acceptable acid addition salt thereof.

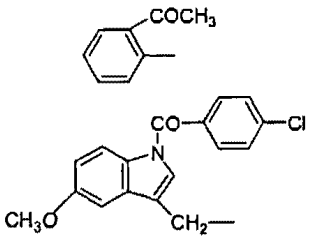
100. A method according to claim 1 wherein a compound of the formula I is selected from the group consisting of 2-[2-(4-methoxy)pyridinylmethysulfinyl]-5-acetyl-6-methyl)benzimidazole, 2-[2-(4-methoxy)pyridylmethysulfinyl]-4,6-dimethyl)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-acetyl-6-methyl)benzimidazole, 2-[2-(4-methoxy)pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)benzimidazole, 2-[2-(4-ethoxy)pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)benzimidazole, 2-[2-(3-methyl-4-methoxy)pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-

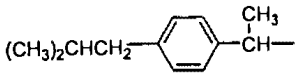
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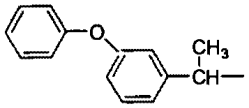
carbomethoxy-6-methyl)benzimidazole, 2-[2-(4-methoxy-5-methyl)pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-carbomethoxy)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-acetyl)benzimidazole, 2-[2-(4-methoxy-5-methyl)pyridinylmethysulfinyl]-(5-methoxy)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-methoxy)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-methyl)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinylbenzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)-pyridinylmethysulfinyl]-(5-chloro)benzimidazole, or a pharmaceutically acceptable addition salt thereof.

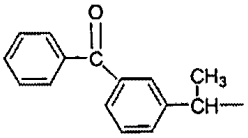
101. A method according to claim 100 wherein R^1 is hydrogen, R^2 is methoxy, R^3 and R^5 are methyl, R^4 is methoxy; and R^6 is hydrogen, which is 5-methoxy-2-[[(4-methocxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

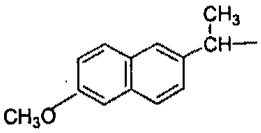
102. A method according to claim 1 wherein the organic radical selected from the group consisting of:

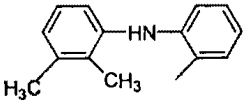


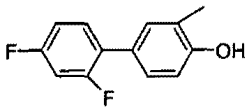


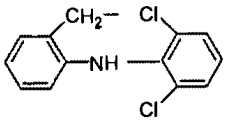


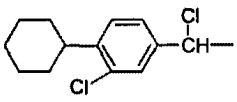


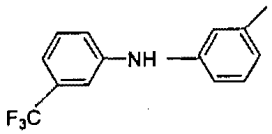


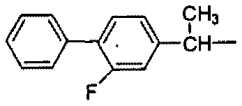


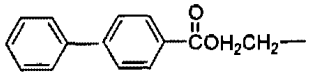


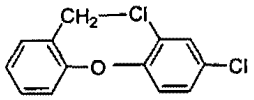




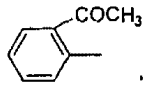


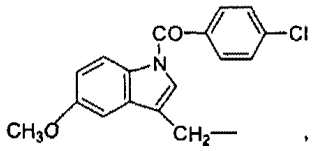


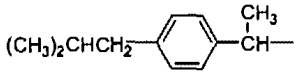


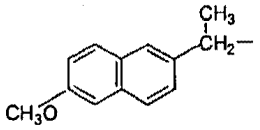


103. A method according to claim 102 wherein the organic radical is selected from the group consisting of:

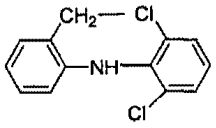




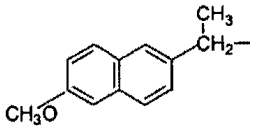




and



104. A method according to claim 103 wherein the organic radical is

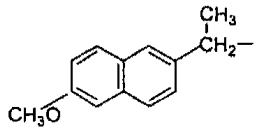


105. The method according to claim 91 wherein M is sodium, potassium, magnesium, calcium, barium or aluminum.

106. The method according to claim 105 wherein M is sodium, potassium, calcium, barium or aluminum.

107. The method according to claim 106 wherein M is sodium.

108. The method according to claim 91 wherein R^1 is hydrogen, R^2 is methoxy; R^3 and R^5 are methyl; R^4 is methoxy, R^6 is hydrogen; R^7 is



and M is sodium.

109. A method according to claim 91 wherein the compound to be stabilized of formula I is in the solid state.

110. A method according to claim 109 wherein the compound to be stabilized is in the fluid state.

111. A method according to claim 110 wherein the compound to be stabilized is in the liquid state.

112. A method according to claim 111 wherein the liquid state is a fluid state.

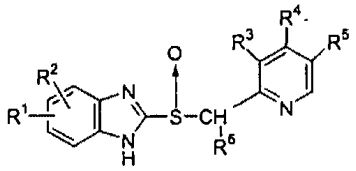
113. A method according to claim 112 wherein the fluid state is an aqueous medium.

114. A method according to claim 113 wherein the aqueous medium is the medium of the gastrointestinal tract of a mammal.

115. A method according to claim 114 wherein the aqueous medium of the gastrointestinal tract is the medium of the stomach.

116. A method according to claim 115 wherein the aqueous medium of the gastrointestinal tract is the medium of the gut.

117. A stabilized pharmaceutical unit dosage form comprising (a) a core comprising a compound of formula I



I

wherein R^1 and R^2 are same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl, and R^3 and R^5 are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, ethoxy, methoxyethoxy and ethoxyethoxy; and R^4 is selected from the group consisting of methoxy, ethoxy, methoxyethoxy or ethoxyethoxy; or a pharmaceutically acceptable acid addition salt thereof, and a compound of formula II

$$R^7CO_2M \quad II$$

wherein R^7 is an organic radical and M is a cation;

(b) a first coating of the core comprising at least one layer of a polymer coating; and

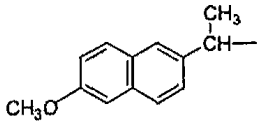
(c) a second coating comprising an enteric coating.

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118. A stabilized pharmaceutical unit dosage form comprising a core according to claim 117 wherein the compound of formula I comprises compounds wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, carbomethoxy, carbethoxy, alkoxy and alkanoyl; R^6 is hydrogen; and R^3, R^4, and R^5 are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy; and ethoxy; or a pharmaceutically acceptable acid addition salt thereof.

119. A stabilized pharmaceutical unit dosage form according to claim 118 wherein the compound of formula I is 2-[2-(3,5-dimethyl-4-methoxy)-pyridinylmethylsulfinyl]-(5-methoxy)benzimidazole.

120. A stabilized pharmaceutical unit dosage form according to claim 117 wherein the organic radical of the compound of formula II is selected from the group consisting of



wherein M is sodium, potassium, calcium, barium or aluminum.

121. The stabilized pharmaceutical unit dosage form according to claim 120 wherein the compound of formula II is sodium 2-(6-methoxy-2-naphthyl)propionic acid.

122. A stabilized pharmaceutical unit dosage form according to claim 117 wherein the core comprises pharmaceutically acceptable excipients.

123. A stabilized pharmaceutical unit dosage form according to claim 122 wherein excipients comprise a filler, a binder or a lubricant.

124. A stabilized pharmaceutical unit dosage form according to claim 123, wherein the filler is a hydroxyalkylcellulose.

125. A stabilized pharmaceutical unit dosage form according to claim 124, wherein the hydroxyalkylcellulose is hydroxypropylcellulose.

126. A stabilized pharmaceutical unit dosage form according to claim 123, wherein the filler is a polyvinylpyrrolidone.

127. A stabilized pharmaceutical unit dosage form according to claim 123, wherein the lubricants are talc or magnesium stearate.

128. A stabilized pharmaceutical unit dosage form according to claim 123, wherein the polymer coating comprises a hydroxyalkylcellulose, polyethylene glycol and a pigment.

129. A stabilized pharmaceutical unit dosage form according to claim 128, wherein the hydroxyalkylcellulose is hydroxypropylmethylcellulose.

130. A stabilized pharmaceutical unit dosage form according to claim 117, wherein the enteric coating is a methacrylic acid copolymer.

131. A stabilized pharmaceutical unit dosage form according to claim 130, wherein the methacrylic acid copolymer is a copolymer of methacrylic acid and ethyl acrylate.

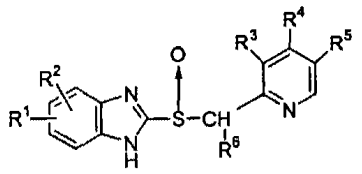
132. A stabilized pharmaceutical unit dosage form according to claim 117, wherein the dosage form is a tablet.

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133. A stabilized pharmaceutical unit dosage form according to claim 117, comprising 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethylsulfinyl]-(5-methoxybenzimidazole, sodium 2-(6-methoxy-2-naphthyl)propionic acid, hydroxypropylcellusoe, polyvinylpyrrolidone, talce and magnesium stearate first coated with hydroxypropylmethylcellulose, polyethylent glycol, pigment) and enteric coated with methacrylic acid ethyl acrylate copolymer.

134. A process for the preparation of a stabilized pharmaceutical unit dosage form comprising the steps of:

(a) granulating a mixture of a compound of formula I



I

wherein R^1 and R^2 are same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl, and R^3 and R^5 are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, ethoxy, methoxyethoxy and ethoxyethoxy; and R^4 is selected from the group consisting of methoxy, ethoxy, methoxyethoxy or ethoxyethoxy; or a pharmaceutically acceptable acid addition salt thereof,

a compound of formula II

$$R^7CO_2M \quad II$$

wherein R^7 is an organic radical and M is a cation, a filler, a binder and a lubricant;

(b) drying the granulation of step (a)

(c) coating the dried granulation of step (b) with a first coating;

(d) drying the first coated granulation of step (c);

(e) coating the dried granulation of step (d) with an enteric coating.

135. The process for the preparation of a stabilized pharmaceutical unit dosage form according to claim 133 comprising the steps of:

(a) granulating a mixture of 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethylsulfinyl]-(5-methoxy)benzimidazole, sodium 2-(6-methoxy-2-naphthyl)propionic acid, hydroxypropylycellulose, polyvinylpyrrolidone, talc and magnesium stearate;

(b) drying the granulate in step (a);

(c) coating the dried granulate of step (b) with a first coating comprising hydroxypropylmethylcellulose, polyethylene glycol and a pigment;

(d) drying the coated formulate from step (c); and

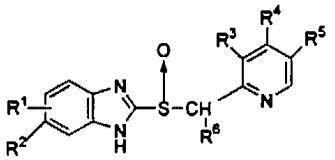
(e) coating the dried granulate from step (d) with an enteric coating comprising a methacrylic acid ethyl acrylate copolymer.

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AMENDED CLAIMS

[received by the International Bureau 04 July 2000 (04.07.00);
original claims 1-134 replaced by new claims 135- 166 (7 pages)]

135. A composition comprising a compound of formula I



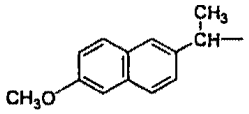
I

wherein R^1 hydrogen; R^2 is methoxy; R^6 is hydrogen: R^3 and R^5 are methyl; and R^4 is methoxy or a pharmaceutically acceptable acid addition salt thereof, and

a compound of formula II

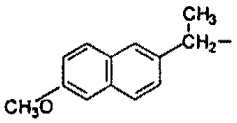
$$R^7CO_2M \quad II$$

wherein R^7 is an organic radical selected from the group consisting of



and M is a cation selected from the group consisting of sodium potassium, magnesium, calcium. barium and aluminum.

136. A composition according to claim 135 wherein R^1 hydrogen; R^2 is methoxy; R^3 and R^5 are methyl; and R^4 is methoxy, R^6 is hydrogen; and R^7 is a group of the formula



and M is sodium.

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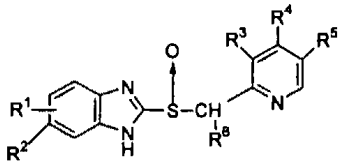
137. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 135.

138. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 136.

139. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 135 and a pharmaceutically acceptable carrier therefor.

140. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 136 and a pharmaceutically acceptable carrier therefor.

141. A method of stabilizing a compound of formula I



I

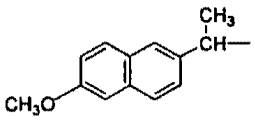
wherein R^1 hydrogen; R^2 is methoxy; R^6 is hydrogen; R^3 and R^5 are methyl; and R^4 is methoxy or a pharmaceutically acceptable acid addition salt thereof, and

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a compound of formula II

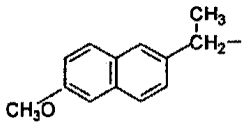
$$R^7CO_2M \quad II$$

wherein R^7 is an organic radical selected from the group consisting of



and M is a cation selected from the group consisting of sodium potassium, magnesium, calcium, barium and aluminum.

142. The method according to claim 141 wherein R^1 is hydrogen, R^2 is methoxy; R^3 and R^5 are methyl; R^4 is methoxy, R^6 is hydrogen; R^7 is



and M is sodium.

143. A method according to claim 141 wherein the compound of formula I to be stabilized is in the solid state.

144. A method according to claim 141 wherein the compound of formula I to be stabilized is in the fluid state.

145. A method according to claim 144 wherein the compound of formula I to be stabilized is in the liquid state.

146. A method according to claim 144 wherein the fluid state is an aqueous medium.

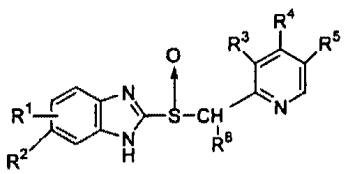
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147. A method according to claim 146 wherein the aqueous medium is the medium of the gastrointestinal tract of a mammal.

148. A method according to claim 147 wherein the aqueous medium of the gastrointestinal tract is the medium of the stomach.

149. A method according to claim 147 wherein the aqueous medium of the gastrointestinal tract is the medium of the gut.

150. A stabilized pharmaceutical unit dosage form comprising (a) a core comprising a compound of formula I



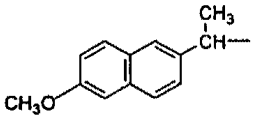
I

wherein R^1 hydrogen; R^2 is methoxy; R^6 is hydrogen; R^3 and R^5 are methyl; and R^4 is methoxy or a pharmaceutically acceptable acid addition salt thereof, and

a compound of formula II

$$R^7CO_2M \quad II$$

wherein R^7 is an organic radical selected from the group consisting of



and M is a cation selected from the group consisting of sodium, potassium, magnesium, calcium, barium and aluminum;

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(b) a first coating of the core comprising at least one layer of a polymer coating; and

(c) a second coating comprising an enteric coating.

151. A stabilized pharmaceutical unit dosage form according to claim 150 wherein the compound of formula I is 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethylsulfinyl]-(5-methoxy)benzimidazole.

152. The stabilized pharmaceutical unit dosage form according to claim 150 wherein the compound of formula II is sodium 2-(6-methoxy-2-naphthyl)propionic acid.

153. A stabilized pharmaceutical unit dosage form according to claim 150 wherein the core comprises pharmaceutically acceptable excipients.

154. A stabilized pharmaceutical unit dosage form according to claim 150 wherein excipients comprise a filler, a binder or a lubricant.

155. A stabilized pharmaceutical unit dosage form according to claim 154, wherein the filler is a hydroxyalkylcellulose.

156. A stabilized pharmaceutical unit dosage form according to claim 155, wherein the hydroxyalkylcellulose is hydroxypropylcellulose.

157. A stabilized pharmaceutical unit dosage form according to claim 154, wherein the filler is a polyvinylpyrrolidone.

158. A stabilized pharmaceutical unit dosage form according to claim 154, wherein the lubricants are talc or magnesium stearate.

159. A stabilized pharmaceutical unit dosage form according to claim 150, wherein the polymer coating comprises a hydroxyalkylcellulose, polyethylene glycol and a pigment.

160. A stabilized pharmaceutical unit dosage form according to claim 159, wherein the hydroxyalkylcellulose is hydroxypropylmethylcellulose.

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161. A stabilized pharmaceutical unit dosage form according to claim 150, wherein the enteric coating is a methacrylic acid copolymer.

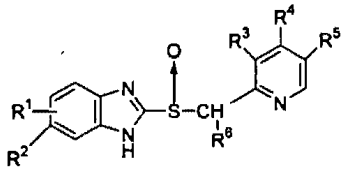
162. A stabilized pharmaceutical unit dosage form according to claim 161, wherein the methacrylic acid copolymer is a copolymer of methacrylic acid and ethyl acrylate.

163. A stabilized pharmaceutical unit dosage form according to claim 150, wherein the dosage form is a tablet.

164. A stabilized pharmaceutical unit dosage form according to claim 150, comprising 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethylsulfinyl]-(5-methoxybenzimidazole, sodium 2-(6-methoxy-2-naphthyl)propionic acid, hydroxypropylcellulose, polyvinylpyrrolidone, talc and magnesium stearate first coated with hydroxypropylmethylcellulose, polyethylent glycol, pigment and enteric coated with methacrylic acid ethyl acrylate copolymer.

165. A process for the preparation of a stabilized pharmaceutical unit dosage form comprising the steps of:

(a) granulating a mixture of a compound of formula I



I

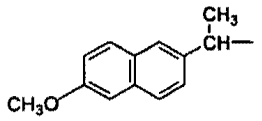
wherein R^1 hydrogen; R^2 is methoxy; R^6 is hydrogen; R^3 and R^5 are methyl; and R^4 is methoxy or a pharmaceutically acceptable acid addition salt thereof, and

a compound of formula II

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R^7CO_2M II

wherein R^7 is an organic radical selected from the group consisting of



and M is a cation selected from the group consisting of sodium potassium, magnesium, calcium, barium and aluminum;

(b) drying the granulate of step (a)

(c) coating the dried granulate of step (b) with a first coating;

(d) drying the first coated granulation of step (c);

(e) coating the dried granulate of step (d) with an enteric coating.

166. The process for the preparation of a stabilized pharmaceutical unit dosage form according to claim 165 comprising the steps of:

(a) granulating a mixture of 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethylsulfinyl]-(5-methoxy)benzimidazole, sodium 2-(6-methoxy-2-naphthyl)propionic acid, hydroxypropylycellulose, polyvinylpyrrolidone, talc and magnesium stearate;

(b) drying the granulate in step (a);

(c) coating the dried granulate of step (b) with a first coating comprising hydroxypropylmethylcellulose, polyethylene glycol and a pigment;

(d) drying the coated granulate from step (c); and

(e) coating the dried granulate from step (d) with an enteric coating comprising a methacrylic acid ethyl acrylate copolymer.

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INTERNATIONAL SEARCH REPORT

Inter... ...onal Application No
PCT/US 99/11389

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/44 A61P1/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 00380 A (ASTRA) 7 January 1999 (1999-01-07) claims 1,11 -/—	1-4, 9-11, 19-23, 28,29, 37-40, 45-47, 55-58, 63-65, 73-76, 81-83, 100,101

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 March 2000	10/03/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Peeters, J

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Form PCT/ISA/210 (second sheet) (July 1992)

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Page 396 of 613

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/11389

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 12817 A (WARNER-LAMBERT) 8 July 1993 (1993-07-08) claims 1,2,5,7-9	1-4, 9-11, 19-23, 28,29, 37-40, 45-47, 55-58, 63-65, 73-76, 81-83, 100,101
X	EP 0 426 479 A (MCNEIL-PPC) 8 May 1991 (1991-05-08) claims 1-4 column 6, line 13 column 6, line 36-38 column 7, line 1-16	1-4, 9-13, 15-23, 28,29, 37-40, 45-47, 55-58, 63-65, 73-76, 81-83, 100-103
X	WO 98 22117 A (PROCTER & GAMBLE) 28 May 1998 (1998-05-28) claims 1-3,5,8,11 page 4, line 31 -page 5, line 6	1-4, 9-13, 19-23, 28,29, 37-40, 45-47, 55-58, 63-65, 73-76, 81-83, 100-103

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

Patent Owner Ex. 2005
IPR2015-01344
Page 397 of 613

INTERNATIONAL SEARCH REPORT
Information on patent family members

Inter...onal Application No
PCT/US 99/11389

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9900380 A	07-01-1999	SE 510643 C	14-06-1999
		AU 8135398 A	19-01-1999
		SE 9702483 A	28-12-1998
WO 9312817 A	08-07-1993	AU 3247593 A	28-07-1993
EP 426479 A	08-05-1991	AT 101515 T	15-03-1994
		AU 646230 B	17-02-1994
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		US 5204118 A	20-04-1993
		ZA 9008775 A	29-07-1992
WO 9822117 A	28-05-1998	EP 0941101 A	15-09-1999
		NO 992469 A	22-07-1999

Form PCT/ISA/210 (patent family annex) (July 1992)

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
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(43) International Publication Date
7 December 2000 (07.12.2000)

PCT

(10) International Publication Number
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(51) International Patent Classification[7]: A61K 31/04, 31/196, 31/33, A61P 1/04, 31/00

(21) International Application Number: PCT/SE00/01071

(22) International Filing Date: 25 May 2000 (25.05.2000)

(25) Filing Language: English

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(30) Priority Data:
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9904704-5 21 December 1999 (21.12.1999) SE

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(74) Agent: **ASTRAZENECA AB**; Global Intellectual Property, Patents, S-151 85 Södertälje (SE).

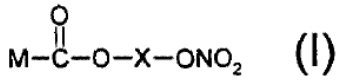
(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NEW USE OF COMPOUNDS AS ANTIBACTERIAL AGENTS



(I)

(57) Abstract: The present invention discloses a new use of NO-releasing NSAIDs, especially NO-releasing NSAIDs of formula (I), or a pharmaceutically acceptable salt or enantiomer thereof, for the manufacture of a medicament for the treatment of bacterial infections, especially caused or mediated by *Helicobacter pylori*. Disclosed is also the new use of a NO-releasing NSAID in combination with an acid susceptible proton pump inhibitor for the treatment of bacterial infections.

WO 00/72838 A1

NEW USE OF COMPOUNDS AS ANTIBACTERIAL AGENTS

Field of the invention

The present invention is directed to a new use of nitric oxide-releasing Non Steriodal Antiinflammatory Drugs (NO-releasing NSAIDs). More particularly the invention is directed to the use of NO-releasing NSAIDs for the manufacture of a medicament for the treatment of bacterial infections, paticularly caused or mediated by *Helicobacter pylori* as well as a combination with acid susceptible proton pump inhibitors for the treatment of bacterial infections.

Background of the invention and prior art

NSAIDs, are among the most commonly prescribed and used drugs world wide. Despite the therapeutic benefits of NSAIDs, their use is limited. The use of NSAIDs may lead to gastric mucosal damage due to inhibited production of prostaglandins which increases the risk of gastrointestinal side-effects.

A recent proposal for reducing the side-effects associated with NSAIDs treatment is to use nitric oxide-releasing NSAID derivatives (NO-releasing NSAIDs) (*del Soldato P et al.. NO-releasing NSAID:s , A novel class of safer and effective antiinflammatory agents: Inflammopharmacology, 1996; 4; 181-188*). NO-releasing NSAIDs reduce the gastrointestinal side-effects but still have the pharmacological activity characteristic of the frequently used NSAIDs.

NO-releasing NSAIDs and pharmaceutically acceptable salts thereof are for instance described in WO 94/04484, WO 94/12463, WO 95/09831 and WO 95/30641.

Helicobacter pylori is a gram-negative spirilliform bacteria which colonises in the gastric mucosa. The relationship between gastrointestinal disorders and infections with

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Helicobacter pylori proposed in 1983 by Warren (*Warren JR Lancet 1983;1.1273*) is well established today.

A number of different therapies have been proposed for the treatment of *Helicobacter pylori* infections. Combination therapies are commonly used. The most commonly used comprise a proton pump inhibitor in combination with one or more antibacterial compounds such as claritromycin and amoxicillin. For instance WO93/00327 discloses the combination of a substance with inhibiting effect on the gastric acid secretion which increases the intragastric pH, and an acid degradable antibacterial compound. Some of these therapies also comprise a bismuth compound, se for instance WO 98/03219 and WO98/22117, which latter application discloses a composition containing bismuth, an antimicrobial agent and a non-steriodal antiinflammatory agent for the treatment of gastrointestinal disorders caused or mediated by *Helicobacter pylori*.

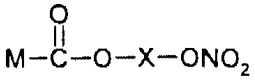
In view of the vast number of the population suffering from gastrointestinal disorders caused or mediated by bacterial infections, such as *Helicobacter pylori* infections, and also in view of the fact that many bacterial strains develop a resistance to commonly used antibiotics, a continuing need exists for a safe and effective medicament having an antibacterial effect, especially for the treatment of *Helicobacter pylori* infections.

Outline of the invention

It has now surprisingly been found that NO-releasing NSAIDs have an antibacterial effect, which makes them useful for the treatment of bacterial infections.

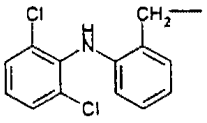
The present invention is related to the use of a NO-releasing NSAID as well as pharmaceutically acceptable salts or enantiomers thereof, for the manufacture of a medicament for the treatment of bacterial infections.

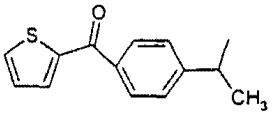
Preferably the NO-releasing NSAID is defined by the formula I

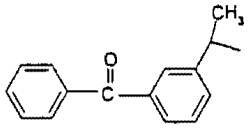


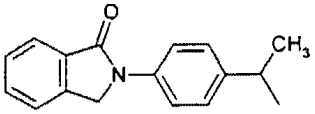
I

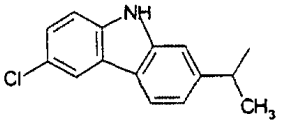
wherein M is selected from anyone of

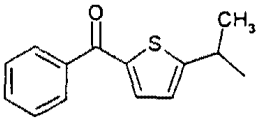


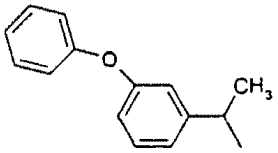


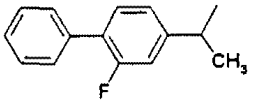


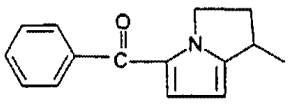


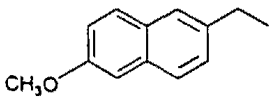


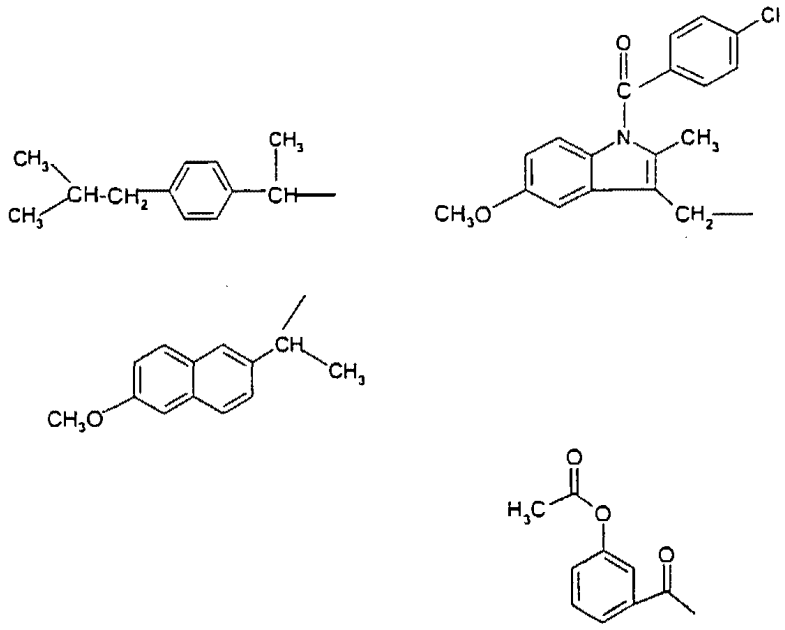










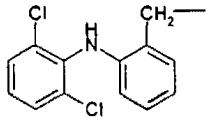
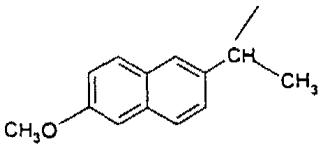
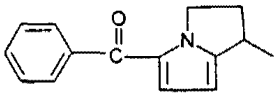
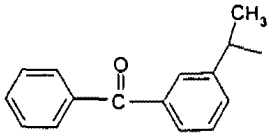


and X is a spacer, i.e. a compound forming a bridge between the nitrogen oxide donating group and the NSAID moiety, or a pharmaceutically acceptable salt or enantiomer thereof;

X is preferably selected from linear, branched or cyclic $-(CH_2)-_n$ wherein n is an integer of from 2 to 10; $-(CH_2)_m-O-(CH_2)_p-$ wherein m and p are integers of from 2 to 10; and $-CH_2-pC_6H_4-CH_2-$.

M is not limited by the above definition but may be any other compound giving the corresponding NSAID by hydrolysis of the compound according to formula I.

In a preferred embodiment of the invention M is selected from

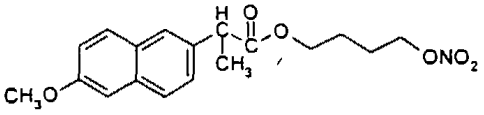





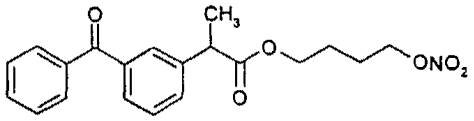
and X is selected from

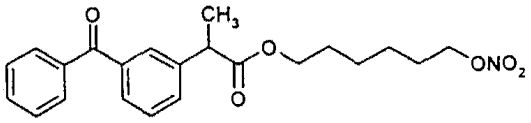
linear $-(CH_2)_n-$ wherein n is an integer of from 2 to 6;

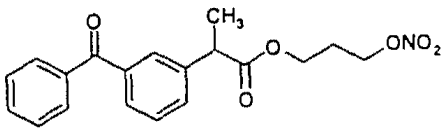
$-(CH_2)_2-O-(CH_2)_2-$ and $-CH_2-pC_6H_4-CH_2-$.

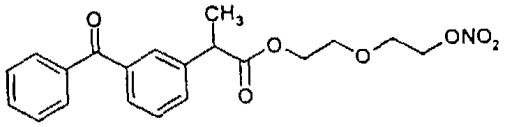
In an even more preferred embodiment of the invention the NO-releasing NSAID is a compound according to any one of the formulas

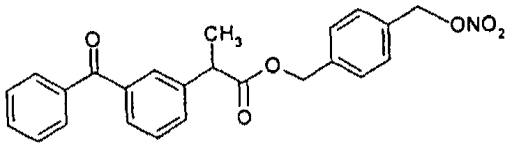

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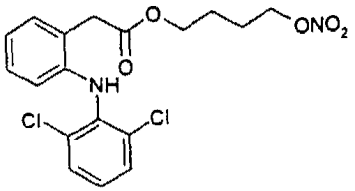

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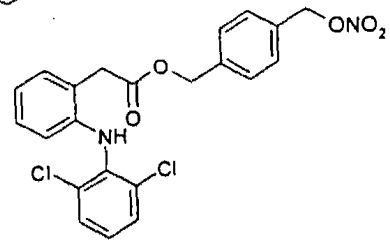

(Id)
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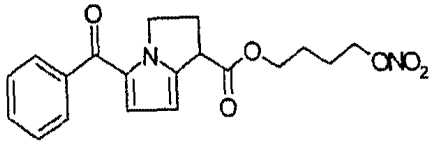

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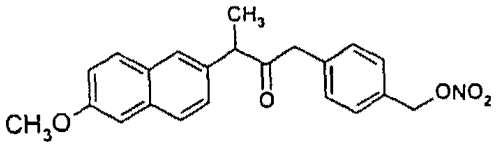

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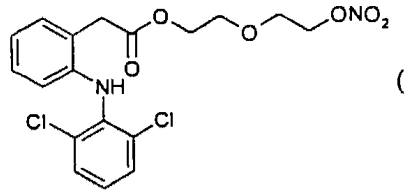

(If) ;


(Ig) ;

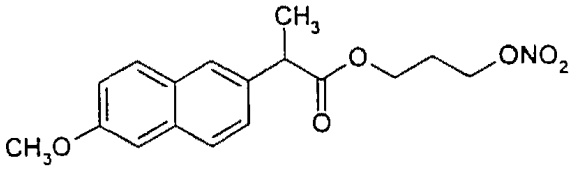

(Ii) ;


(Ij) ;

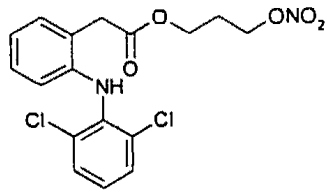

(Ik) ;



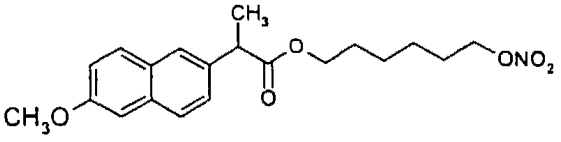
(IL) ;



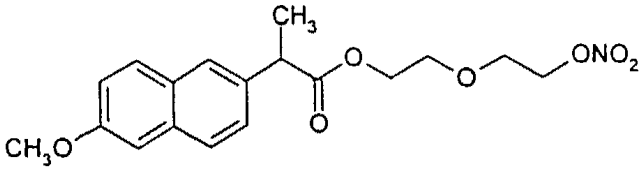
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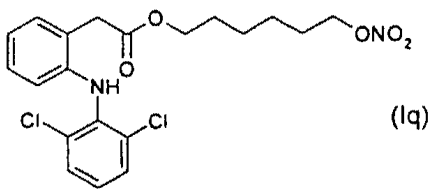
(In) ;



(Io) ;



(Ip) ; and



(Iq)

In a particularly preferred embodiment of the invention the NO-releasing NSAID is a compound according to formula Ia.

A further aspect of the invention is the use of a NO-releasing NSAID, preferably a compound of the formula I above, in the manufacture of a medicament for use in the treatment of *Helicobacter pylori* infections, especially in the treatment of gastrointestinal disorders caused or mediated by *Helicobacter pylori*.

Still a further aspect of the invention is a method for the treatment of bacterial infections, in particular *Helicobacter pylori* infections, whereby an effective amount of a medicament comprising a NO-releasing NSAID, preferably a compound of the formula I, as active agent is administered to a subject suffering from said bacterial infection.

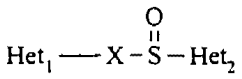
Also a pharmaceutical formulation suitable for use in the treatment of bacterial infections, which formulation comprising a NO-releasing NSAID, preferably a compound of the formula I, is within the scope of the invention.

Furthermore, the invention is related to the use of a NO-releasing NSAID, preferably a compound of the formula I, in combination with an acid susceptible proton pump inhibitor or a salt thereof or an enantiomer or a salt of the enantiomer in the manufacture of pharmaceutical formulations intended for simultanous, separate or sequential administration in the treatment of bacterial infections, especially *Helicobacter pylori* infections.

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The invention may be applied in combination with other agents generally associated with treatment of bacterial infections, such as for instance antibacterial agents.

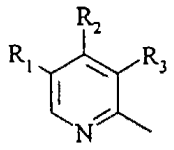
An acid susceptible proton pump inhibitor is, for instance, a compound of the general formula II



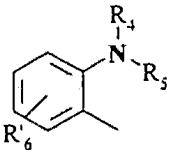
II

wherein

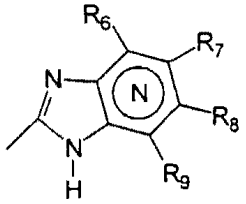
Het_1 is



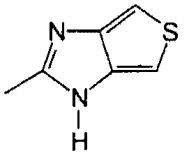
or



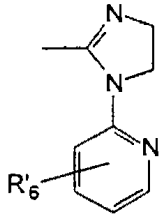
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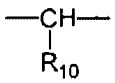
or



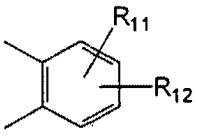
or



X =



or



wherein

N in the benzimidazole moiety means that one of the carbon atoms substituted by R_6-R_9 optionally may be exchanged for a nitrogen atom without any substituents;

R_1, R_2 and R_3 are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R_4 and R_5 are the same or different and selected from hydrogen, alkyl and aralkyl;

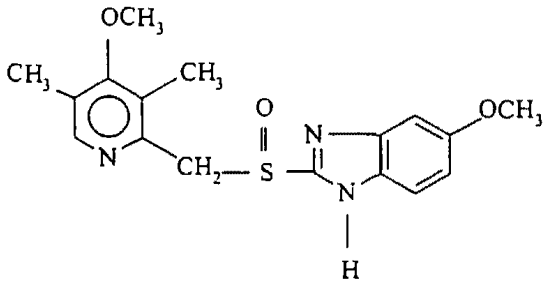
R_6' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

R_6-R_9 are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_6-R_9 form ring structures which may be further substituted;

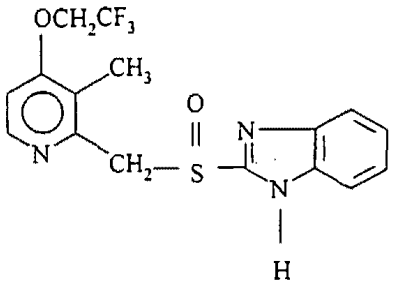
R_{10} is hydrogen or forms an alkylene chain together with R_3 and

R_{11} and R_{12} are the same or different and selected from hydrogen, halogen or alkyl, alkyl groups, alkoxy groups and moities thereof. The substituents may be branched or straight C_1 - C_9 -chains or comprise cyclic alkyl groups, such as cycloalkyl-alkyl.

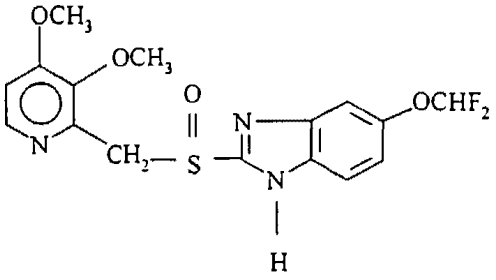
Examples of proton pump inhibitors according to formula II are



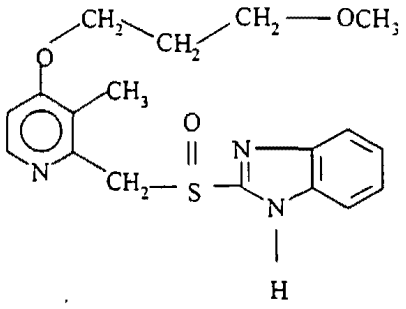
Omeprazole



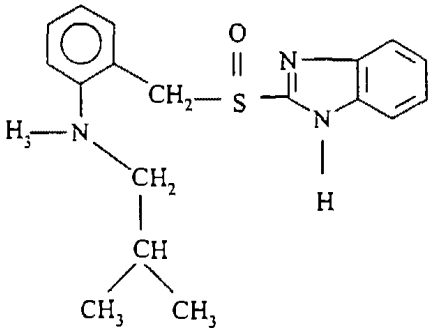
Lansoprazole



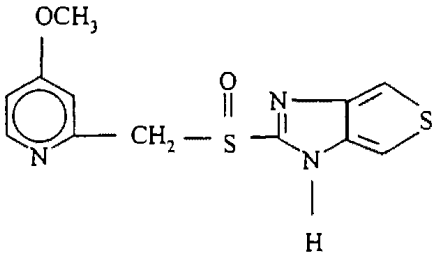
Pantoprazole

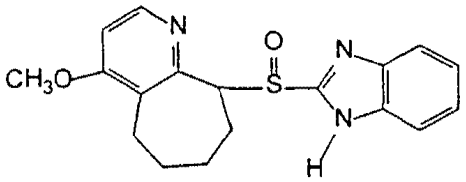


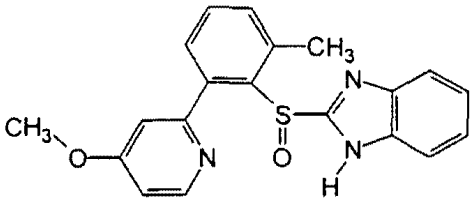
Pariprazole

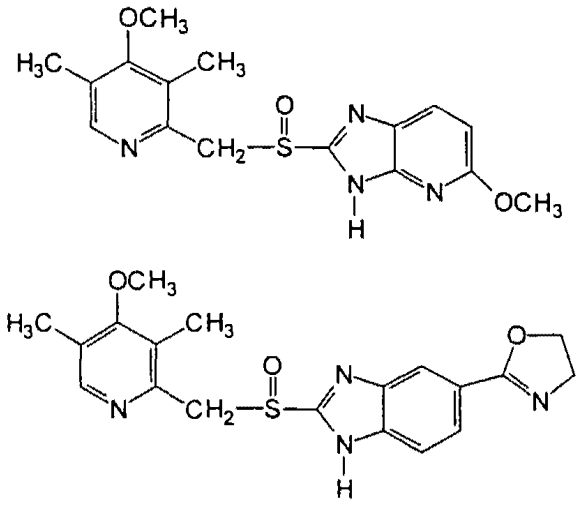


Leminoprazole









The proton pump inhibitor may also be used in the form of a pharmaceutical acceptable salt or a single enantiomer in the claimed combination.

Preferably the proton pump inhibitor omeprazole, or an alkaline salt of omeprazole, such as the magnesium salt, or (*S*)-omeprazole or an alkaline salt of (*S*)-omeprazole, such as the magnesium salt is used in the claimed combination.

Suitable proton pump inhibitors are for example disclosed in EP-A1-0005129, EP-A1-174 726, EP-A1-166 287, GB 2 163 747 and WO90/06925, and further the especially suitable compounds are described in WO95/01977 and WO94/27988.

According to the invention there is further provided a method for treating bacterial infections, particularly *Helicobacter Pylori* infections, which method comprises simultaneous, separate or sequential administration to a subject suffering from a bacterial infection one or more pharmaceutical formulations comprising a NO-releasing NSAID, preferably a compound according to the formula I, and an acid susceptible proton pump

inhibitor. Also pharmaceutical formulations for simultaneous, separate or sequential administration to be used in the treatment of bacterial infections, which formulations comprise an NO-releasing NSAID, preferably a compound of the formula I and an acid susceptible proton pump inhibitor are within the scope of the invention.

The NO-releasing NSAID alone or in combination with an acid susceptible compound may be in a dosage form administered orally, rectally, epidurally, intravenously, intramuscularly, subcutanously, by infusion, nasally or any other way suitable for administration. Preferably the active compound(-s) is administered orally.

The active compound(-s) are administered one to several times a day, preferably once or twice daily. The typical daily dose of the active compound(-s) varies and will depend on various factors such as the individual requirements of the patients, the mode of administration and disease. In general each dosage form will comprise 0.5 – 5000 mg, preferably 5 – 1000 mg, of the NO-releasing NSAID. If a combination with a proton pump inhibitor is used 0.5 – 5000 mg of the NO-releasing NSAID, and 0.1 – 200 mg of the proton pump inhibitor will be comprised in each dosage form, or in two separate dosage forms. Preferably, the amount of the NO-releasing NSAID in each dosage form is 5 – 1000 mg, and the amount of the proton pump inhibitor 10 - 80 mg.

Detailed description of the invention

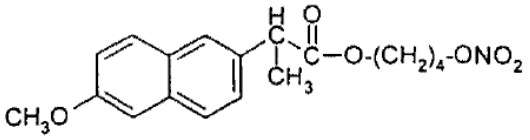
The invention is described in more detail by the following non-limiting examples.

The examples below support that NO-releasing NSAIDs are active against *Helicobacter pylori*, and that the antibacterial activity is concentration dependent.

Example 1.

Strain: *Helicobacter pylori* reference strain NCTC 11 637 (National Type Culture Collection, from Smittskyddsinstitutet in Solna, Sweden), an antibiotic sensitive reference strain

Substance:



Ia

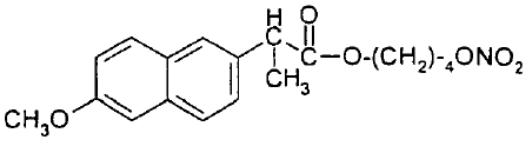
Helicobacter pylori was grown on blood agar plates, having a diameter of 90 mm, for three days under microaerophilic conditions at 37°C. The bacteria were suspended in PBS (phosphate buffer saline) to approximately 10^8 cfu/ml. Approximately 2 ml of the suspension was added to one agar plate and spread even on the surface of the agar. Overflow was removed with a syringe. Wells, like small holes, 3 mm in diameter, were made in the agarplate by removing agar. Three wells per plate were made.
A stock solution of a compound of the formula Ia having the concentration 100 000 µg/ml was prepared. 30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.
Result: The inhibition zone around each well was large, i.e. it was not possible to measure the diameter of the zone.

Example 2.

Strain: *Helicobacter pylori* reference strain NCTC 11 637 (see Example 1), an antibiotic sensitive reference strain

Substance:

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Ia

The plates with the wells were prepared according to Example 1.

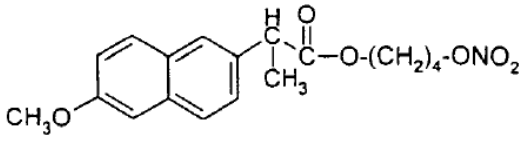
A stock solution of a compound of the formula Ia having the concentration 10 000 µg/ml was prepared. 30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

Result: The inhibition zone around each well was large, i.e. it was not possible to measure the diameter of the zone.

Example 3.

Strain: *Helicobacter pylori* reference strain NCTC 11 637, an antibiotic sensitive reference strain (see Example 1)

Substance:



Ia

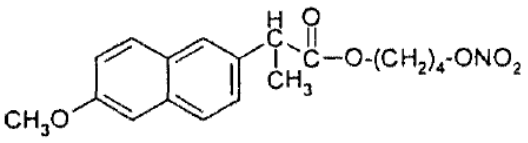
The plates with the wells were prepared according to Example 1.
A stock solution of a compound of the formula Ia having the concentration 1 000 µg/ml was prepared. 30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

Result: The inhibition zone around each well was 13 mm.

Example 4.

Strain: *Helicobacter pylori* reference strain NCTC 11 637, an antibiotic sensitive reference strain (see Example 1)

Substance:



Ia

The plates with the wells were prepared according to Example 1.

A stock solution of a compound of the formula Ia having the concentration 100 µg/ml was prepared. 30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

Result: The inhibition zone around each well was 10.4 mm.

Comparative tests

Example A

Strain: *Helicobacter pylori* reference strain NCTC 11 637, an antibiotic sensitive reference strain (see Example 1)

Substance: Naproxen

The plates with the wells were prepared according to Example 1.

A stock solution of Naproxen having the concentration 10 000 µg/ml was prepared.

30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

Result: The inhibition zone around the each well was 16.6 mm.

Example B

Strain: *Helicobacter pylori* reference strain NCTC 11 637, an antibiotic sensitive reference strain (see Example 1)

Substance: Naproxen

The plates with the wells were prepared according to Example 1.

A stock solution of Naproxen having the concentration 1000 µg/ml was prepared. 30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

Result: No inhibition zones around the wells were formed.

Example C

Strain: *Helicobacter pylori* reference strain NCTC 11 637, an antibiotic sensitive reference strain (see Example 1)

Substance: Naproxen

The plates with the wells were prepared according to Example 1.

A stock solution of Naproxen having the concentration 100 µg/ml was prepared.

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30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

Result: No inhibition zones around the wells were formed.

Example D

Strain: *Helicobacter pylori* reference strain NCTC 11 637, an antibiotic sensitive reference strain (see Example 1)

Substance: S-nitroso-N-acetyl-penicillamin (SNAP)

The plates with the wells were prepared according to Example 1.

A stock solution of SNAP with the concentration 10 000 µg/ml was prepared.
30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

Result: No inhibition zones around the wells were formed.

Example E

Strain: *Helicobacter pylori* reference strain NCTC 11 637, an antibiotic sensitive reference strain (see Example 1)

Substance: Di-methyl-sulphate-oxide (DMSO)

The plates with the wells were prepared according to Example 1.

A solution of DMSO alone with the concentration 20 µg/ml was prepared.

30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

Result: No inhibition zones around the wells were formed.

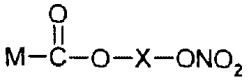
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Claims

1. Use of a NO-releasing NSAID as well as a pharmaceutically acceptable salt or an enantiomer thereof, for the manufacture of a medicament for the treatment of bacterial infections.

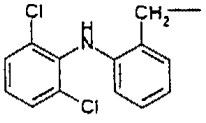
2. Use of a NO-releasing NSAID and an acid susceptible proton pump inhibitor or a salt thereof or an enantiomer or a salt of the enantiomer in the manufacture of pharmaceutical formulations intended for simultaneous, separate, or sequential administration in the treatment of bacterial infections.

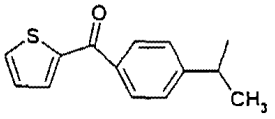
3 Use according to claim 1 or 2 wherein the NO-releasing NSAID is a compound of the formula I

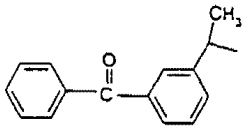


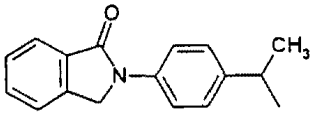
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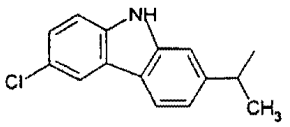
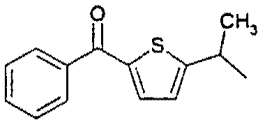
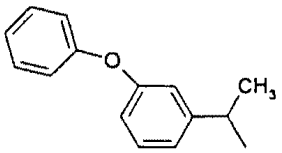
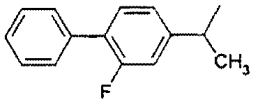
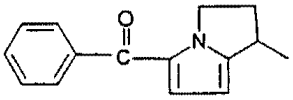
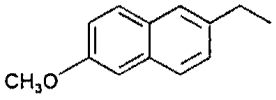
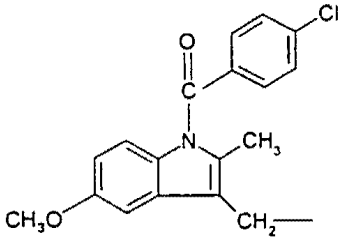
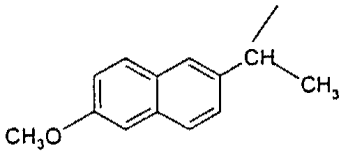
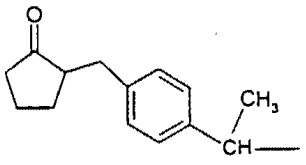
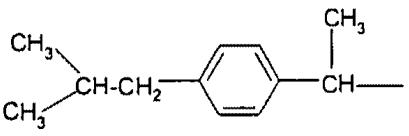
wherein M is selected from anyone of









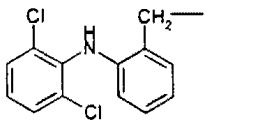
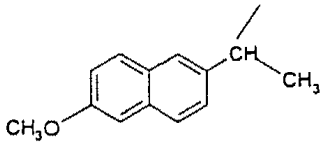
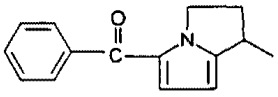
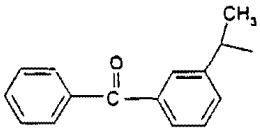
and X is selected from

linear, branched or cyclic $-(CH_2)_n-$ wherein n is an integer of from 2 to 10;

$-(CH_2)_m-O-(CH_2)_p-$ wherein m and p are integers of from 2 to10; and $-CH_2-pC_6H_4-CH_2-$,

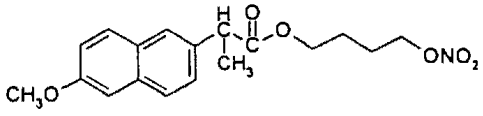
or a pharmaceutically acceptable salt or enantiomer thereof.

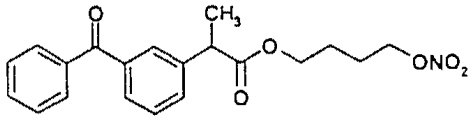
4. Use according to claim 3 wherein M in formula I is selected from

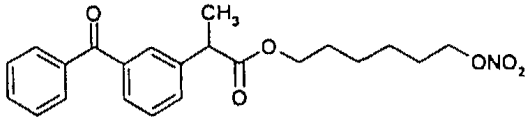





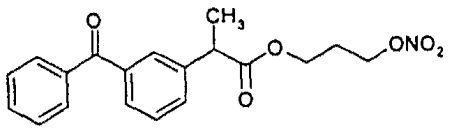
5. Use according to claim 3 or 4 wherein X in formula I is selected from linear $-(CH_2)_n-$ wherein n is an integer of from 2 to 6, $-(CH_2)_2-O-(CH_2)_2-$ and $-CH_2-pC_6H_4-CH_2-$.

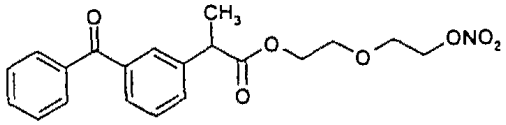
6. Use according to any one of claims 1 - 3 wherein the NO-releasing NSAID is a compound according to any one of the formulas Ia - Iq

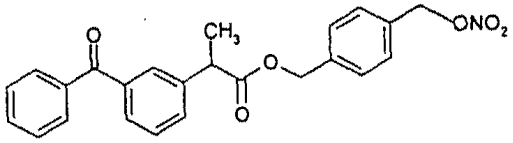

(Ia) ;

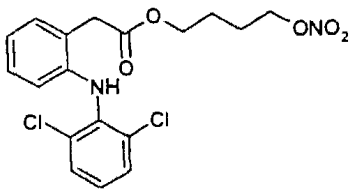

(Ib) ;

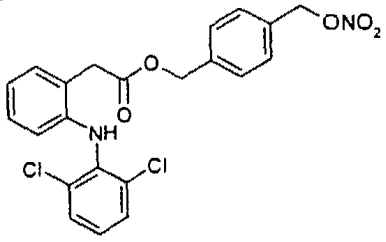

(Id) ;

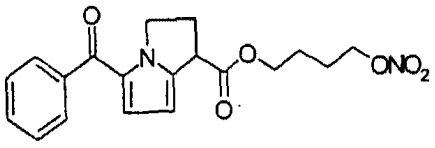

(Ic) ;

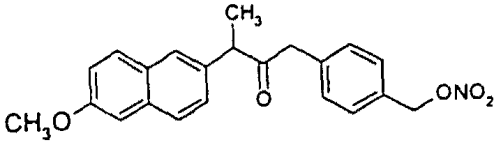

(Ie) ;

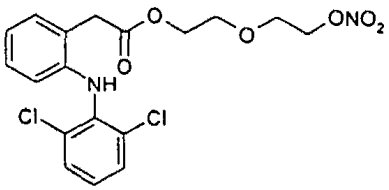

(If) ;


(Ig) ;

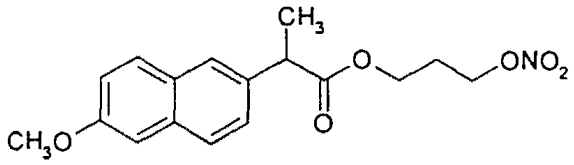

(Ii) ;


(Ij) ;

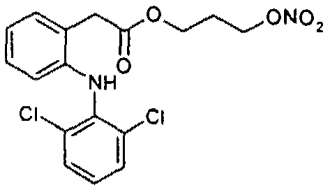

(Ik) ;



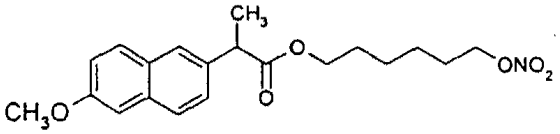
(IL) ;



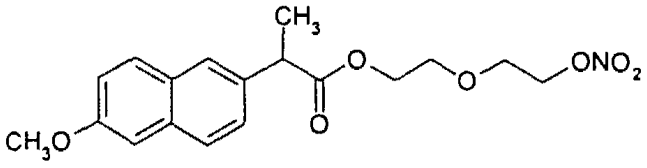
(Im) ;



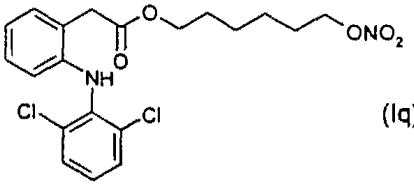
(In) ;



(Io) ;

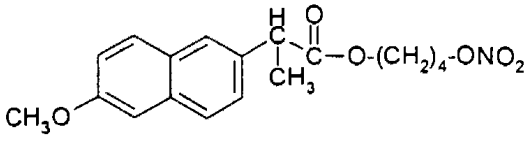


(Ip) ; and



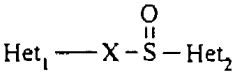
(Iq)

7. Use according to claim 6, wherein the NO-releasing NSAID is a compound of formula Ia



(Ia)

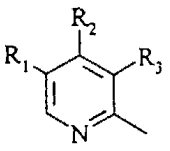
8. Use according to claim 2 wherein the acid susceptible proton pump inhibitor is a compound of the formula II



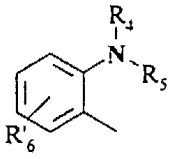
II

wherein

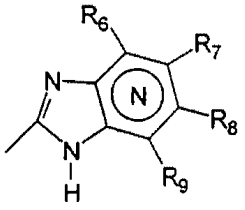
Het_1 is



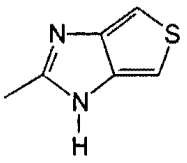
or



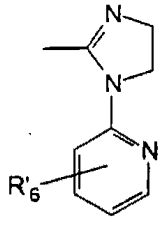
Het_2 is



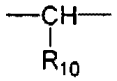
or



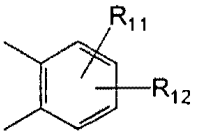
or



X =



or



wherein

N in the benzimidazole moiety means that one of the carbon atoms substituted by R_6-R_9 optionally may be exchanged for a nitrogen atom without any substituents;

R_1, R_2 and R_3 are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R_4 and R_5 are the same or different and selected from hydrogen, alkyl and aralkyl;

R_6' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

R_6-R_9 are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_6-R_9 form ring structures which may be further substituted;

R_{10} is hydrogen or forms an alkylene chain together with R_3 and

R_{11} and R_{12} are the same or different and selected from hydrogen, halogen or alkyl, alkyl groups, alkoxy groups and moities thereof , they may be branched or straight C_1 - C_9 - chains or comprise cyclic alkyl groups, such as cycloalkyl-alkyl.

9. Use according to claim 8 wherein the acid susceptible proton pump inhibitor is selected from omeprazole, an alkaline salt thereof, (S)-omeprazole and an alkaline salt thereof .

10. Use according to claim 8 wherein the acid susceptible proton pump inhibitor is lansoprazole or a pharmaceutically acceptable salt thereof or an enantiomer or a salt of the enantiomer.

11. Use according to claim 8 wherein the acid susceptible proton pump inhibitor is pantoprazole or a pharmaceutically acceptable salt thereof or an enantiomer or a salt of the enantiomer.

12. Use according to any one of the preceeding claims 1 to 11, wherein the bacterial infection is caused or mediated by *Helicobacter pylori*.

13. Use according to claim 1, wherein the amount of NO-releasing NSAID in each dosage form is 0.5 – 5000 mg.

14. Use according to claim 13, wherein the amount of NO-releasing NSAID is 5 – 1000 mg.

15. Use according to claim 2, wherein the amount of NO-releasing NSAID is 0.5 – 5000 mg and the amount of proton pump inhibitor is 0.1 – 200 mg together in one dosage form or in two separate dosage forms.

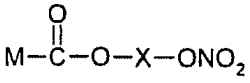
16. Use according to claim 15, wherein the amount of NO-releasing NSAID is 5 – 1000 mg and the amount of proton pump inhibitor is 10 – 80 mg.

17. A method for the treatment of a bacterial infection, comprising administering to a patient suffering from said bacterial infection, an effective amount of a NO-releasing NSAID or a pharmaceutically acceptable salt or an enantiomer thereof.

18. A method for the treatment of a bacterial infection, comprising simultaneously, separately or sequentially administration to a patient suffering from said bacterial infection,

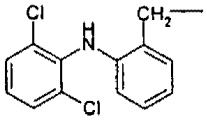
an effective amount of a NO-releasing NSAID and an acid susceptible proton pump inhibitor or a salt thereof or an enantiomer or a salt of the enantiomer.

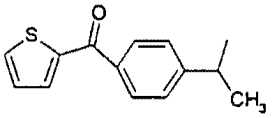
19. A method according to claim 17 or 18 wherein the NO-releasing NSAID is a compound of the formula I

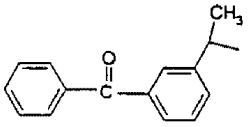


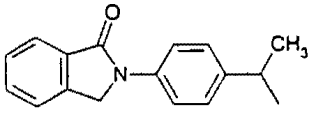
I

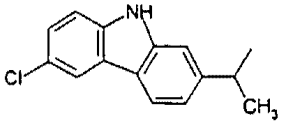
wherein M is selected from

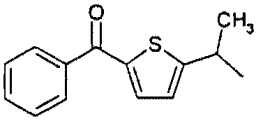


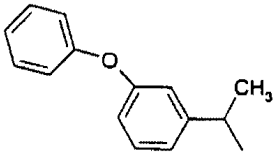


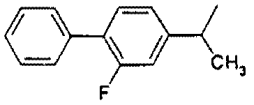


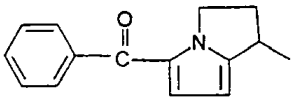
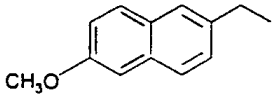
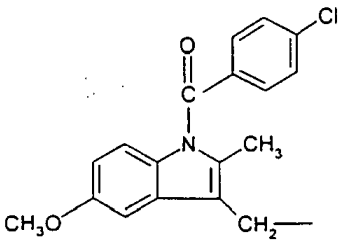
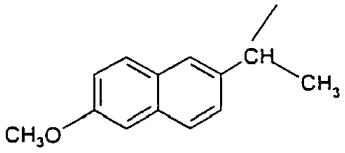


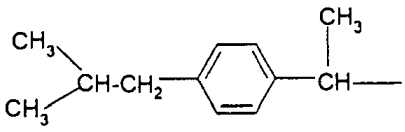










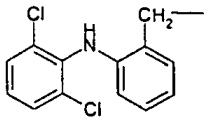
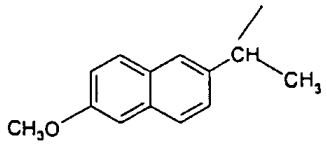
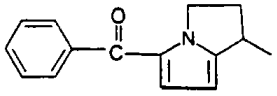
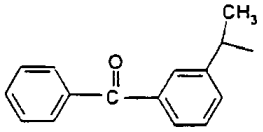
and X is selected from

linear, branched or cyclic $-(CH_2)_n-$ wherein n is an integer of from 2 to 10;

$-(CH_2)_m-O-(CH_2)_p-$ wherein m and p are integers of from 2 to 10; and $-CH_2-pC_6H_4-CH_2-$,

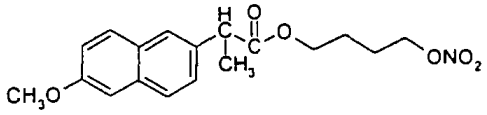
or a pharmaceutically acceptable salt or enantiomer thereof.

20. A method according to claim 19 wherein M in formula I is selected from

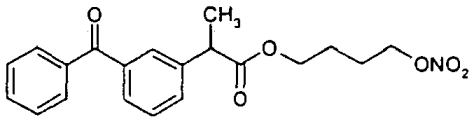





21. A method according to claim 19 or 20 wherein X in formula I is selected from linear $-(CH_2)_n-$ wherein n is an integer of from 2 to 6, $-(CH_2)_2-O-(CH_2)_2-$ and $-CH_2-pC_6H_4-CH_2-$.

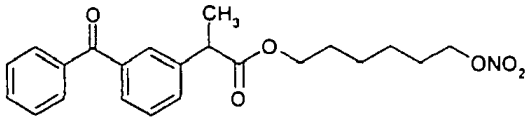
22. A method according to any one of claim 17 – 19, wherein the NO-releasing NSAID is a compound according to any one of the formulas Ia - Iq



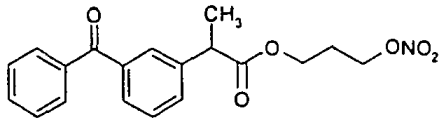
(Ia) ;



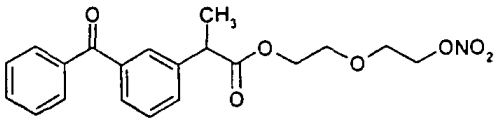
(Ib) ;



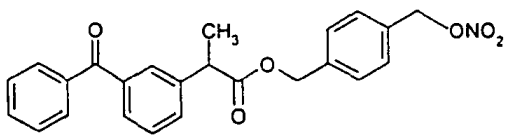
(Id) ;



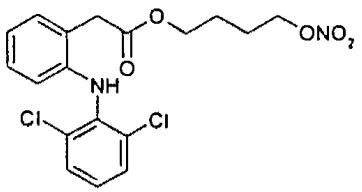
(Ic) ;



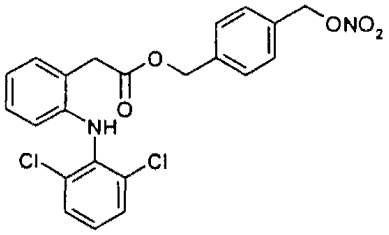
(Ie) ;



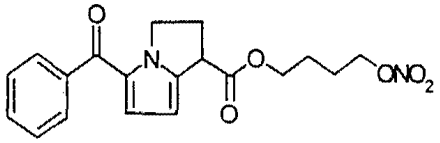
(If) ;



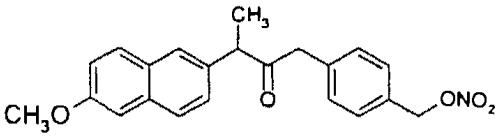
(Ig) ;



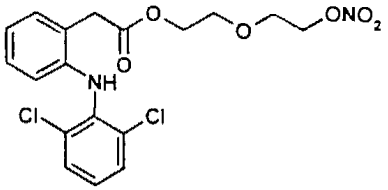
(Ii) ;



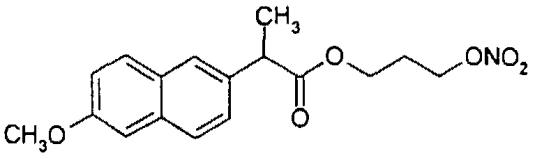
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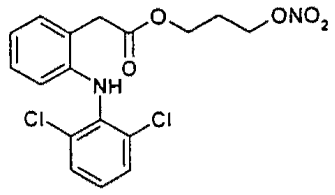
(Ik) ;



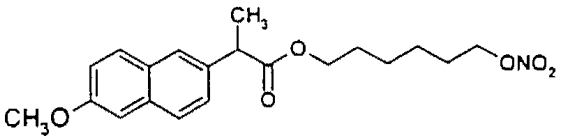
(IL) ;



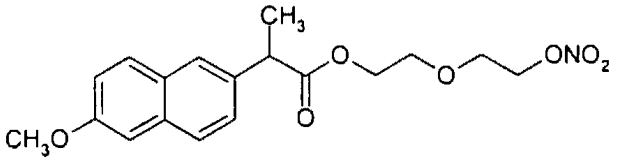
(Im) ;



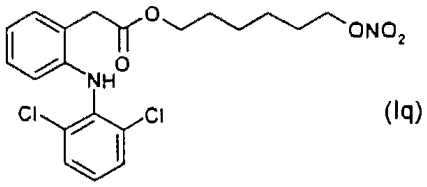
(In) ;



(Io) ;

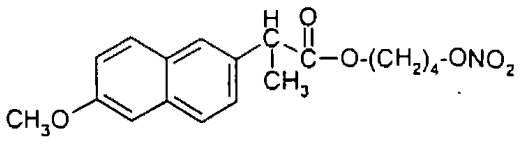


(Ip) ; and



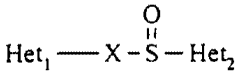
(Iq)

23. A method according to claim 22, wherein the NO-releasing NSAID is a compound of formula Ia



(Ia)

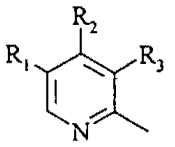
24. A method according to claim 18 wherein the acid susceptible proton pump inhibitor is a compound of the formula II



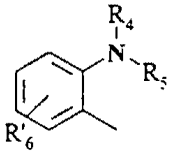
II

wherein

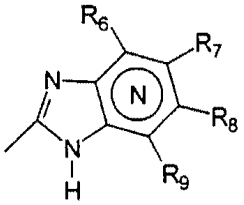
Het_1 is



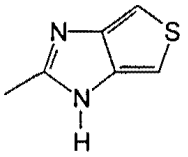
or



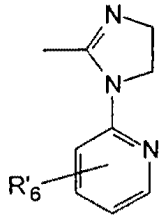
Het_2 is



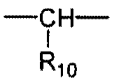
or



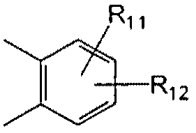
or



X =



or



wherein

N in the benzimidazole moiety means that one of the carbon atoms substituted by R_6-R_9 optionally may be exchanged for a nitrogen atom without any substituents;

R_1, R_2 and R_3 are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R_4 and R_5 are the same or different and selected from hydrogen, alkyl and aralkyl;

R_6' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

R_6-R_9 are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_6-R_9 form ring structures which may be further substituted;

R_{10} is hydrogen or forms an alkylene chain together with R_3 and

R_{11} and R_{12} are the same or different and selected from hydrogen, halogen or alkyl, alkyl groups, alkoxy groups and moities thereof , they may be branched or straight C_1 - C_9 - chains or comprise cyclic alkyl groups, such as cycloalkyl-alkyl.

25. A method according to claim 24 wherein the acid susceptible proton pump inhibitor is selected from omeprazole, an alkaline salt thereof, (*S*)-omeprazole and an alkaline salt thereof .

26. A method according to claim 24 wherein the acid susceptible proton pump inhibitor is lansoprazole or a pharmaceutically acceptable salt thereof or an enantiomer or a salt of the enantiomer.

27. A method according to claim 24 wherein the acid susceptible proton pump inhibitor is pantoprazole or a pharmaceutically acceptable salt thereof or an enantiomer or a salt of the enantiomer.

28. A method according to any one of the preceeding claims 17 to 27, wherein the bacterial infection is caused or mediated by *Helicobacter pylori*.

29. A method according to claim 17, wherein the amount of NO-releasing NSAID in each dosage form is 0.5 – 5000 mg.

30. A method according to claim 29, wherein the amount of NO-releasing NSAID is 5 – 1000 mg.

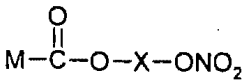
31. A method according to claim 18, wherein the amount of NO-releasing NSAID is 0.5 – 5000 mg and the amount of proton pump inhibitor is 0.1 – 200 mg together in one dosage form or in two separate dosage forms.

32. A method according to claim 31, wherein the amount of NO-releasing NSAID is 5 – 1000 mg and the amount of proton pump inhibitor is 10 – 80 mg.

33. A pharmaceutical formulation suitable for use in the treatment of bacterial infections, comprising a NO-releasing NSAID or a pharmaceutically acceptable salt or an enantiomer thereof as active agent.

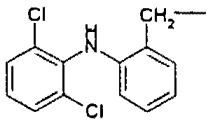
34. A pharmaceutical formulation suitable for use in the treatment of bacterial infections, comprising a NO-releasing NSAID and an acid susceptible proton pump inhibitor or a salt thereof or an enantiomer or a salt of the enantiomer as active agents.

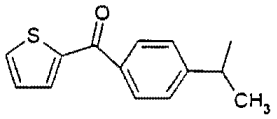
35. A pharmaceutical formulation according to claim 25 or 26 wherein the NO-releasing NSAID is a compound of the formula I

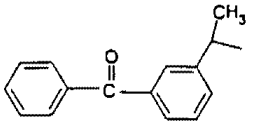


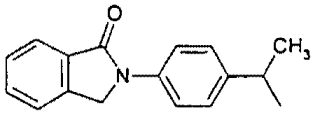
I

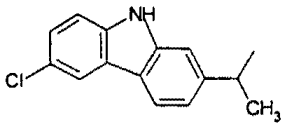
wherein M is selected from

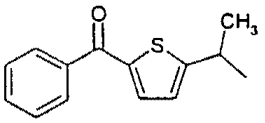


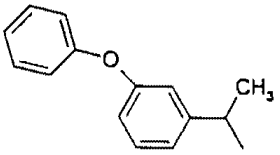


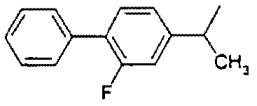


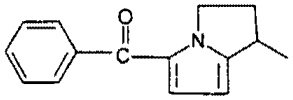


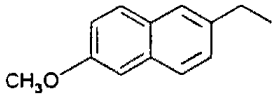


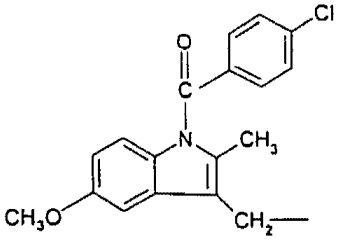


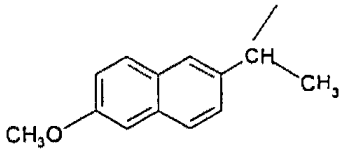


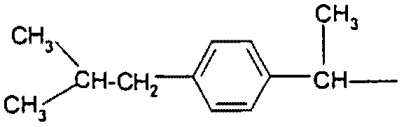












and X is selected from

linear, branched or cyclic $-(CH_2)_n-$ wherein n is an integer of from 2 to10;

$-(CH_2)_m-O-(CH_2)_p-$ wherein m and p are integers of from 2 to 10; and $-CH_2-pC_6H_4-CH_2-$;

or a pharmaceutically acceptable salt or enantiomer thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/01071

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/04, A61K 31/196, A61K 31/33, A61P 1/04, A61P 31/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STN International, File CAPLUS, CAPLUS accession no. 1999:500417, Document no. 131:255524, Yanaka, Akinori: "Role of nitric oxide in the pathogenesis of gastrointestinal deseases"; & Ensho (1999), 19 (3), 129-135 --	1-32
X	Pharmacol Ther, Volume 11, 1997, N.M. DAVIES et al, "NO-naproxen vs. naproxen: ulcerogenic, analgesic and anti-inflammatory effects" page 69 - page 79 --	1-32
X	WO 9967210 A1 (DUKE UNIVERSITY MEDICAL CENTER), 29 December 1999 (29.12.99), see part. page 3, line 18-19, page 15, line 17-20 --	1-32

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 Sept 2000	20 -09- 2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Eva Johansson/GH Telephone No. +46 8 782 25 00

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/01071

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9509612 A1 (ENTREMED, INC. ET AL), 13 April 1995 (13.04.95), see part. page 8, line 26, page 9, line 3 and 7	1-32
X	WO 9404484 A1 (CORLAY S.L. ET AL), 3 March 1994 (03.03.94)	33-35
X	WO 9509831 A1 (NICOX LIMITED), 13 April 1995 (13.04.95)	33-35
X	WO 9412463 A1 (HCT-HEALTH CARE TRADING LTD.), 9 June 1994 (09.06.94)	33-35
X	WO 9530641 A1 (NICOX LIMITED), 16 November 1995 (16.11.95)	33-35
A	WO 9731654 A1 (NICOX S.A.), 4 Sept 1997 (04.09.97)	1-35
A	WO 9822117 A1 (THE PROCTER & GAMBLE COMPANY), 28 May 1998 (28.05.98)	1-35
A	Am J Med, Volume 104, No 3A, 1998, Adrian Schmassmann, "Mechanisms of Ulcer Healing and Effects of Nonsteriodal Anti-inflammatory Drugs" page 43S - page 51S	1-35
A	Aliment Pharmacol Ther, Volume 13, 1999, S. FIORUCCI et al, "Nitric oxide-releasing NSAIDs inhibit interleukin-1.beta. converting enzyme-like cysteine proteases and protect endothelial cells from apoptosis induced by TNF.alfa." page 421 - page 435	1-35

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IPR2015-01344
Page 439 of 613

INTERNATIONAL SEARCH REPORT

on on patent family members

01/08/00

International application No.
PCT/SE 00/01071

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WO 9509612 A1	13/04/95	AU 7972294 A	01/05/95
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WO 9404484 A1	03/03/94	AT 143941 T	15/10/96
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		SE 0609415 T3	
		ES 2093979 T	01/01/97
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		IT 1256345 B	01/12/95
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Form PCT/ISA/210 (patent family annex) (July 1992)

INTERNATIONAL SEARCH REPORT

on on patent family members

01/08/00

International application No.
PCT/SE 00/01071

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9509831 A1	13/04/95	AT 168986 T	15/08/98
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		DE 69412109 D,T	21/01/99
		EP 0722434 A,B	24/07/96
		SE 0722434 T3	
		ES 2120070 T	16/10/98
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		AU 2215695 A	29/11/95
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(54) **Title:** STABLE PHARMACEUTICAL COMPOSITIONS COMPRISING ACID LABILE BENZIMIDAZOLES

(57) **Abstract:** This invention provides a solid preparation without enteric coating which contains an acid labile active ingredient, particularly, a benzimidazole compound having an antiulcer action, and can neutralize the acid in stomach quickly, and exerts quickly the pharmacological effect of the active ingredient and suppresses the generation of a carbon dioxide gas as much as possible. A gastric disintegrable solid preparation contains an acid labile active ingredient, particularly, a benzimidazole compound, and at least one component selected from metal oxides and metal hydroxides. The preparation does not enteric-coated, but has a disintegration time of 7 minutes or less.

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DESCRIPTION

STABLE PHARMACEUTICAL COMPOSITIONS COMPRISING ACID LABILE BENZIMIDAZOLES

Technical Field

The present invention relates to a solid preparation, further in detail, to a medical solid preparation containing an acid labile active ingredient, particularly, an acid labile active ingredient such as a benzimidazole compound useful as an antiulcer agent.

Background Art

Benzimidazole compounds such as lansoprazole, omeprazole, rabeprazole and the like are widely used as a digestive ulcer therapeutic agent because of its gastric acid secretion suppressing action and gastric mucous membrane preventing action and the like.

However, these compounds have poor stability, and unstable to humidity, temperature and light. They are particularly unstable to an acid, and become extremely unstable in aqueous solution or suspension as the pH of the solution or suspension lowers.

In a preparation, namely, a tablet, powder, fine particles, capsule and the like, benzimidazole compounds become unstable since mutual interaction with other components of the preparation is stronger in a preparation

than that of the compounds alone, and consequently, coloration change or decomposition is observed in production and storage. For stabilization of them, JP-A 10-36290 discloses enteric granules or enteric fine particles obtained by compounding a stabilizer composed of an inorganic base salt of magnesium and/or calcium for a medical solid composition, then, applying an enteric coating.

However, for producing such an enteric preparation, a process is required in which fine particles or granules containing a benzimidazole compound are produced, then, an enteric coating is applied. Further, since it takes a longer time until an enteric film is dissolved and a medicine is absorbed in a digestive tract after administration, a quick pharmacological effect can not be expected in the early stages after administration.

On the other hand, USP 5,840,737 and WO 00/26185 disclose a solution, suspension, tablet and capsule obtained by combining omeprazole or lansoprazole, which is not enteric-coated, with an alkali metal salt of bicarbonate.

However, since these preparations are combined with a bicarbonate, they react with an acid in stomach to evolve carbon dioxide gas which causes burping, and therefore they are not preferable from the viewpoint of compliance.

Objects of the Invention

An object of the present invention is to provide a solid preparation having no enteric coating which is capable of neutralizing quickly an acid in stomach, realizing quick occurrence of pharmacological effect of an active ingredient, and suppressing the evolution of carbon dioxide gas as much as possible, by solving the above-mentioned problems in medical solid preparations containing an acid labile active ingredient typically including benzimidazole compounds.

Summary of the Invention

The present inventors have found that a metal oxide and/or metal hydroxide is suitable for a gastric acid neutralizing agent in a solid preparation containing an acid labile active ingredient and having no enteric coating, and further investigation resulted in completion of the present invention.

Namely, the present invention provides:

(1) A gastric disintegrable solid preparation comprising an acid labile active ingredient and at least one component selected from metal oxides and metal hydroxides;

(2) A solid preparation according to the above-

mentioned (1), wherein the disintegration time is within 7 minutes;

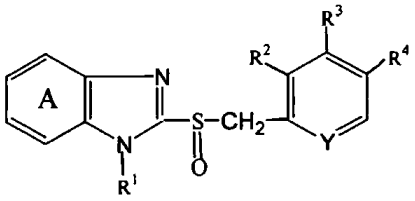
(3) A solid preparation according to the above-mentioned (1), which is the preparation without enteric coating;

(4) A solid preparation according to the above-mentioned (1), which comprises further at least one component selected from carbonates of alkali earth metal and basic additives having high water-solubility;

(5) A solid preparation according to the above-mentioned (1), wherein an acid labile active ingredient is a proton pump inhibitor (hereinafter, referred to as "PPI");

(6) A solid preparation according to the above-mentioned (5), wherein the PPI is a benzimidazole compound;

(7) A solid preparation according to the above-mentioned (6), wherein a benzimidazole compound is a compound represented by the formula (I):



(I)

wherein ring A is an optionally substituted benzene ring, R^1 is hydrogen atom, an optionally substituted aralkyl group, acyl group or acyloxy group, R^2, R^3 and R^4 are the

same or different and each represent a hydrogen atom, an optionally substituted alkyl group, an optionally substituted alkoxy group or an optionally substituted amino group, and Y represents a nitrogen atom or CH, or a salt thereof;

(8) A solid preparation according to the above-mentioned (6), wherein a benzimidazole compound is lansoprazole, omeprazole, rabeprazole or pantoprazole, or an optically active compound thereof;

(9) A solid preparation according to the above-mentioned (1), wherein the metal oxides and the metal hydroxides are those of which 1% aqueous solution or 1% aqueous suspension has a pH of 8.0 or more;

(10) A solid preparation according to the above-mentioned (1) which comprises at least one metal oxide selected from the group consisting of magnesium oxide, magnesium silicate, dry aluminum hydroxide gel and magnesium metasilicate aluminate;

(11) A solid preparation according to the above-mentioned (1) which comprises at least one metal hydroxide selected from the group consisting of magnesium hydroxide, aluminum hydroxide, synthetic Hydrotalcite, coprecipitate of aluminum hydroxide and magnesium hydroxide, coprecipitate of aluminum hydroxide, magnesium carbonate and calcium carbonate, and coprecipitate of aluminum

hydroxide and sodium bicarbonate;

(12) A solid preparation according to the above-mentioned (4), wherein the carbonate of alkali earth metal is calcium carbonate or magnesium carbonate;

(13) A solid preparation according to the above-mentioned (4), wherein the basic additive having high water-solubility is trometamol, disodium succinate, sodium hydrogen phosphate, trisodium phosphate, dipotassium phosphate or L-arginine;

(14) A solid preparation according to the above-mentioned (1) which contains magnesium oxide;

(15) A solid preparation according to the above-mentioned (1) which contains magnesium hydroxide;

(16) A solid preparation according to the above-mentioned (1) which contains magnesium oxide and magnesium hydroxide;

(17) A solid preparation according to the above-mentioned (14) or (16), wherein the magnesium oxide is one obtained by calcination at a temperature ranging from about 500°C to about 1000°C and of purity higher than 95%;

(18) A solid preparation according to the above-mentioned (14), wherein the magnesium oxide has a BET specific surface area of about $10m^2/g$ to about $50m^2/g$.

(19) A solid preparation according to the above-mentioned (6), which contains at least one component

selected from metal oxides and metal hydroxides at a ratio of 0.1 to 1500 parts by weight relative to 1 part by weight of the benzimidazole compound;

(20) A solid preparation according to the above-mentioned (6), which contains at least one component selected from metal oxides and metal hydroxides together with a salt of alkali earth metal at a total ratio thereof of 0.1 to 1800 parts by weight relative to 1 part by weight of the benzimidazole compound;

(21) A solid preparation according to the above-mentioned (1), which is a tablet, a granule or a capsule;

(22) A solid preparation according to the above-mentioned (1), wherein a group containing an acid labile active ingredient and a group containing a metal oxide or a metal hydroxide but containing no active ingredient are separately compounded; and

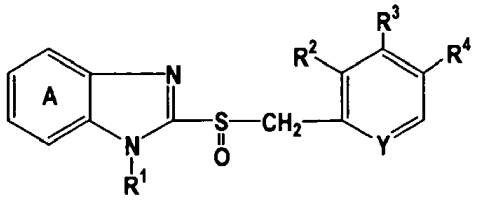
(23) A solid preparation according to the above-mentioned (4), wherein (1) a group containing both an active ingredient and at least one component selected from metal oxides, metal hydroxides, carbonates of alkali earth metal and basic additives having high water-solubility and (2) a group not containing an acid labile active ingredient but containing at least one component selected from metal oxides, metal hydroxides, carbonates of alkali earth metal and basic additives having high water-solubility are

separately compounded.

Detailed Description of the Invention

The acid labile active ingredient in the present invention is not particularly restricted, and any active components becoming unstable when exposed to gastric acid can be applied. Examples of the acid labile active ingredient include PPIs, erythromycin antibacterial compounds, anti-inflammatory enzymatic agents such as serrapeptase, semialkali proteinase and the like. Particularly, the present invention is suitable for PPIs. Such PPIs include benzimidazole compounds and similar compounds such as imidazopyridine compounds, e.g. tenatoprazole. Examples of benzimidazole compounds will be described below, however, the present invention is not limited to them and can be also applied to other active components unstable to an acid.

The benzimidazole compound which is a PPI, used in the present invention, includes a compound represented by the formula (I):



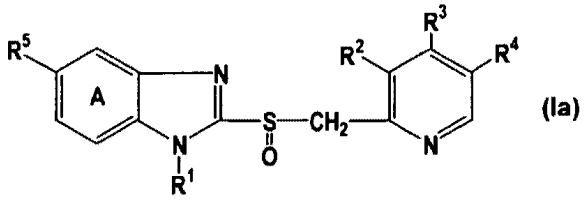
(I)

wherein, ring A represents an optionally substituted

benzene ring, R^1 represents a hydrogen atom, an optionally substituted aralkyl group, acyl group or acyloxy group, R^2, R^3 and R^4 are the same or different and each represent a hydrogen atom, an optionally substituted alkyl group, an optionally substituted alkoxy group or an optionally substituted amino group, and Y represents a nitrogen atom or CH, or a salt thereof.

In the formula (I), the compound is preferably a compound wherein ring A is a benzene ring which may optionally have a substituent group selected from a halogen atom, an optionally halogenated C_{1-4} alkyl group, an optionally halogenated C_{1-4} alkoxy group and 5 or 6-membered heterocyclic group, R^1 is a hydrogen atom, R^2 is a C_{1-6} alkyl group, C_{1-6} alkoxy group, C_{1-6} alkoxy-C_{1-6} alkoxy group or di-C_{1-6} alkylamino group, R^3 is a hydrogen atom, C_{1-6} alkoxy-C_{1-6} alkoxy group or optionally halogenated C_{1-6} alkoxy group, R^4 is a hydrogen atom or C_{1-6} alkyl group, and Y is a nitrogen atom.

Particularly preferable is the compound represented by the formula (Ia):



(Ia)

wherein, R^1 is a hydrogen atom, R^2 is a C_{1-3} alkyl group or

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C_{1-3} alkoxy group, R^3 is a C_{1-3} alkoxy group which may be halogenated or substituted by C_{1-3} alkoxy group, R^4 is a hydrogen atom or C_{1-3} alkyl group, and R^5 is a hydrogen atom, optionally halogenated C_{1-3} alkoxy group or pyrrolyl group (e.g., 1-, 2- or 3-pyrrolyl group).

In the formula (Ia), particularly preferable is the compound wherein R^1 is a hydrogen atom, R^2 is a C_{1-3} alkyl group, R^3 is an optionally halogenated C_{1-3} alkoxy group, R^4 is a hydrogen atom, and R^5 is a hydrogen atom or an optionally halogenated C_{1-3} alkoxy group.

In the compound represented by the formula (I) above (hereinafter, referred to as compound (I)), the "substituent groups" in "an optionally substituted benzene ring" represented by ring A include, for example, a halogen atom, cyano group, nitro group, an optionally substituted alkyl groups, hydroxyl group, optionally substituted alkoxy group, aryl group, aryloxy group, carboxyl group, acyl group, acyloxy group, 5 to 10-membered heterocyclic group and the like, and 1 to 3 of these substituent groups may be substituted on a benzene ring. When the number of substituent groups is 2 or more, each substituent groups may be the same or different. Among these substituents, a halogen atom, an optionally substituted alkyl group and an optionally substituted alkoxy group are preferable.

As the halogen atom, a fluorine atom, chlorine atom,

bromine atom and the like are exemplified, among which a fluorine atom is preferable.

Examples of "alkyl group" in "an optionally substituted alkyl group" include C_{1-7} alkyl group (for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, heptyl and the like). Examples of "substituent group" in "an optionally substituted alkyl group" include a halogen atom, hydroxy group, C_{1-6} alkoxy group (for example, methoxy, ethoxy, propoxy, butoxy, etc.), C_{1-6} alkoxy-carbonyl group (for example, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, etc.), carbamoyl group and the like, and the number of these substituent groups may be 1 to 3. When the number of substituent groups is 2 or more, each substituent groups may be the same or different.

Examples of "alkoxy group" in "an optionally substituted alkoxy group" include C_{1-6} alkoxy group (for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentoxy, etc.). Examples of "substituent group" in "an optionally substituted alkoxy group" include groups identical with the "substituent group" of the "optionally substituted alkyl group" described above, and the number of substituent groups is also the same as that of the "optionally substituted alkyl group".

The "aryl group" includes, for example, C_{6-14} aryl

group (e.g., phenyl, 1-naphtyl, 2-naphthyl, biphenyl, 2-anthryl, etc.) and the like.

The "aryloxy group" includes, for example, C_{6-14} aryloxy group (e.g., phenyloxy, 1-naphtyloxy, 2-naphthyloxy, etc.) and the like.

The "acyl group" includes, for example, formyl, alkylcarbonyl, alkoxycarbony, carbamoyl, alkylcarbamoyl, alkylsulfinyl, alkylsulfonyl and the like.

The "alkylcarbonyl group" includes, for example, C_{1-6} alkyl-carbonyl group (e.g., acetyl, propionyl, etc.) and the like.

The "alkoxycarbonyl group" includes, for example, C_{1-6} alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, etc.) and the like.

The "alkylcarbamoyl group" includes $N-C_{1-6}$ alkyl-carbamoyl group (e.g., methylcarbamoyl, ethylcarbamoyl, etc.), $N,N-diC_{1-6}$ alkyl-carbamoyl group (e.g., N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, etc.) and the like.

The "alkylsulfinyl group" includes, for example, C_{1-7} alkylsulfinyl group (e.g., methylsulfinyl, ethylsulfinyl, propylsulfinyl, isopropylsulfinyl, etc.) and the like.

The "alkylsulfonyl group" includes, for example, C_{1-7} alkylsulfonyl group (e.g., methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, etc.) and the like.

The "acyloxy group" includes, for example, alkylcarbonyloxy group, alkoxycarbonyloxy group, carbamoyloxy group, alkylcarbamoyloxy group, alkylsulfinyloxy group, alkylsulfonyloxy group and the like.

The "alkylcarbonyloxy group" includes C_{1-6} alkyl-carbonyloxy group (e.g., acetyloxy, propionyloxy, etc.) and the like.

The "alkoxycarbonyloxy group" includes, for example, C_{1-6} alkoxy-carbonyloxy group (e.g., methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, butoxycarbonyloxy, etc.) and the like.

The "alkylcarbamoyloxy group" includes C_{1-6} alkyl-carbamoyloxy group (e.g., methylcarbamoyloxy, ethylcarbamoyloxy, etc.) and the like.

The "alkylsulfinyloxy group" includes, for example, C_{1-7} alkyl-sulfinyloxy group (e.g., methylsulfinyloxy, ethylsulfinyloxy, propylsulfinyloxy, isopropylsulfinyloxy, etc.) and the like.

The "alkylsulfonyloxy group" includes, for example, C_{1-7} alkyl-sulfonyloxy group (e.g., methylsulfonyloxy, ethylsulfonyloxy, propylsulfonyloxy, isopropylsulfonyloxy, etc.) and the like.

The "5 to 10-membered heterocyclic group" includes, for example, 5 to 10-membered (preferably, 5 or 6-membered) heterocyclic group having 1 or more (for example, 1 to 3)

hetero atoms selected from a nitrogen atom, sulfur atom and oxygen atom in addition to a carbon atom, and specific examples thereof include 2- or 3-thienyl group, 2-, 3- or 4-pyridyl group, 2- or 3-furyl group, 1-, 2- or 3-pyrrolyl group, 2-, 3-, 4-, 5- or 8-quinolyl group, 1-, 3-, 4- or 5-isoquinolyl group, 1-, 2- or 3-indolyl group and the like. Among them, preferable are 5 or 6-membered heterocyclic group such as 1-, 2- or 3-pyrrolyl group.

Preferably, ring A is a benzene ring which may have one or two substituent groups selected from a halogen atom, an optionally halogenated C_{1-4} alkyl group, an optionally halogenated C_{1-4} alkoxy groups and 5 or 6-membered heterocyclic group.

Examples of "aralkyl group" in "an optionally substituted aralkyl group" represented by R^1 include, for example, C_{7-16} aralkyl group (e.g., C_{6-10} aryl C_{1-6} alkyl group such as benzyl, phenetyl, etc.) and the like. Examples of "substituent group" in "an optionally substituted aralkyl group" include the same substituent groups as those of the "optionally substituted alkyl group" described above, and the number of substituent groups is 1 to 4. When the number of substituent groups is 2 or more, each substituent groups may be the same or different.

The "acyl group" represented by R^1 includes, for example, the "acyl group" exemplified as the substituent

group on ring A described above.

The "acyloxy group" represented by R^1 includes, for example, the "acyloxy group" exemplified as the substituent group on ring A described above.

Preferably, R^1 is a hydrogen atom.

The "optionally substituted alkyl group" represented by R^2, R^3 or R^4 includes the "optionally substituted alkyl group" exemplified as the substituent group on ring A described above.

The "optionally substituted alkoxy group" represented by R^2, R^3 or R^4 includes the "optionally substituted alkoxy group" exemplified as the substituent group on ring A described above.

The "optionally substituted amino group" represented by R^2, R^3 or R^4 includes, for example, amino group, mono-C_{1-6} alkylamino group (e.g., methylamino, ethylamino, etc.), mono-C_{6-14} arylamino group (e.g., phenylamino, 1-naphthylamino, 2-naphthylamino, etc.), di-C_{1-6} alkylamino group (e.g., dimethylamino, diethylamino, etc.), di-C_{6-14} arylamino group (e.g., diphenylamino, etc.) and the like.

Preferably, R^2 is a C_{1-6} alkyl group, C_{1-6} alkoxy group, C_{1-6} alkoxy-C_{1-6} alkoxy group or di-C_{1-6} alkylamino group. More preferably, R^2 is a C_{1-3} alkyl group or C_{1-3} alkoxy group.

Preferably, R^3 is a hydrogen atom, C_{1-6} alkoxy-C_{1-6}

alkoxy group or optionally halogenated C_{1-6} alkoxy group. More preferably, R^3 is a C_{1-3} alkoxy group which is halogenated or may be substituted with a C_{1-3} alkoxy group.

Preferably, R^4 is a hydrogen atom or C_{1-6} alkyl group. More preferably, R^4 is a hydrogen atom or C_{1-3} alkyl group (particularly, hydrogen atom).

Preferably, Y is a nitrogen atom.

Specific examples of the compound (I) include the following compounds.

2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole, 2-[[3,5-dimethyl-4-methoxy-2-pyridinyl)methyl]sulfinyl]-5-methoxy-1H-benzimidazole, 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole•sodium salt, 5-difluoromethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and the like.

Among these compounds, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole(Lansoprazole) is preferable.

The above-mentioned compound (I) may be a racemic compound, or may be an optically active compound such as R-compound, S- compound and the like. For example, optically active substances such as (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (sometimes referred to as Lansoprazole R

enantiomer) may also be permissible and preferable.

The salt of the compound (I) is preferably a pharmaceutically acceptable salt, and examples thereof include salts with inorganic bases, salts with organic bases, salts with basic amino acids, and the like.

Suitable examples of the salt with an inorganic base include, for example, alkali metal salts such as sodium salts, potassium salts, etc.; alkaline earth metal salts such as calcium salts, magnesium salts, etc.; ammonium salts, and the like.

Suitable examples of the salt with an organic base include, for example, salts with alkylamines (trimethylamine, triethylamine, etc.), heterocyclic amines (pyridine, picoline, etc.), alkanolamines (ethanolamine, diethanolamine, triethanolamine, etc.), dicyclohexylamine, N,N'-dibenzylethylenediamine and the like.

Suitable examples of the salt with a basic amino acid include, for example, salts with alginine, lysine, ornithine and the like.

Among these salts, alkali metal salts or alkaline earth metal salts are preferable. Particularly, sodium salts are preferable.

The compound (I) can be produced by a method known per se, and produced by methods described, for example, JP-A 61-50978, USP 4,628,098, JP-A 10-195068, WO 98/21201 and

the like, or methods according to these methods. The optically active compound (I) can be obtained by optical resolution methods (fractional re-crystallization method, chiral column method, diastereomer method, method using microorganism or enzyme, etc.), asymmetric oxidation and the like. For example, in the case of Lansoprazole R enantiomer, it can also be produced in accordance with the methods described in WO 00-78745, WO 01-83473, WO 01-87874 and WO 02-44167.

As the PPIs used in the present invention, the benzimidazole compound having an antiulcer action such as lansoprazole, omeprazole, rabeprazole and pantoprazole and the imidazopyridine compound such as tenatoprazole or optically active compounds thereof and pharmaceutically acceptable salts thereof are preferable.

The compounding amount of the benzimidazole compound used in the present invention varies depending on the kind and dosage of an active ingredient, and for example, the amount is from 0.001 to 0.3 parts by weight, preferably from 0.002 to 0.2 parts by weight relative to 1 part by weight of the solid preparation of the present invention.

The metal oxide and metal hydroxide used in the present invention are preferably those of which 1% aqueous solution or 1% aqueous suspension has a pH of 8.0 or more, and examples of the metal oxide include medical magnesium

oxide, magnesium silicate ($2MgO \cdot 3SiO_2 \cdot xH_2O$), dry aluminum hydroxide gel ($Al_2O_3 \cdot xH_2O$), magnesium metasilicate aluminate ($Al_2O_3 \cdot MgO \cdot 2SiO_2 \cdot xH_2O$) and the like. Particularly, magnesium oxide can be suitably used.

Preferable magnesium oxides are those that are available for medical use and that have an excellent reactivity to acid and neutralization ability. As these magnesium oxides, magnesium oxide obtained by a usual production method and commercially available magnesium oxide can be used, and preferable is one obtained by calcination at low temperature, so-called, calcining magnesia. The magnesium oxide calcined at a temperature of about 500 to about 1000°C is generally preferable, and particularly from the viewpoint of neutralization ability the magnesium oxide calcined at a temperature of about 600 to about 900°C is preferable, and the magnesium oxide calcined at about 800°C is most preferable. Among these magnesium oxides, favorable is the one that neutralizes the environment prior to the release of the acid labile active ingredient by the disintegration of the preparation in stomach and has the function to enhance the remaining ratio of the active ingredient. Such magnesium oxide is preferably the one that has usually a BET specific surface area of about $10m^2/g$ to about $50m^2/g$, preferably about $20m^2/g$ to about $50m^2/g$.

Hereupon, a BET specific surface area means the specific surface area measured by nitrogen gas adsorption method, and the specific surface area containing the surface of given amount magnesium oxide and its cavity in which nitrogen gas can enter is determined by the amount of adsorbed nitrogen gas.

The magnesium oxide includes, for example, commercially available heavy magnesium oxide (manufactured by Kyowa Kagaku Kogyo K.K.), heavy magnesium oxide (Tomita Pharmaceutical Co. Ltd.), heavy N magnesium oxide (manufactured by Kyowa Kagaku Kogyo K.K.), light magnesium oxide (manufactured by Kyowa Kagaku Kogyo K.K.) and the like. Particularly heavy N magnesium oxide (manufactured by Kyowa Kagaku Kogyo K.K.) is preferable.

The metal hydroxide includes, for example, medical magnesium hydroxide, aluminum hydroxide, synthetic hydrotalcite ($Mg_6Al_2(OH)_{16}CO_3 \cdot 4H_2O$), co-precipitate of aluminum hydroxide and magnesium hydroxide, co-precipitate of aluminum hydroxide, magnesium carbonate and calcium carbonate, and co-precipitate of aluminum hydroxide and sodium hydrogen carbonate. Among these compounds, magnesium hydroxide is particularly preferable from the viewpoint of the disintegrating property and dissolution property of a preparation.

These may be used alone or in combination of two or

more. Some of metal oxides and metal hydroxides may whittle the surface of a preparation apparatus in production. As a result of such whittling, the resulting tablets sometimes become partially or wholly darkish or blackish and are imparted with black spots, lines or surfaces. Sticking of the resulting preparations on a die in production of tablets is also sometimes caused, depending on the metal hydroxides or metal oxides used. These properties deteriorate remarkably the productivity. It has been found that, when metal oxides or metal hydroxides having whittling property and adhesiveness on a die are used, the whittling action and adhesiveness on a die can be suppressed by wet or dry granulation using metal oxides or metal hydroxides having no such properties or pharmaceutically acceptable additives described bellow (excipients, binders, disintegrants, etc.) in combination. In the case of preparations of PPIs, preferred are magnesium hydroxides, magnesium oxides and combination of a magnesium hydroxide and magnesium oxide from the viewpoint of compatibility with PPIs, dissolution property, and disintegrating property of a preparation.

These metal oxides and/or metal hydroxides are compounded in such an amount that they are quickly dissolved and neutralize gastric acid simultaneously with disintegration of a solid preparation in stomach,

preferably, prior to dissolution of an active ingredient, in order to prevent unstabilization of substantial parts of an active ingredient by being exposed to gastric acid. Metal oxides and metal hydroxides are compounded usually in an amount of about 0.05 to 2000 parts by weight, preferably about 0.1 to 1000 parts by weight, more preferably about 0.1 to 800 parts by weight relative to 1 part by weight of an acid labile active ingredient, though the amount varies depending on the gastric acid neutralization ability of each metal oxide and metal hydroxide. For example, metal oxides and metal hydroxides are compounded in an amount of about 0.1 to 1500 parts by weight, preferably about 0.5 to 800 parts by weight, more preferably 0.1 to 400 parts by weight relative to 1 part by weight of a benzimidazole compound. When the active ingredient is a benzimidazole compound, the pH in stomach usually increases simultaneously with initiation of dosing, and they are compounded preferably in an amount that pH increases to 4 or more within about 60 minutes, more preferably within 40 minutes after administration, in stomach of usual pH range.

Usually, metal oxides and metal hydroxides are compounded preferably in an amount that pH increases to 7 or more within 10 minutes, more preferably within 7 minutes, by a measuring method as shown in the following experiment example.

In the present invention, at least one component selected from carbonates of alkaline earth metals and basic additives having high water-solubility may be compounded, in addition to these metal oxides and/or metal hydroxides, if necessary. The carbonates of alkaline earth metals include, for example, calcium carbonate and magnesium carbonate for medical use. The basic additives having high water-solubility include medical additives having an antacid action such as trometamol, disodium succinate, sodium hydrogen phosphate, trisodium phosphate, dipotassium phosphate, L-arginine and the like. These may also be used alone or in combination of two or more.

These are also compounded in such an amount that they are quickly dissolved and neutralize gastric acid simultaneously with disintegration of a solid preparation in stomach, preferably, prior to dissolution of an active ingredient, in order to prevent unstabilization of substantial parts of an active ingredient by being exposed to gastric acid, and are compounded usually in a total amount with metal oxides and metal hydroxides of about 0.05 to 2000 parts by weight, preferably about 0.1 to 1200 parts by weight, more preferably about 0.1 to 800 parts by weight relative to 1 part by weight of a acid labile active ingredient, though the amount varies depending on the gastric acid neutralization ability of each additives.

Usually, neutralization agents are compounded in a total amount of 0.1 to 1800 parts by weight, preferably about 0.5 to 1000 parts by weight, more preferably 1 to 800 parts by weight relative to 1 part by weight of a benzimidazole compound. Preferably, they are compounded in an amount that pH increases to 4 or more within about 60 minutes, more preferably within 40 minutes after administration, in stomach of usual pH range.

In the solid preparation of the present invention, additives can be further used such as excipients for preparation (e.g., glucose, fructose, lactose, sucrose, D-mannitol, erythritol, maltitol, trehalose, sorbitol, corn starch, potato starch, wheat starch, rice starch, microcrystalline cellulose (crystalline cellulose), anhydrous silic acid, anhydrous calcium phosphate, precipitated calcium carbonate, calcium silicate, etc.), binder (e.g., hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, methylcellulose, polyvinyl alcohol, carboxymethylcellulose sodium, partial α-starch, α-starch, sodium alginate, pullulan, gum Arabic powder, gelatin, etc.), disintegrating agent (e.g., low-substituted hydroxypropylcellulose, calmellose, calmellose calcium, carboxymethyl starch sodium, cross calmellose sodium, crospovidone, hydroxypropyl starch, etc.), flavoring agent (e.g., citric acid, ascorbic acid,

tartaric acid, malic acid, aspartame, acesulfam potassium, somatin, saccharin sodium, dipotasium glycirrhizinate, sodium glutamate, sodium 5'-inosinate, sodium 5'-guanylate, etc), surfactant (e.g., polysorbate, polyoxyethylene•polyoxypropylene copolymer, sodium laurylsulfate, etc.), aromatics (e.g., lemon oil, orange oil, menthol, peppermint oil, etc.), lubricant (e.g., magnesium stearate, sucrose fatty acid ester, stearyl sodium fumarate, stearic acid, talc, polyethylene glycol, etc.), coloring agent (e.g., edible yellow No. 5, edible blue No. 2, ferric oxide, yellow ferric oxide, etc.) and antioxidant (e.g., sodium ascorbate, L-cysteine, sodium sulfite, etc.).

The particle size of a raw material used in them is not particularly restricted, and preferably 500 μm or less from the standpoint of a production property and dosing property.

The method of producing the solid preparation of the present invention may be a method known per se, and for example, benzimidazole compounds, metal oxides and/or metal hydroxides, if necessary, carbonates of alkaline earth metals and/or basic additives having higher water-solubility and an antacid action, excipients, further, binders, disintegrating agents, lubricants, flavoring agents, coloring agents, aromatics are combined suitably to

give a tablet, powder, granule, capsule, fine particles and the like. These can be produced by a method described in the preparation general rule of The Pharmacopoeia of Japan, 14th revision.

Particularly, the granulation by wet granulation is preferred.

Herein, the wet granulation means a method for obtaining granulated materials or powders such as granules and fine granules by granulating a dispersion or solution of the mixture of a drug and excipient in water, binder or solvent and then drying, and the granulation mechanism may be any type such as extrusion, fluidization, rolling, centrifuging, stirring, spraying etc.

Further, these preparations may be coated with a coating agent (for example, coating film containing hydroxypropylmethylcellulose, hydroxypropylcellulose, polyvinyl alcohol, polyvinyl pyrrolidone, etc.), however, an enteric coating is not applied.

In the present invention, preparation raw materials may be formulated in one portion, or may be divided into two or more groups and formulated (for example, layer separation, granulations having different disintegrating properties, etc.). In any case, metal oxides and/or metal hydroxides, further, carbonates of alkaline earth metals and/or basic additives having higher water-solubility and

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an antacid property are quickly dissolved and neutralize gastric acid simultaneously with disintegration of a solid preparation in stomach, preferably, prior to dissolution of an active ingredient, and prevent unstabilization of substantial parts of an active ingredient by being exposed to gastric acid. For example, a method in which a group containing an active ingredient is compounded near the nucleus of a preparation and a metal oxide and/or metal hydroxide is compounded in an outer layer of the preparation are exemplified.

Also in either case of one-group formulation or divided or separate-groups formulation, it is possible to neutralize gastric acid by compounding a basic additive having high water solubility and dissolving it quickly.

Further, by dividing preparation raw materials into a group containing an acid labile active ingredient and a group containing no active ingredient and compounding them separately in the preparation to give a time difference of disintegration of components, the group containing no active component can be formulated to disintegrate more quickly. A metal oxide and/or metal hydroxide may be compounded in both groups or in the group containing no active ingredient. Further, a carbonate of an alkaline earth metal and/or a basic additive having high water solubility and an antacid action may be compounded in

either group or both groups.

Furthermore, a preparation containing a group which contains neither an active ingredient nor a metal oxide and metal hydroxide but contains mainly a carbonate of an alkaline earth metal and/or a basic additive having high water solubility and an antacid action, may also be formulated. Particularly, this preparation is suitable to increase the pH in stomach by dissolving this group more quickly.

Further, when the components are grouped and formulated separately, an additive having bonding ability to a group containing an active ingredient (e.g., hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, polyvinylpyrrolidone, methylcellulose, polyvinyl alcohol, carboxymethylcellulose sodium, partial α-starch, α-starch, sodium alginate, pullulan, gum Arabic powder, gelatin, polyethylene oxide, carboxymethylethylcellulose, carboxyvinyl polymer, ethylcellulose, ethyl acrylate•methyl methacrylate•trimethylammoniumethyl methacrylate copolymer, etc.) may be compounded to delay the dissolution of the active ingredient. Further, a group containing an active component may be coated to delay the dissolution with a component containing hydroxypropylmethylcellulose, hydroxypropylcellulose, polyvinyl alcohol,

polyvinylpyrrolidone, ethylcellulose or ethyl acrylate•methyl methacrylate•trimethylammoniumethyl methacrylate copolymer.

More specifically, a tablet can be produced, for example, by several methods such that a benzimidazole compound, metal hydroxide, excipient, binder, disintegrating agent and lubricant are mixed and compressed directly into tablets; a benzimidazole compound, a metal hydroxide, excipient and additive having high water solubility and an antacid action are mixed, then, a binder is added to the mixture to form granules, and a disintegrating agent and lubricant are added to the granules, and then the resultant mixture is compressed into tablets; and a benzimidazole compound, a metal hydroxide and excipient are mixed, then, a binder is added to the mixture to obtain granules, and separately, a metal hydroxide, additive having high water solubility and an antacid action and excipent are mixed, then, a binder is added to the mixture to obtain granules, and these obtained granules, disintegrating agent and lubricant are mixed and compressed into tablets.

Further, in the case of production of two or more kinds of granules, it is also possible that one or more kinds of binders are added to a group containing a benzimidazole compound to suppress its dissolution.

Granules can be produced by an ordinary method. For example, granules can be produced by the same methods as the production methods of a tablet, or by an extrusion granulation method. For obtaining granules having higher sphericity and smaller particle size distribution, for example, nucleus-containing granules may be produced by a method described in JP-A 63-301816. Nucleus-containing granules are obtained by coating a powdery spray agent containing a benzimidazole compound having an antiulcer action, metal hydroxide, excipient, disintegrating agent and the like while spraying binding liquid such as hydroxypropylcellulose on a sugar nucleus. The nucleus granule includes, for example, Nonparell obtained by coating sucrose (75 parts by weight) with corn starch (25 parts by weight) by a method known per se, and spherical nucleus granules using crystalline cellulose, and further, the nucleus granule itself may be the active ingredient component mentioned above. The average particle size of the nucleus granule is generally 14 to 80 mesh.

In the case of a capsule, it can be obtained by filling with a simply mixed powder or the particles for a tablet or granule obtained above.

The solid preparation obtained in the present invention is a gastric disintegrable solid preparation without enteric coating having an disintegration time of 7

minutes or less, preferably 5 minutes or less, more preferably 4 minutes or less, by the measurement of disintegrating time based on the method described in United States Pharmacopoeia <701> Disintegration.

The solid preparation of the present invention can be itself administered orally. The solid preparation of the present invention can be taken in the form of liquid or semisolid by dispersing or dissolving it previously in water, juice, yoghurt and the like.

In the solid preparation of the present invention, when the active ingredient is, for example, a benzimidazole compound represented by the formula (I) such as lansoprazole and optically active compounds thereof, these compounds are useful as a medicine since they have excellent antiulcer action, gastric acid secretion-suppressing action, mucous membrane protecting action, anti-Helicobacter pylori action and the like, and have low toxicity. In this case, the solid preparation of the present invention can be orally administered to mammal animals (for example, human, monkey, sheep, horse, dog, cat, rabbit, rat, mouse, etc.), for the purpose of treating and preventing peptic ulcer (for example, gastric ulcer, duodenal ulcer, stomal ulcer, Zollinger-Ellison syndrome, etc.), gastritis, Gastroesophageal Reflux Diseases (GERD) e.g. reflux esophagitis, Symptomatic GERD, erosive

esophagitis; NUD (Non Ulcer Dyspepsia), stomach cancer (including stomach cancer caused by promotion of production of interleukin-1ß by gene polymorphism of interleukin-1), stomach MALT lymphoma and the like, removing Helicobacter pylori, suppression of upper digestive canal hemorrhage caused by peptic ulcer, acute stress ulcer, and hemorrhagic gastritis, suppressing upper digestive canal hemorrhage caused by invasive stress (stress caused by cerebral vascular disorder requiring major operation or intensive care needing intensive management after operation, head trauma, multi-organ disorder, wider range heat injury), treating and preventing ulcer ascribed to nonsteroidal anti-inflammatory agent; and treating and preventing gastric hyperacidity and ulcer by stress after operation. For removal of Helicobacter pylori, it is preferable to use the solid preparation and, penicillin antibiotics (e.g., amoxicillin) and erythromycin antibiotics (e.g., clarithromycin), together.

The preparation of this invention is especially applicable for GERD (e.g., Symptomatic GERD and erosive esophagitis).

The daily dose differs depending on severity of symptom, age, sex and body weight of the patient, period and interval of administration, kind of the active ingredient employed and the like, and is not particularly

restricted, and for example, the solid preparation can be administered as an antiulcer agent to an adult (60 kg) at an oral daily dose of about 0.5 to 1500 mg/day, preferably about 5 to 150 mg/day as an active ingredient. These benzimidazole compound-containing preparations may be administered once or in two or three divided portions a day.

Examples

Hereinafter, the present invention is further detailed by the following Examples, which are not intended to restrict the present invention.

Example 1

Production of active ingredient group

240 g of lansoprazole, 1160 g of magnesium hydroxide, 616 g of D-mannitol and 264 g of corn starch were charged into a fluidized bed granulator, and 8% aqueous solution prepared by dissolving 120 g of hydroxypropylcellulose in 1380 g of purified water was sprayed, and these materials were granulated, and dried to obtain 2188 g of granules.

Production of outer layer group

870 g of magnesium hydroxide, 1107 g of D-mannitol and 474 g of corn starch were charged in a fluidized bed granulator, and 750 g of purified water was sprayed, and these materials were granulated, and dried to obtain 2199 g

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of granules.

300 g of a active ingredient group, 408.5 g of an outer layer group, 37.5 g of crospovidone and 11 g of magnesium stearate were mixed in a bag to obtain a mixture. The resultant mixture was compressed into tablets (750 mg per tablet) by a die having a 13 mmΦ flat bevel edge using tabletting machine. No darkishness by whittled powders or sticking of the mixture on the die was observed in the resulting tablets.

Example 2

Production of active ingredient group

120 g of lansoprazole, 200 g of magnesium hydroxide, 580 g of D-mannitol and 240 g of corn starch were charged into a fluidized bed granulator, and 8% aqueous solution prepared by dissolving 60 g of hydroxypropylcellulose in 690 g of purified water was sprayed, and these materials were granulated, and dried to obtain 1161.1 g of granules.

Production of outer layer group

720 g of magnesium hydroxide, 259.5 g of D-mannitol, 225 g of microcrystalline cellulose (Ceolus KG-801) and 112.5 g of crospovidone were charged in a fluidized bed granulator, and 500 g of purified water was sprayed, and these materials were granulated, and dried to obtain 1138.8 g of granules.

300 g of a active ingredient group, 439 g of an outer layer group and 11 g of magnesium stearate were mixed in a bag to obtain a mixture. The resultant mixture was compressed into tablets (750 mg per tablet) by a die having a 13 mmΦ flat bevel edge using tabletting machine. No darkishness by whittled powders or sticking of the mixture on the die was observed in the resulting tablets.

Example 3

Production of active ingredient group

120 g of lansoprazole, 580 g of magnesium hydroxide, 332 g of D-mannitol and 108 g of corn starch were charged into a fluidized bed granulator, and 8% aqueous solution prepared by dissolving 60 g of hydroxypropylcellulose in 690 g of purified water was sprayed, and these materials were granulated, and dried to obtain 982.1 g of granules.

Production of outer layer group

108.8 g of magnesium hydroxide, 453.8 g of trometamol, 52.5 g of D-mannitol, 127.5 g of microcrystalline cellulose (Ceolus KG-801) and 63.7 g of crospovidone were charged in a fluidized bed granulator, and 400 g of purified water was sprayed, and these materials were granulated, and dried to obtain 758.7 g of granules.

270 g of a active ingredient group, 483.8 g of an outer layer group and 11.2 g of magnesium stearate were

mixed in a bag to obtain a mixture. The resultant mixture was compressed into tablets (850 mg per tablet) by a die having a 13 mmΦ flat bevel edge using tabletting machine. No darkishness by whittled powders or sticking of the mixture on the die was observed in the resulting tablets.

Example 4

150 g of lansoprazole, 500 g of magnesium oxide (manufactured by Kyowa Kagaku Kogyo K.K., grade: heavy N), 725 g of magnesium hydroxide, 1390 g of D-mannitol and 70 g of aspartame were charged into a fluidized bed granulator, and 2.8% aqueous solution prepared by dissolving 70 g of hydroxypropylcellulose in 2430 g of purified water was sprayed, and these materials were granulated, and dried to obtain 2771.5 g of granules.

2614.5 g of the obtained granules, 315 g of microcrystalline cellulose (Ceolus KG-801), 157.5 g of crospovidone and 63 g of magnesium stearate were mixed in a bag to obtain a mixture. The resultant mixture was compressed into tablets (700 mg per tablet) by a die having a 13 mmΦ flat bevel edge using tabletting machine. No darkishness by whittled powders or sticking of the mixture on the die was observed in the resulting tablets.

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60 g of lansoprazole, 120 g of magnesium oxide, 406 g of magnesium hydroxide and 584 g of D-mannitol were charged into a fluidized bed granulator, and 5.6% aqueous solution prepared by dissolving 28 g of hydroxypropylcellulose in 472 g of purified water was sprayed, and these materials were granulated, and dried to obtain 1144.3 g of granules.

581 g of the granules, 70 g of microcrystalline cellulose (Ceolus KG-801), 35 g of crospovidone and 14 g of magnesium stearate were mixed in a bag to obtain a mixture. The resultant mixture was compressed into tablets (700 mg per tablet) by a die having a 13 mmΦ flat bevel edge using tabletting machine. No darkishness by whittled powders or sticking of the mixture on the die was observed in the resulting tablets.

Example 6

150 g of lansoprazole, 500 g of magnesium oxide (manufactured by Kyowa Kagaku Kogyo K.K., N grade), 725 g of magnesium hydroxide, 1316.5 g of D-mannitol and 70 g of aspartame were charged into a fluidized bed granulator, and an aqueous solution prepared by dispersing and dissolving 140 g of hydroxypropylcellulose and 3.5 g of yellow ferric oxide in 2256.5 g of purified water was sprayed, and these materials were granulated, and dried to obtain 2817.7 g of granules.

2614.5 g of the granules, 315 g of microcrystalline cellulose (Ceolus KG-801), 157.5 g of crospovidone and 63 g of magnesium stearate were mixed in a bag to obtain a mixture. The resultant mixture was compressed into tablets (700 mg per tablet) by a die having a 13 mmΦ flat bevel edge using tabletting machine. No darkishness by whittled powders or sticking of the mixture on the die was observed in the resulting tablets.

Example 7

105 g of lansoprazole, 525 g of magnesium oxide (manufactured by Kyowa Kagaku Kogyo K.K., N grade), 761.3 g of magnesium hydroxide, 1300.3 g of D-mannitol and 70 g of aspartame were charged into a fluidized bed granulator, and an aqueous solution prepared by dispersing and dissolving 140 g of hydroxypropylcellulose and 3.5 g of yellow ferric oxide in 2376.5 g of purified water was sprayed, and these materials were granulated, and dried to obtain 2754.6 g of granules.

2573 g of the granules, 310 g of microcrystalline cellulose (Ceolus KG-801), 155 g of crospovidone and 62 g of magnesium stearate were mixed in a bag to obtain a mixture. The resultant mixture was compressed into tablets (1000 mg per tablet) by a die having a 16 mmΦ flat bevel edge using tabletting machine. No darkishness by whittled

powders or sticking of the mixture on the die was observed in the resulting tablets.

Example 8

75 g of lansoprazole, 500 g of magnesium oxide (manufactured by Kyowa Kagaku Kogyo K.K., N grade), 725 g of magnesium hydroxide, 1391.5 g of D-mannitol and 70 g of aspartame were charged into a fluidized bed granulator, and an aqueous solution prepared by dispersing and dissolving 140 g of hydroxypropylcellulose, 1.75 g of yellow ferric oxide and 1.75 g of ferric oxide in 2256.5 g of purified water was sprayed, and these materials were granulated, and dried to obtain 2828.0 g of granules.

2614.5 g of the granules, 315 g of microcrystalline cellulose (Ceolus KG-801), 157.5 g of crospovidone and 63 g of magnesium stearate were mixed in a bag to obtain a mixture. The resultant mixture was compressed into tablets (700 mg per tablet) by a die having a 13 mmΦ flat bevel edge using tabletting machine. No darkishness by whittled powders or sticking of the mixture on the die was observed in the resulting tablets.

Example 9

52.5 g of lansoprazole, 525 g of magnesium oxide (manufactured by Kyowa Kagaku Kogyo K.K., N grade), 761.3 g

of magnesium hydroxide, 1352.8 g of D-mannitol and 70 g of aspartame were charged into a fluidized bed granulator, and an aqueous solution prepared by dispersing and dissolving 140 g of hydroxypropylcellulose, 1.75 g of yellow ferric oxide and 1.75 g of ferric oxide in 2376.5 g of purified water was sprayed, and these materials were granulated, and dried to obtain 2771.6 g of granules.

2573 g of the granules, 310 g of microcrystalline cellulose (Ceolus KG-801), 155 g of crospovidone and 62 g of magnesium stearate were mixed in a bag to obtain a mixture. The resultant mixture was compressed into tablets (1000 mg per tablet) by a die having a 16 mmΦ flat bevel edge using tabletting machine. No darkishness by whittled powders or sticking of the mixture on the die was observed in the resulting tablets.

Example 10

300 g of lansoprazole, 500 g of magnesium oxide (manufactured by Kyowa Kagaku Kogyo K.K., N grade), 725 g of magnesium hydroxide, 1166.5 g of D-mannitol and 70 g of aspartame were charged into a fluidized bed granulator, and an aqueous solution prepared by dispersing and dissolving 140 g of hydroxypropylcellulose, 2.5 g of yellow ferric oxide and 1 g of ferric oxide in 2256.5 g of purified water was sprayed, and these materials were granulated, and dried

to obtain 2783.0 g of granules.

2614.5 g of the granules, 315 g of microcrystalline cellulose (Ceolus KG-801), 157.5 g of crospovidone and 63 g of magnesium stearate were mixed in a bag to obtain a mixture. The resultant mixture was compressed into tablets (700 mg per tablet) by a die having a 13 mmΦ flat bevel edge using tabletting machine. No darkishness by whittled powders or sticking of the mixture on the die was observed in the resulting tablets.

Example 11

210 g of lansoprazole, 525 g of magnesium oxide (manufactured by Kyowa Kagaku Kogyo K.K., N grade), 761.3 g of magnesium hydroxide, 1195.3 g of D-mannitol and 70 g of aspartame were charged into a fluidized bed granulator, and an aqueous solution prepared by dispersing and dissolving 140 g of hydroxypropylcellulose, 2.45 g of yellow ferric oxide and 1.05 g of ferric oxide in 2376.5 g of purified water was sprayed, and these materials were granulated, and dried to obtain 2823.7 g of granules.

2573 g of the granules, 310 g of microcrystalline cellulose (Ceolus KG-801), 155 g of crospovidone and 62 g of magnesium stearate were mixed in a bag to obtain a mixture. The resultant mixture was compressed into tablets (1000 mg per tablet) by a die having a 16 mmΦ flat bevel

edge using tabletting machine. No darkishness by whittled powders or sticking of the mixture on the die was observed in the resulting tablets.

Example 12

150 g of lansoprazole, 700 g of magnesium oxide (manufactured by Kyowa Kagaku Kogyo K.K., N grade), 435 g of magnesium hydroxide, 1406.5 g of D-mannitol and 70 g of aspartame were charged into a fluidized bed granulator, and an aqueous solution prepared by dispersing and dissolving 140 g of hydroxypropylcellulose and 3.5 g of yellow ferric oxide in 1906.5 g of purified water was sprayed, and these materials were granulated, and dried to obtain 2756.4 g of granules.

2614.5 g of the granules, 350 g of microcrystalline cellulose (Ceolus KG-801), 175 g of crospovidone and 70 g of magnesium stearate were mixed in a bag to obtain a mixture. The resultant mixture was compressed into tablets (700 mg per tablet) by a die having a 13 mmΦ flat bevel edge using a tabletting machine. No darkishness by whittled powders or sticking of the mixture on the die was observed in the resulting tablets.

Experiment Example 1

Disintegration test

The disintegration time was measured according to a method described in USP <701> Disintegration.

Condition: purified water 1000 mL, no disk

The results are shown in Table 1.

Table 1

	Example 1	Example 2	Example 3
Average disintegration time (min)	0.92	0.70	0.45

Measurement of pH change

Test solution of 0.05 mol hydrochloric acid 100 mL (37 ℃) was charged into a 100 mL beaker, and each one tablet obtained in example 1, example 2 and example 3 was added and a test was carried out under the condition of 100 revolutions per minute using a basket according to the dissolution test method of USP. pH change by time was measured.

As shown in Table 2, pH of the test solution increased quickly, and pH of 7 or more could be reached over 3 minutes.

Table 2

	1 min	2 min	3 min	4 min	5 min	10 min
Example 1	1.42	3.12	7.63	8.83	9.04	9.15
Example 2	2.01	6.77	7.97	8.46	8.64	8.85
Example 3	3.08	6.99	7.49	7.72	7.83	8.06

Measurement of dissolution profile

One tablet obtained in example 1, example 2 or example 3, or one Takepron capsule (30 mg) filled with lansoprazole granules with an enteric coating was added to 900 mL of phosphate buffer solution having a pH of 6.8 at 37℃, and the amount of dissolved lansoprazole was measured under rotation at 75 rpm by the absorbancy at 286 nm in the ultraviolet range, and the dissolution ratio was calculated.

The results are shown in Table 3.

The dissolution profile was quick as compared with the dissolution of a capsule.

Table 3

	5 min	10 min	15 min	20 min
Example 1	91.8%	97.9%	98.2%	97.5%
Example 2	99.4%	101.9%	101.1%	100.3%
Example 3	81.5%	87.7%	88.3%	87.7%
Capsule	38.1%	94.2%	96.8%	97.7%

Experiment Example 2

Disintegration test

The disintegration time was measured according to a method described in USP <701> Disintegration.

Condition: purified water 1000 mL, no disk

The results are shown in Table 4.

Table 4

	Example 4	Example 5
disintegration time (min)	1.25	1.28

Measurement of dissolution profile

One tablet obtained in example 4 or example 5 was added to 900 mL of phosphate buffer solution having a pH of 6.8 at 37℃, and the amount of dissolved lansoprazole was measured by the absorbancy at 286 nm in the ultraviolet range under the same conditions as Experiment Example 1, and the dissolution ratio was calculated.

The dissolution profile was quick as compared with that of the above-mentioned Takepron capsule.

The results are shown in Table 5.

Table 5

	5 min	10 min	15 min	20 min
Example 4	86.4%	95.8%	97.5%	97.5%
Example 5	93.3%	96.9%	96.2%	95.7%

Experiment Example 3

Disintegration test

The disintegration time was measured according to a method described in USP <701> Disintegration.

Condition: purified water 1000 mL, no disk

The results are shown in Table 6.

Table 6

	Example 6	Example 7	Example 8	Example 9
disintegration time (min)	1.8	1.98	1.95	1.98

Measurement of dissolution profile

One tablet obtained in example 6, example 7, example 8

or example 9 was added to 900 mL of phosphate buffer solution having a pH of 6.8 at 37℃, and the amount of dissolved lansoprazole was measured by the absorbancy at 286 nm in the ultraviolet range under the same conditions as Experiment Example 1, and the dissolution ratio was calculated.

The dissolution profile was quick as compared with the dissolution of the capsule described above.

The results are shown in Table 7.

Table 7

	5 min	10 min	15 min	20 min
Example 6	78.7%	88.3%	90.0%	90.7%
Example 7	54.9%	81.1%	86.6%	87.6%
Example 8	76.4%	91.8%	96.2%	97.2%
Example 9	78.1%	92.5%	97.6%	96.2%

Experiment Example 4

Disintegration test

The disintegration time was measured according to a method described in USP <701> Disintegration.

Condition: purified water 1000 mL, no disk

The results are shown in Table 8.

Table 8

	Example 10	Example 11	Example 12
disintegration time (min)	1.60	1.28	1.52

Measurement of dissolution profile

One tablet obtained in example 10, example 11 or example 12 was added to 900 mL of phosphate buffer solution having a pH of 6.8 at 37℃, and the amount of dissolved lansoprazole was measured by the absorbancy at 286 nm in the ultraviolet range under the same conditions as Experiment Example 1, and the dissolution ratio was calculated.

The results are shown in Table 9.

The dissolution profile was quick as compared with that of a capsule mentioned above.

Table 9

	5 min	10 min	15 min	20 min
Example 10	73.7%	82.4%	83.7%	83.7%
Example 11	59.1%	72.6%	76.4%	78.8%
Example 12	85.4%	95.2%	96.7%	97.9%

Industrial Applicability

The medical solid preparation of the present invention can be obtained by a simple production method since no enteric coating is applied, though containing an acid labile active ingredient, for example, a benzimidazole compound which is a PPI. Further, since the initial dissolution of an active component from the preparation is quicker as compared with a preparation with an enteric coating, the initiation time of a pharmacological action can be shortened. Furthermore, since a metal oxide and

metal hydroxide is mainly used for neutralization and stabilization in stomach, the generation of carbon dioxide gas which is generated in stomach by the administration of a preparation containing a bicarbonate or carbonate in a large amount can be suppressed, and therefore burp can be suppressed in the preparation.

CLAIMS

1. A gastric disintegrable solid preparation comprising an acid labile active ingredient and at least one component selected from metal oxides and metal hydroxides.

2. A solid preparation according to claim 1, wherein the disintegration time is within 7 minutes.

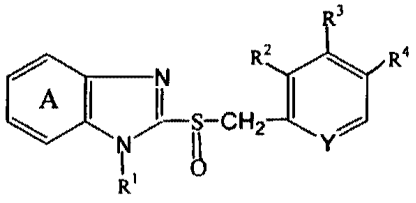
3. A solid preparation according to claim 1, which is the preparation without enteric coating.

4. A solid preparation according to claim 1, which comprises further at least one component selected from carbonates of alkali earth metal and basic additives having high water-solubility.

5. A solid preparation according to claim 1, wherein an acid labile active ingredient is a proton pump inhibitor (PPI).

6. A solid preparation according to claim 5, wherein the PPI is a benzimidazole compound.

7. A solid preparation according to claim 6, wherein a benzimidazole compound is a compound represented by the formula (I):



(I)

wherein ring A is an optionally substituted benzene ring,

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R^1 is hydrogen atom, an optionally substituted aralkyl group, acyl group or acyloxy group, R^2, R^3 and R^4 are the same or different and each represent a hydrogen atom, an optionally substituted alkyl group, an optionally substituted alkoxy group or an optionally substituted amino group, and Y represents a nitrogen atom or CH, or a salt thereof.

8. A solid preparation according to claim 6, wherein a benzimidazole compound is lansoprazole, omeprazole, rabeprazole or pantoprazole, or an optically active compound thereof.

9. A solid preparation according to claim 1, wherein the metal oxides and the metal hydroxides are those of which 1% aqueous solution or 1 % aqueous suspension has a pH of 8.0 or more.

10. A solid preparation according to claim 1 which comprises at least one metal oxide selected from the group consisting of magnesium oxide, magnesium silicate, dry aluminum hydroxide gel and magnesium metasilicate aluminate.

11. A solid preparation according to claim 1 which comprises at least one metal hydroxide selected from the group consisting of magnesium hydroxide, aluminum hydroxide, synthetic Hydrotalcite, coprecipitate of aluminum hydroxide and magnesium hydroxide, coprecipitate of aluminum hydroxide, magnesium carbonate and calcium carbonate, and

coprecipitate of aluminum hydroxide and sodium bicarbonate.

12. A solid preparation according to claim 4, wherein the carbonate of alkali earth metal is calcium carbonate or magnesium carbonate.

13. A solid preparation according to claim 4, wherein the basic additive having high water-solubility is trometamol, disodium succinate, sodium hydrogen phosphate, trisodium phosphate, dipotassium phosphate or L-arginine.

14. A solid preparation according to claim 1 which contains magnesium oxide.

15. A solid preparation according to claim 1 which contains magnesium hydroxide.

16. A solid preparation according to claim 1 which contains magnesium oxide and magnesium hydroxide.

17. A solid preparation according to claim 14 or claim 16, wherein the magnesium oxide is one obtained by calcination at a temperature ranging from about 500°C to about 1000°C and of purity higher than 95%.

18. A solid preparation according to claim 14, wherein the magnesium oxide has a BET specific surface area of about $10m^2/g$ to about $50m^2/g$.

19. A solid preparation according to claim 6, which contains at 1east one component selected from metal oxides and metal hydroxides at a ratio of 0.1 to 1500 parts by weight relative to 1 part by weight of the benzimidazole

compound.

20. A solid preparation according to claim 6, which contains at least one component selected from metal oxides and metal hydroxides together with a salt of alkali earth metal at a total ratio thereof of 0.1 to 1800 parts by weight relative to 1 part by weight of the benzimidazole compound.

21. A solid preparation according to claim 1, which is a tablet, a granule or a capsule.

22. A solid preparation according to claim 1, wherein a group containing an acid labile active ingredient and a group containing a metal oxide or a metal hydroxide but containing no active ingredient are separately compounded.

23. A solid preparation according to claim 4, wherein (1) a group containing both an active ingredient and at least one component selected from metal oxides, metal hydroxides, carbonates of alkali earth metal and basic additives having high water-solubility and (2) a group not containing an acid labile active ingredient but containing at least one component selected from metal oxides, metal hydroxides, carbonates of alkali earth metal and basic additives having high water-solubility are separately compounded.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 02/08704

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/16 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 51050 A (UNIV MISSOURI) 19 July 2001 (2001-07-19) page 31, line 13,14 See examples I-C, I-D, I-E. ---	1-23
X Y	EP 1 004 305 A (EISAI CO LTD) 31 May 2000 (2000-05-31) examples 24-26; table 3 ---	1-9, 19-23 1-23
X	WO 01 28559 A (EISAI) 26 April 2001 (2001-04-26) examples 4,5; table 2 See table 2, examples 4,5: disintegration time claims 1,2 --- -/--	1-3,5-9, 19-22

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 December 2002	16/12/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Veronese, A

Form PCT/ISA/210 (second sheet) (July 1992)

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 235 311 B1 (ULLAH ISMAT ET AL) 22 May 2001 (2001-05-22) Example 1: Tablet comprising: Pravastatin, Magnesium Oxide, Magnesium Carbonate. column 1, line 31,32	1-4,9-23
X	WO 97 25066 A (ASTRA AB ;DEPUI HELENE (SE); HALLGREN AGNETA (SE)) 17 July 1997 (1997-07-17) page 23, line 21-30	1-4,9-23
X	PATENT ABSTRACTS OF JAPAN vol. 2000, no. 15, 6 April 2001 (2001-04-06) & JP 2000 355540 A (EISAI CO LTD), 26 December 2000 (2000-12-26) abstract	1,3,5-9
X	TETSURO TABATA ET AL: "STABILIZATION OF A NEW ANTIULCER DRUG (LANSOPRAZOLE) IN THE SOLID DOSAGE FORMS" DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, NEW YORK, NY, US, vol. 18, no. 13, 1992, pages 1437-1447, XP002921226 ISSN: 0363-9045	1,3, 5-10,14, 21
Y	See table 5, magnesium oxide.	1-23

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims 22 and 23 relate to compositions according to claims 1 comprising " a group containing an acid labile ingredient and a group containing a metal oxide or metal hydroxide but containing no active ingredient". No reference to any "group" is made in claim 1. Claims 22 and 23 are therefore considered not clear. Consequently the search has been carried out for the compositions as claimed in claims 1-21 and the ones described in the description.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 02/08704

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/JP 02/08704

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		EP 1246622 A1	09-10-2002
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		EP 1004305 A1	31-05-2000
		WO 9953918 A1	28-10-1999
		US 2002039597 A1	04-04-2002

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(19) Europäisches Patentamt
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A1

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(54) **Nonsteroidal anti-inflammatory drug composition containing h1 blockers, h2 blockers, beta adrenergic agonists or combinations thereof and an alkalizing agent, and process for administration.**

(57) A nonsteroidal anti-inflammatory drug composition containing as protectants against gastrointestinal injury, H_1 blockers, H_2 blockers, beta-adrenergic agonists, or combinations thereof, and an alkalizing agent and a process for administering such compositions.

EP 0 320 550 A1

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NONSTEROIDAL ANTI-INFLAMMATORY DRUG COMPOSITION CONTAINING H_1 BLOCKERS, H_2 BLOCKERS, BETA-ADRENERGIC AGONISTS OR COMBINATIONS THEREOF AND AN ALKALIZING AGENT, AND PROCESS FOR ADMINISTRATION.

This invention relates to nonsteroidal anti-inflammatory compositions containing, as protectants against gastrointentinal injury caused by said nonsteroidal anti-inflammatory drug (hereinafter sometimes referred to as NSAID), a protectant selected from the group consisting of H_1 blockers, H_2 blockers, beta-adrenergic agonists, and combinations thereof. More particularly, it concerns compositions of this character, that also contain an alkalizing agent, and a process that uses such compositions. The terms H_1 blockers and H_2 blockers are used herein to refer to the histamine H_1- and H_2-receptor blockers, respectively.

H_1 blockers, H_2 blockers, as well as beta-adrenergic agonists, have been shown to offer some protection against gastrointestinal injury that is sometimes caused by the administration of NSAIDs. These, however, have suffered from some very distinct disadvantages. Among such advantages is the delay in relieving the subjective symptoms of gastric distress that is experienced by individuals who have taken such products.

It has now been found that the aforesaid disadvantages may be avoided by also incorporating an alkalizing agent in said NSAID composition containing a gastrointestinal protectant selected from the group consisting of H_1 blockers. H_2 blockers, beta-adrenergic agonists, and combinations thereof. In addition, it has been found that by incorporating said alkalizing agent in the compositions of interest there is often also observed an improvement in the ability of such compositions to protect against gastrointestinal injury that may be caused by said NSAIDs.

It has been suggested in the prior art that the coadministration of cimetidine with an antacid is to be avoided. In this connection, attention is directed to the "Physicians Desk Reference", 40th Edition, 1986, page 1726 and AMA Drug Evaluations" 5th Edition p. 1267. The latter is prepared and published by the American Medical Association, Chicago, Illinois. In contrast to this, applicants did not observe any reduction in efficacy when the alkalizing agents were coadministered with H_2- or H_1-blockers and a NSAID.

It has also been reported in prior art that H_2-receptor blocking agents or antagonists protect against aspirin-induced lesions in certain laboratory animals. One such study is reported in Gastroenterology Vol. 88, NO. 5 part 2. p. 1344. This reference teaches nothing with regard to the use of an alkalizing agent as is characteristic of the present invention.

Cyproheptadine has been evaluated as a protectant against aspirin-induced gastric injury (Indian J. Med. Res. 1980, 71, p. 926-32). Although cyproheptadine may have some H_1-receptor antagonist properties, it does not act exclusively at the H_1-receptor sites but rather acts predominantly at serotonin-receptor sites (Goodman and Gilman "The Pharmacological Basis of Therapeutics", 7th Edition, p. 634). In addition, in the Indian Journal reference, the aspirin and cyproheptadine are not coadministered but are given serially. This is to be contrasted with the present invention in which the H_2- or H_2-receptor blocker or the beta-adrenergic agonist is coadministered with the aspirin. Furthermore, the treatment with cyproheptadine in accordance with the Indian reference is reported as not modifying the gastric acidity. This is also in contrast with the experience in this invention in which significant modification of gastric acidity takes place with the administration of aspirin and gastroprotectants utilized for the present purposes. Still a further distinction of the instant invention over the Indian Journal teaching is the fact that in the latter cyproheptadine was administered by intraperitoneal injection prior to the intragastric administration of the aspirin. This is to be contrasted with the fact that the compositions of the present invention lend themselves to oral administration at which time the NSAID and the H_1- or H_2-receptor blocker are coadministered. Most importantly perhaps, like the other reference discussed above, the Indian Journal reference nowhere suggests the use nor the advantages that follow from its use of an alkalizing agent. This, as will be made clear below, is an essential feature of the present invention.

The NSAIDs form a well-known class of drugs that are anti-inflammatory analgesics. These have the common property of inhibiting the formation of prostaglandins, which have a protective affect on the gastrointestinal mucosa (Goodman and Gilman "The Pharmacological Basis for Therapeutics" 7th Edition, p. 678). It is because of this inhibiting effect that the oral administration of drugs of this class may result in gastrointestinal injury and/or bleeding and is at least part of the problem that the present invention seeks to reduce or eliminate.

A number of NSAIDs are known in the prior art to which the present invention has application. The most commonly known group are the salicylates of which aspirin is the prime example. A further group of NSAIDs that have utility in connection with the instant invention are the proprionic acid derivatives. Included in this group are ibuprofen and naproxen. A further group of NSAIDs, employable herein, are the fenamates

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and compounds closely related to them structurally. These may be illustrated by such compounds as mefenamic acid, meclofenamate sodium, diclofenac and its sodium salt. Also belonging to the class NSAIDs with which the present invention is concerned are the indole derivates (e.g. indomethacin); pyrrole alkanoic acid derivatives (e.g. tolmetin); pyrazalone derivates (e.g. phenylbutazone); oxicams (e.g. piroxicam), etc.

The NSAID will be contained in the composition of this invention at concentrations at which it is generally found in therapeutic NSAID compositions intended for oral administration. This will usually be a pharmaceutically acceptable analgesic/anti-inflammatory dose.

A number of H_1- and H_2-receptor blockers are known in the prior art which are useful for the purposes of the present invention. By way of illustrating the H_1-receptor blockers that may be employed herein, mentioned may be made of the following: ethanolamines (e.g. diphenhydramine or its hydrochloride salt; carbinoxamine or its maleate salt); ethylenediamines (e.g. tripelennamine or its hydrochloride or nitrate salts); alkylamines (e.g. chlorpheniramine or its maleate salt, brompheniramine or its maleate salt); piperazines (e.g. hydroxyzine or its hydrochloride or pamoate salts, cyclizine or its hydrochloride or lactate salts, meclizine or sits hydrochloride salts); etc. To exemplify the H_2-receptor blockers that may be advantageously used in the practice of this invention the following are given: cimetidine, ranitidine, famotidine, etc.

The H_1- and H_2-receptors blockers may be used in the form of their bases or in the form of their pharmaceutically acceptable salts. When employed as salts these will usually be acid addition salts wherein the acid portion may be hydrochloride, maleate, ascorbate, citrate, pamoate, lactate, tartrate, sulfate, etc.

The quantity of H_1-receptor blocker that will be contained in the composition of this invention may vary somewhat because of the variations in the anticholinergic activity that these agents exhibit. All that is required is that an effective amount be present so that the H_1-receptor blocker can make its contribution as a protectant against NSAID-induced gastrointestinal injury.

Similarly, the quantity of H_2-receptor blocker in the present composition may also vary. Again, all that is required is that amount employed be an effective protectant quantity which will enable the H_2-receptor blocker to play its part as a gastrointestinal protectant.

A number of beta-adrenergic agonists are known in the prior art which are useful for the purpose of this invention. Of special interest are isoproterenol which is a mixed beta-1 and beta-2 agonist and terbutaline which is a more selective beta-2 agonist. By way of illustrating the other beta-adrenergic agonists that may be employed herein, the following are given: metaproterenol, albuterol, ritodrine. All of these may be employed as such or as pharmaceutically acceptable salts.

As with the other active ingredients contained in the compositions of this invention, the quantity of beta-adrenergic agonist that will be contained therein may also vary somewhat. Again, all that is required is that it be contained in said composition in an amount which will enable the beta-adrenergic agonist to play its part as a gastrointestinal protectant.

As indicated above, it is a feature of the present invention to incorporate in the instant composition an alkalizing agent. Since this composition is intended for oral administration, the akalizing agent employed will be one which is a pharmaceutically acceptable one that may be tolerated at the concentrations at which it is administered. A number of such alkalizing agents are known in this art which are suitable for the present purpose. By way of illustration, the following may be mentioned: sodium bicarbonate, magnesium carbonate, calcium carbonate, magnesium oxide, magnesium hydroxide, magnesium trisilicate, aluminum hydroxide, aluminum carbonate, potassium bicarbonate, etc.

The quantitive relationships of the various components of the composition of this invention may be expressed on the basis of the average daily dose of the ingredient contained in the product. This will take the form of weight of the ingredient per kg of body weight of the subject per day (e.g. milligrams or grams/kg of body weight/day). In general, this relationship may be expressed for the various ingredients as follows:

(a) NSAID: from about 10 mg/kg/day to about 100 mg/kg/day; preferred range from about 15 mg/kg/day to about 75 mg/kg/day.

(b) H_2-receptor blocker (when employed): from about 0.01 mg/kg/day to about 1g/kg/day; preferred range from about 0.01 mg/kg/day to about 10 mg/kg/day.

(c) H_1-receptor blocker (when employed): from about 2.5 ug/kg/day to about 500 mg/kg/day; preferred range from about 0.1 mg/kg/day to about 50 mg/kg/day.

(d) beta-adrenergic agonist (when employed): from about 0.30 ug/kg/day to about 500 mg/kg/day; preferred range from about 0.01 mg/kg/day to about 10 mg/kg/day.

(e) alkalizing agent: from about 0.02 mEq/kg/day to about 10 mEq/kg/day; preferred range from about 0.04 mEq/kg/day to about 2 mEq/kg/day.

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The compositions of the present invention may also be made up in unit dosage forms. Each unit doage form will be sized and contain the ingredients in such amount that they may be taken orally in comfortable and convenient manner. Given below are the quantities of each type of active ingredient, when present in the composition, that will be contained in each:

TABLE I

Ingredient	mg. per Unit dose General
NSAID	about 200 mg to about 600 mg.
H_1 Blocker	about 0.01 mg to about 70 mg.
H_2 Blocker	about 0.5 mg to about 350 mg
Beta-Adrenergic Agonist	about 0.7 mg to about 70 mg.
Alkalizing Agent	about 2 mEq to about 10 mEq

The present products may be made into capsules, tablets, powders or caplets and may be film-coated, enteric-coated or formulated into sustained-release dosage forms or liquid dosage compositions. When formed into tablets or caplets they may contain adjuvants that facilitate the tableting of the product or enhance its elegance or dissolution rates. Generally illustrative of the adjuvants that may be contained in the various dosage forms encompassed in the present invention, the following may be mentioned: disintegrating agents, binders, lubricants, fillers, glidents, surfactants, flavoring agents, sweeteners, solvents, liquid carriers, suspending agents, preservatives, etc. More particularly, the adjuvants that may be contained in the various dosage forms over and above the active ingredients are as follows:

Caplet and Tablet

Cellulose, lactose, corn starch, stearic acid, water, gelatin, talc, sterotix, magnesium stearate, terra alba, sucrose, agar, pectin, Cab-O-Sil, acacia, etc.

Capsule:

Spray-dried lactose, dimethylsiloxane, corn starch, water, magnesium stearate, sucrose, agar, pectin, Cab-O-Sil, etc.

Liquid Dosage Forms:

Polyethylene glycol, sucrose, povidone, sodium citrate, citric acid, flavor, color, quinine, salicylic acid, water, peanut oil, olive oil, sesame oil, etc.

Sustained-release compositions may contain such things as glyceryl monostearate or glyceryl distearate.

In addition, these products may also contain other pharmaceutically active ingredients, such as decongestants, analgesic adjuvants, antihistamines, expectorants, antitussives, diuretics, other analgesics, other anti-inflammatory agents, other antipyretics, other antirheumatics, antioxidants, vasodilators, smooth muscle relaxants, skeletal muscle relaxants, bronchodilators, vitamins, trace minerals, amino acids, biological peptides, etc.

The compositions of this invention are useful in treating conditions and symptoms that are classically treated by the administration of NSAIDs. These include headache pain, pain and inflammation associated with arthritis and other systemic diseases, elevated body temperatures, etc. A variety of regimens may be employed in treating these conditions in accordance with the present invention. This will depend upon the particular unit dosage form that is used in the regimen. In the typical case one or two tablets will be taken every 4 to 6 hours, as needed.

The following examples are given to further illustrate the present invention. It is to be understood, however, that the invention is not limited thereto.

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Example 1

Aspirin 325 mg
Diphenhydramine hydrochloride 16.67 mg
Sodium bicarbonate 5 mEq

The above ingredients are mixed in powdered or granular form and loaded into gelatin capsules.

Example 2

Aspirin 325 mg
Ranitidine hydrochloride 3.33 mg
Sodium bicarbonate 5 mEq

Prepared as described in Example 1

Example 3

Aspirin 325 mg
Metaproterenol sulfate 0.83 mg
Sodium bicarbonate 5 mEq

Prepared as described in Example 1

To test the effectiveness of the composition of this invention in protecting the stomach against NSAID-induced muscosal injury each protectant, in combination with an alkalizing agent, is administered orally with aspirin in capsules. For purposes of comparison, the protectant alone or the alkalizing agent alone is administered with the aspirin. A standard dose of 975 mg of aspirin is administered with varying doses of protectant and or alkalizing agent.

All test formulations are prepared on the day of the tests. The capsules are placed in the back of the dog's throat. A catheter, with funnel attached, is positioned in the dog's stomach and 50 ml of deionized water is administered.

Healthy adult beagle dogs of either sex are selected for testing. Dogs are housed individually in stainless steel cages with grid floors to allow excreta to pass through. Room temperature in the holding rooms and test laboratories is maintained between 65° F and 85° F and relative humidity between 30% and 80%. Room lights remain on from 6:00 AM to 4:00 PM.

Each dog is trained to stand in a stanchion with sling support and to accept a bit tied in its mouth. A gastroscope is then passed through the bit into the dog's stomach. This training requires ten days to two weeks in most dogs.

To determine whether a dog is suitable for test purposes, its stomach is examined for a normal mucosa, and its gastric responsiveness to aspirin is evaluated (as under Test Procedure). An acceptable gastric irritation score in the antrum must be 5 or greater (on a scale of 0-7) 2 hours after dosage.

Food is withheld from test dogs for 24 hours before the test and during the test and water is allowed ad lib. The dogs are moved into a holding area away from the kennel. Fasted dogs of either sex are examined gastroscopically to ensure that their stomachs have normal healthy mucosal linings. The dogs are dosed orally with test formulations, which are flushed into their stomachs with 50 ml of deionized water. They are then re-examined 20 hours later for gastric petechiae and signs of bleeding according to the following scale:

0 = uniform, pale to dark pink mucosa
1 = darker pink or blotchy mucosa
2 = petechiae and/or light-red streaks
3 = few small lesions
4 = many or connected small lesions (striations)
5 = few large lesions
6 = many large lesions

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7 = massive hemorrhagic damage

Severity of bleeding for each treatment and at each time is calculated as the mean gastric irritation score.

In addition to the endoscopic observation of the gastric mucosa of each dog, a qualitative description of gastric fluid is recorded and a pH measurement is made of the gastric fluid. All of these are done 2 hours after administration of the test product.

A base line is established by measuring the various parameters after the administration of 975 mg of aspirin. The normal resting stomach has an irritation score of 0 and a pH of 5 to 5.5. Aspirin given alone, produced injury with scores of approximately 5.5 after 2 hours. The gastric pH at this time was about 3.1.

The results of these tests are summarized in Tables II, III and IV below. Table II summarizes the results obtained with an H_1 blocker and alkalizing agents; Table III the results obtained with H_2 blockers and an alkalizing agent; and Table IV the results obtained with beta-adrenergic agonists and alkalizing agents. These tables also include the data obtained with the protectant or alkalizing agent alone. With each of the test compositions set forth in these tables, 975 mg of aspirin was simultaneously administered. The aspirin was contained in the same capsule along with the other test ingredients.

In these tests the active ingredients were administered in the following forms:

diphenhydramine: [hydrochloride]
ranitidine: [hydrochloride]
cimetidine: [free base]
terbutaline: [sulfate]
albuterol: [free base]
isoproterenol: [hydrochloride]

Table II

Non-steroidal Anti-inflammatory Compositions Protected Against Gastrointestinal Injury with Combinations of H_1 Blocker and Alkalizing Agents.

Data Summary

	2-Hour Data		
	(N)	Irritation Score	pH
Control	13	0	5.7
Aspirin 975 mg	8	5.5	3.3
Diphenhydramine (12.5 mg) + Aspirin (975 mg)	4	5.5	1.4
" (25.0 mg) + Aspirin (975 mg)	4	5.75	2.1
" (50.0 mg) + Aspirin (975 mg)	5	4.0	3.6
Magnesium Oxide (12 mEq) + Aspirin (975 mg)	12	3.50	---
Sodium Bicarbonate (15 mEq) + Aspirin (975 mg)	6	2.0	5.5
Diphenhydramine (25 mg) + Magnesium Oxide (15 mEq) + Aspirin (975 mg)	4	1.0	5.8
Diphenhydramine (25 mg) + Sodium Bicarb. (15 mEq) + Aspirin (975 mg)	4	1.25	6.0
Diphenhydramine (12.5 mg) + Magnesium Oxide (15 mEq) + Aspirin (975 mg)	4	3.00	2.7
Diphenhydramine (12.5 mg) + Sodium Bicarb. (15 mEq) + Aspirin (975 mg)	4	3.25	3.4
Diphenhydramine (6.25 mg) + Magnesium Oxide (15 mEq) + Aspirin (975 mg)	3	5.33	1.8

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Table III

Non-steroidal Anti-inflammatory Composition Protected Against Gastrointestinal Injury with Combinations of Certain H_2 Blockers and Alkalizing Agents.

Data Summary

	2-Hour Data		
	(N)	Irritation Score	pH
Control	13	0	5.7
Aspirin (975 mg)	8	5.5	3.3
Ranitidine (10 mg) + Aspirin (975 mg)	6	3.50	5.3
" (20 mg) + Aspirin (975 mg)	8	1.88	5.9
" (50 mg) + Aspirin (975 mg)	6	0.67	6.1
$NaHCO_3$ (12 mEq) + Aspirin (975 mg)	11	4.1	3.8
" (15mEq) + Aspirin (975 mg)	6	2.0	5.5
Ranitidine (10 mg) + $NaHCO_3$ (10 mEq) + Aspirin (975 mg)	5	3.00	5.3
Ranitidine (50 mg) + $NaHCO_3$ (10 mEq) + Aspirin (975 mg)	5	0.60	6.7
Cimetidine (50 mg) + Aspirin (975 mg)	5	2.40	5.6
Cimetidine (150 mg) + Aspirin (975 mg)	6	0.33	6.0
Cimetidine (50 mg) + $NaHCO_3$ (4.8 mEq) + Aspirin (975 mg)	6	2.83	4.4
Cimetidine (50 mg) + $NaHCO_3$ (9.6 mEq) + Aspirin (975 mg)	6	2.83	3.9
Cimetidine (50 mg) + $NaHCO_3$ (14.4 mEq) + Aspirin (975 mg)	6	1.33	5.1
Cimetidine (150 mg) + Sodium Bicarb. (15 mEq) + Aspirin (975 mg)	6	0.67	7.2

Note: At the highest dose tested, the alkalizing agent gave added protection against aspirin-induced injury and reduction in pH.

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Table IV

Non-steroidal Anti-inflammatory Compositions Protected Against Gastrointestinal Injury with Combinations of Certain Beta Agonists and Alkalizing Agents.			
Data Summary			
	2-Hour Data		
	(N)	Irritation Score	pH
Control	13	0	5.7
Aspirin (975 mg)	8	5.5	3.3
Terbutaline (1.25 mg) + Aspirin (975 mg)	4	4.0	2.9
" (2.50 mg) + Aspirin (975 mg)	4	2.0	3.8
" (5.00 mg) + Aspirin (975 mg)	8	1.4	4.0
" (10.0 mg) + Aspirin (975 mg)	5	1.2	4.6
Albuterol (2.0 mg) + Aspirin (975 mg)	4	2.8	2.7
" (4.0 mg) + Aspirin (975 mg)	4	1.5	4.8
" (8.0 mg) + Aspirin (975 mg)	4	1.0	5.4
Isoproterenol (7.5 mg) + Aspirin (975 mg)	9	3.9	3.5
" (15.0 mg) + Aspirin (975 mg)	9	2.7	3.8
" (30.0 mg) + Aspirin (975 mg)	10	1.3	5.0
Sodium Bicarbonate (15 mEq) + Aspirin (975 mg)	6	2.0	5.5
Magnesium Oxide (12 mEq) + Aspirin (975 mg)	12	3.5	
Terbutaline (5.0 mg) + Sodium Bicarbonate (15 mEq) + Aspirin (975 mg)	4	1.0	5.8
Terbutaline (5.0 mg) + Magnesium Oxide (15 mEq) + Aspirin (975 mg)	4	2.0	6.3
Terbutaline (1.25 mg) + Sodium Bicarbonate (15 mEq) + Aspirin (975 mg)	4	3.2	2.0
Albuterol (2.0 mg) + Sodium Bicarbonate (15 mEq) + Aspirin (975 mg)	4	0.75	5.7
Isoproterenol (30 mg) + Sodium Bicarbonate (15 mEq) + Aspirin (975 mg)	5	1.2	7.4

Note: The concomitant use of these drugs may permit the use of a lower dose of the beta agonist without compromising objective or subjective tolerance.

Claims

1. A nonsteroidal anti-inflammatory drug composition having reduced potential for gastrointestinal injury induced by said anti-inflammatory drug, comprising an anti-inflammatory amount of said anti-inflammatory drug, a gastrointestinal protective amount of a protectant selected from the group consisting of histamine H_1-receptor blockers, histamine H_2-receptor blockers, beta-adrenergic agonists and combinations thereof, and effective alkalizing amount of an alkalizing agent.

2. A composition according to claim 1 wherein said protectant is an histamine H_1-receptor blocker.

3. A composition according to claim 1 wherein said histamine H_1-receptor blocker is diphenhydramine or a pharmaceutically acceptable salt thereof.

4. A composition according to claim 1 wherein said histamine H_1- receptor blocker is diphenhydramine or a pharmaceutically acceptable salt thereof, said nonsteroidal anti-inflammatory drug is selected from the group consisting of aspirin and ibuprofen and said alkalizing agent is selected from the group consisting of sodium bicarbonate and magnesium oxide.

5. A composition according to claims, 1, 2, 3, or 4 having a daily average dose for the active ingredients as follows:

(a) nonsteroidal anti-inflammatory drug; from about 10 mg/kg/day to about 100 mg/kg/day;

(b) histamine H_1-receptor blocker; from about 2.5 ug/kg/day to about 500 mg/kg/day; and

(c) alkallzing agent; from about 0.02 mEq/kg/day to 10 mEq/kg/day.

6. A composition according to claims 1, 2, 3, or 4 having a daily average dose for the active ingredients as follows:

(a) nonsteroidal anti-inflammatory agent; from about 15 mg/kg/day to about 75 mg/kg/day;

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(b) histamine H_1-receptor blocker; from about 0.1 mg/kg/day to about 50 mg/kg/day; and
(c) alkalizing agent; from about 0.04 mEq/kg/day to about 2 mEq/kg/day.

7. A nonsteroidal anti-inflammatory composition according to claims 1, 2, 3 or 4 in unit dosage form containing the active ingredients in the following amounts per unit dose:
(a) nonsteroidal anti-inflammatory drug; from about 200 mg to about 600 mg;
(b) histamine H_1-receptor blocker; from 0.01 mg to about 70 mg; and
(c) alkalizing agent; from about 2 mEq to about 10 mEq.

8. A composition according to claim 1 wherein said protectant is an histamine H_2-receptor blocker.

9. A composition according to claim 8 wherein said histamine H_2-receptor blocker is selected from the group consisting of ranitidine, cimetidine, and pharmaceutically acceptable salts thereof.

10. A composition according to claim 8 wherein said histamine H_2-receptor blocker is selected from the group consisting of ranitidine, cimetidine, and pharmaceutically acceptable salts thereof, said nonsteroidal anti-inflammatory drug is selected from the group consisting of aspirin and ibuprofen, and said alkalizing agent is selected from the group consisting of sodium bicarbonate and magnesium oxide.

11. A composition according to claims 8, 9, or 10 having a daily average dose for the active ingredients as follows:
(a) nonsteroidal anti-inflammatory drug; from about 10 mg/kg/day to about 100 mg/kg/day;
(b) histamine H_2-receptor blocker; about 0.01 mg/kg/day to about 1 g/kg/day; and
(c) alkalizing agent; from about 0.02 mEq/kg/day to about 10 mEq/kg/day.

12. A composition according to claims 8, 9, or 10 having a daily average dose for the active ingredients as follows:
(a) nonsteroidal anti-inflammatory agent; from about 15 mg/kg/day to about 75 mg/kg/day;
(b) histamine H_2-receptor blocker; from about 0.01 mg/kg/day to about 10 mg/kg/day; and
(c) alkalizing agent; from about 0.04 mEq/kg/day to about 2 mEq/kg/day.

13. A nonsteroidal anti-inflammatory composition according to claims 8, 9 or 10 in unit dosage form containing the active ingredients in the following amounts per unit dose:
(a) nonsteroidal anti-inflammatory drug; from about 200 mg to about 600 mg;
(b) histamine H_2-receptor blocker; from 0.5 mg to about 350 mg; and
(c) alkalizing agent; from about 2 mEq to about 10 mEq.

14. A composition according to claim 1 wherein said protectant is a beta-adrenergic agonist.

15. A composition according to claim 14 wherein said protectant is selected from the group consisting of metaproterenol, terbutaline, albuterol, isoproterenol, and pharmaceutically acceptable salts thereof.

16. A composition according to claim 14 wherein said protectant is selected from the group consisting of metaproterenol, terbutaline, albuterol, isoproterenol and pharmaceutically acceptable salts thereof, said nonsteroidal anti-inflammatory drug is selected from the group consisting of aspirin and ibuprofen and said alka- lizing agent is selected from the group consisting of sodium bicarbonate and magnesium oxide.

17. A composition according to claims 14, 15 or 16 having a daily average dose for the active ingredients as follows:
(a) nonsteroidal anti-inflammatory drug; from about 10 mg/kg/day to about 100 mg/kg/day;
(b) beta-adrenergic agonist from about 0.3 ug/kg/day to about 500 mg/kg/day; and
(c) alkalizing agent; from about 0.02 MEq/kg/day to about 10 mEq/kg/day.

18. A composition according to claims 14, 15, and 16 having a dally average dose for the active ingredients as follows:
(a) nonsteroidal anti-inflammatory drug; from about 15 mg/kg/day to about 75 mg/kg/day;
(b) beta-adrenergic agonist from about 0.1 mg/kg/day to about 10 mg/kg/day; and
(c) alkalizing agent; from about 0.04 MEq/kg/day to about 2 mEq/kg/day.

19. A nonsteroidal anti-inflammatory composition according to claims 14, 15 or 16 in unit dosage form containing the active ingredients in the following amounts per unit dose:
(a) nonsteroidal anti-inflammatory drug; from about 200 mg to about 600 mg;
(b) beta-adrenergic agonist; from 0.7 mg to about 70 mg; and

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(c) alkalizing agent; from about 2 mEq to about 10 mEq.

20. A process for administering a therapeutically effective amount of a nonsteroidal anti-inflammatory composition which comprises administering said anti-inflammatory compound in the compositions defined in claims 1, 2, 3, 4, 8, 9, 10, 14, 15 or 16.

Claims for the following contracting States: ES, GR

1. A method of preparing a nonsteroidal anti-inflammatory drug composition having reduced potential for gastrointestinal injury induced by said anti-inflammatory drug, comprising combining an anti-inflammatory amount of said anti-inflammatory drug, a gastrointestinal protective amount of a protectant selected from the group consisting of histamine H_1-receptor blockers, histamine H_2-receptor blockers, beta-adrenergic agonists and combinations thereof, and adding an effective alkalizing amount of an alkalizing agent.

2. A method according to claim 1 wherein said histamine H_1-receptor blocker is diphenhydramine or a pharmaceutically acceptable salt thereof.

3. A method according to claim 2 wherein said histamine H_1-receptor blocker is diphenhydramine or a pharmaceutically acceptable salt thereof, said nonsteroidal anti-inflammatory drug is selected from the group consisting of aspirin and ibuprofen and said alkalizing agent is selected from the group consisting of sodium bicarbonate and magnesium oxide.

4. A method according to claims 1 to 3 wherein there are combined into units for a daily average dose for the active ingredients as follows:

(a) nonsteroidal anti-inflammatory drug; from about 10 mg/kg/day to about 100 mg/kg/day;
(b) histamine H_1-receptor blocker; from about 2.5 ug/kg/day to about 500 mg/kg/day; and
(c) alkalizing agent; from about 0.02 mEq/kg/day to 10 mEq/kg/day.

5. A method according to any one of claims 1 to 3 having a daily average dose for the active ingredients as follows:

(a)nonsteroidal anti-inflammatory agent; from about 15 mg/kg/day to about 75 mg/kg/day;
(b) histamine H_1-receptor blocker; from about 0.1 mg/kg/day to about 50 mg/kg/day; and
(c) alkalizing agent; from about 0.04 mEq/kg/day to about 2 mEq/kg/day.

6. A method according to claim 1 of preparing a nonsteroidal anti-inflammatory composition in unit dosage form comprising combining the active ingredients in the following amounts per unit dose;

(a) nonsteroidal anti-inflammatory drug; from about 200 mg to about 600 mg;
(b) histamine H_1-receptor blocker; from 0.01 mg to about 70 mg; and
(c) alkalizing agent; from about 2 mEq to about 10 mEq.

7. A method according to claim 1 wherein said histamine H_2-receptor blocker is selected from the group consisting of ranitidine, cimetidine, and pharmaceutically acceptable salts thereof.

8. A method according to claim 7 wherein said histamine H_2-receptor blocker is selected from the group consisting of ranitidine, cimetidine, and pharmaceutically acceptable salts thereof, said nonsteroidal anti-inflammatory drug is selected from the group consisting of aspirin and ibuprofen, and said alkalizing agent is selected from the group consisting of sodium bicarbonate and magnesium oxide.

9. A method according to either of claims 7 and 8 comprising forming a daily average dose by combining the active ingredients as follows :

(a) nonsteroidal anti-inflammatory drug; from about 10 mg/kg/day to about 100 mg/kg/day;
(b) histamine H_2-receptor blocker; about 0.01 mg/kg/day to about 1 g/kg/day; and
(c) alkalizing agent; from about 0.02 mEq/kg/day to about 10 mEq/kg/day.

10. A method according to either of claims 7 and 8 comprising forming a daily average dose by combining the active ingredients as follows:

(a) nonsteroidal anti-inflammatory agent; from about 15 mg/kg/day to about 75 mg/kg/day;
(b) histamine H_2-receptor blocker; from about 0.01 mg/kg/day to about 10 mg/kg/day; and
(c) alkalizing agent; from about 0.04 mEq/kg/day to about 2 mEq/kg/day.

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11. A method according to either of claims 7 and 8 comprising forming a nonsteroidal anti-inflammatory composition in a unit doage form by combining the active ingredients in the following amounts per unit dose:

(a) nonsteroidal anti-inflammatory drug; from about 200 mg to about 600 mg.

(b) histamine H_2-receptor blocker; from 0.5 mg to about 350 mg; and

(c) alkalizing agent; from about 2 mEq to about 10 mEq.

12. A method according to claim 1 wherein said protectant is selected from the group consisting of metaproterenol, terbutaline, albuterol, isoproterenol, and pharmaceutically acceptable salts thereof.

13. A method according to claim 12 wherein said protectant is selected from the group consisting of metaproterenol, terbutaline, albuterol, isoproterenol and pharmaceutically acceptable salts thereof, said nonsteroidal anti-inflammatory drug is selected from the group consisting of aspirin and ibuprofen and said alkalizing agent is selected from the group consisting of sodium bicarbonate and magnesium oxide.

14. A method of according to either of claims 12 and 13 comprising forming a daily average dose by combining the active ingredients as follows :

(a) nonsteroidal anti-inflammatory drug; from about 10 mg/kg/day to about 100 mg/kg/day;

(b) beta-adrenergic agonist from about 0.3 ug/kg/day to about 500 mg/kg/day; and

(c) alkalizing agent; from about 0.02 mEq/kg/day to about 10 mEq/kg/day.

15. A method according to either of claims 12 and 13 comprising forming a daily average dose by combining the active ingredients as follows :

(a) nonsteroidal anti-inflammatory drug; from about 15 mg/kg/day to about 75 mg/kg/day;

(b) beta-adrenergic agonist; from about 0.1 mg/kg/day to about 10 mg/kg/day; and

(c) alkalizing agent; from about 0.04 mEq/kg/day to about 2 mEq/kg/day.

16. A method of preparing a nonsteroidal anti-inflammatory composition in unit dosage form by combining the active ingredients in the following amounts per unit dose:

(a) nonsteroidal anti-inflammatory drug; from about 200 mg to about 600 mg;

(b) beta-adrenergic agonist; from 0.7 mg to about 70 mg; and

(c) alkalizing agent; from about 2 mEq to about 10 mEq.

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European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application number: EP 87 31 1171

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X	GB-A-2 082 456 (BRISTOL-MYERS COMP.) * Page 2, lines 50-55; page 9, line 9 - page 10, line 16 * --	1-19	A 61 K 33/08 A 61 K 33/00// (A 61 K 33/08, 33:00, 31:60, 31:415, 31:34, 31:19, 31:135)
X	EP-A-0 248 150 (BRISTOL-MYERS COMP.) * Page 3, lines 29-33; page 11, lines 1-40 * --	1-19	
A	GB-A-2 105 193 (GLAXO GROUP LTD.) * Whole document * --	1-19	
A	US-A-4 522 826 (ABRAHAM SUNSHINE) * Whole document * --	1-19	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

A 61 K

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.

Claims searched completely: 1-19

Claims searched incompletely:

Claims not searched: 20

Reason for the limitation of the search:

Method for treatment of the human or animal body by surgery or therapy (See art. 52(4) of the European Patent Convention)

Place of search	Date of completion of the search	Examiner
The Hague	31-08-1988	BRINKMANN

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
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& : member of the same patent family, corresponding document

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(54) Pharmaceutical composition and methods for treating the symptoms of overindulgence.

(57) This invention relates to a pharmaceutical composition for treating the symptoms of overindulgence comprising an analgesic effective amount of acetaminophen or a non-steroidal anti-inflammatory drug and a gastric acid inhibiting effective amount of an H_1 or H_2 blocker, proton pump inhibitor or a combination thereof and methods of treating the symptoms of overindulgence comprising administering such pharmaceutical compositions.

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PHARMCEUTICAL COMPOSITIONS AND METHODS FOR TREATING THE SYMPTOMS OF OVERINDULGENCE

Field of the Invention

This invention relates to pharmaceutical compositions for treating the symptoms of overindulgence. More particularly, the invention comprises treating the symptoms of overindulgence with a combination of non-steroidal anti-inflammatory drug or acetaminophen and a histamine receptor blocker and/or a proton pump inhibitor composition

Background of the Invention

Non-steroidal anti-inflammatory drugs (hereinafter referred to as "NSAID(S)") and acetaminophen (hereinafter referred to as "APAP") are known to be effective analgesics for the treatment of mild to moderate pain Histamine receptor blockers (referred to generically herein as H_1 or H_2 blockers) are effective inhibitors of gastric acid production. Proton pump inhibitors have been recently introduced as effective gastric acid inhibitors

The symptoms of overindulgence due to excessive or inappropriate intake of food and/or alcoholic beverage are well known and include headache as well as indigestion, upper abdominal discomfort, bloating, heartburn or pyrosis These latter symptoms collectively are sometimes referred to as acid indigestion or sour stomach. Indigestion has been variously described and will be defined herein as encompassing one or more of the following symptoms: abdominal pain and/or pressure, heartburn, a sense of abdominal fullness or bloating, excessive belching or flatulence and a vague feeling that digestion has not proceeded naturally (See Friedman, L.S., and K. J. Isselbacher, "Indigestion", Harison's Principles of Internal Medicine , 11th Edition, McGraw Hill Book Company, N.Y., p 171-175, 1986).

The pathophysiology of indigestion is generally believed to be related to increased intraluminal acidity. The effects of alcohol and/or food on the gastrointestinal tract are influenced by a number of factors, including the mental state of the patient, the amount and type of food concurrently ingested, the individual subject's tolerance for alcohol and the presence or absence of disease. Gastric secretions stimulated by alcohol are rich in acid and normal in pepsin content. Stimulation of the antral mucosa by alcohol also leads to increased gastric secretion. Histamine has also been shown to be released in response to the alcohol-gastrin interrelationship. (See Glass, G. B. J., B. L. Slomiany and A. Slomiany, "Biochemical and Pathological Derangements of the Gastrointestinal Tract following Acute and Chronic Ingestion of Ethanol", Biochemistry and Pharmacology of Ethanol , Vol 1, Plenum Press, N.Y., p 551-586, 1979.)

Alcohol in concentrations of about 10% in the stomach results in an acid rich secretion. Alcoholic drinks of 40% concentration and over are quite irritating to the gastric mucosa and cause congestive hyperemia and inflammation of the gastric mucosa and can produce erosive gastritis (See Ritchie, J. M., "The Aliphatic Alcohols", The Pharmacological Basis of Therapeutics , 7th Edition, MacMillan Publishing Co, N.Y., p 372-386, 1985). The irritation produced by alcohol stimulates sensitized visceral afferent nerves which accompany the abdominal sympathetic pathway and is responsible for the symptom of abdominal discomfort which accompanies overindulgence. Inflammation also generally lowers the threshold for pain from visceral distention or exaggerated muscular contraction (See Lorber, S. H., and V. P. Dimoso, Jr., "Diseases of the Gastrointestinal Tract", The Biology of Alcoholism , Vol 3, Clinical Pathology, Plenum Press, N.Y., p 339-357, 1974).

Heartburn or pyrosis is frequently associated with overindulgence and is the result of reflux of acidic gastric content into the lower esophagus after a large meal or excessive alcohol intake. Heartburn is described as a sensation of warmth or burning located substernally or high in the epigastrum with occasional radiation into the neck and occasionally to the arms.

Treatment of the gastric mucosal irritation and heartburn associated with overindulgence due to alcohol has traditionally been directed toward reducing gastric acidity with various oral antacids. Recent introduction of H_2 receptor blocking agents has added another dimension to the treatment regimen and has only lately been considered as a routine therapy for gastric mucosal irritation due to a variety of causes. Histamine is known to stimulate the release of gastric acid. Evidence is available that blocking the histamine gastric response is possible with agents which selectively block the H_1 receptor. Similarly, combinations of H_1 and H_2 receptor blocking agents have been shown to have a synergistic effect on protecting the gastric mucosa. An appropriate treatment of heartburn or pyrosis could encompass a composition containing an H_1 receptor blocking agent, an H_2 receptor blocking agent or a combination of the two depending upon the desired result or severity of the condition.

Headache due to excessive food or alcohol ingestion is a much more obscure subject. While

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the etiology of the common headache due to overindulgence may be related to the essential oils, metabolic by-products of ethyl alcohol metabolism or osmotic changes induced by the anhydrous nature of the alcohol itself, specific details of the mechanism are difficult to determine. Should etiologies and mechanisms of headache production be more precisely known, therapy can be more specifically oriented. Meanwhile, treatnient has been directed at avoidance and symptomatic therapy with analgesic compositions, e.g. aspirin or APAP (See Adams, A. D. and J. B. Martin, "Headache", Harrison's Principles of Internal Medicine , 11th Edition, McGraw Hill Book Company, N.Y., p 26-33, 1988).

The treatment of the symptoms of overindulgence often requires the co-administration of an analgesic to relieve the headache along with an agent to reduce gastric acidity which is generally believed to cause the indigestion and heartburn. For example, effervescent products comprising aspirin or APAP combined with an antacid such as sodium or calcium carbonates have been commercially available as treatments for the symptoms of overindulgence.

The concept of combining an agent to reduce or inhibit the production of gastric acid with an analgesic in a single composition has, however, heretofore been overlooked as a method of treating overindulgence. Such a combination would be a significant advance and meet a long felt need for treating the symptoms of overindulgence, permitting a single composition to more effectively treat all the symptoms concurrently.

Summary of the Invention

The foregoing object of fulfilling a long felt need for pharmaceutical compositions which can relieve the symptoms of overindulgence defined herein as headache and acid indigestion has now been accomplished in accordance with the compositions and methods of the present invention.

In accordance with the purposes of the invention, as embodied and fully described herein, the invention comprises pharmaceutical compositions for treating the symptoms of overindulgence comprising an analgesic effective amount of an NSAID or APAP and a gastric acid inhibiting effective amount of an H_1 or H_2 blocker, a proton pump inhibitor or a combination thereof.

In preferred embodiments the NSAID is selected from the group consisting of propionic acid derivatives including ibuprofen, fenoprofen, naproxen and ketoprofen; fenamic acid derivatives, including meclofenamate and mefenamic acid; oxicams,. including piroxicam; indole acetic acids, including indomethacin, sulindac, tolmetin; and pharmaceutically acceptable salts thereof. The preferred H_1 or H_2 or proton pump inhibitors are selected from the group consisting of the H_2 receptor blocking drugs cimetidine, ranitidine and famotidine; the proton pump inhibitor drug omeprazole; and the H_1 receptor blocking drugs, from the group ethanolamines including diphenhydramine, dimenhydrimate, carbinoxamine, from the group ethylenediamines, including tripelennamine, pyrilamine, from the group alkylamines, including cholphenirdmine, from the group piperazines, including hydroxyzine, cyclizine, meclizine, from the group phenothiarinec, including promethazine. In more preferred embodiments the APAP or ibuprofen are used in combination with cimetidine.

As embodied and broadly described herein, the invention further comprises a method for treating the symptoms of overindulgence comprising administering a combination pharmaceutical composition to a patient comprising an analgesic effective amount of APAP or an NSAID and a gastric acid inhibiting effective amount of an H_1 or H_2 blocker, a proton pump inhibitor or a combination thereof as is described above.

Detailed Description of Preferred Embodiments of the Invention

Reference will now be made in detail to preferred embodiments of the invention, examples of which are illustrated in the following examples section.

To achieve the object of the invention of providing a pharmaceutical composition for treating the symptoms of overindulgence an analgesic effective amount of APAP or an NSAID is combined with a gastric acid inhibiting effective amount of an H_1 or H_2 blocker or a proton pump inhibitor or a combination thereof.

The treatment of overindulgence is directed to the symptomatic relief of the complaints of acid indigestion and headache. This requires the use of an agent which would treat the headache, abdominal discomfort and reduce the intraluminal gastric acidity. Since no single agent has been found to be capable of treating the multiple symptons of overindulgence, a composition such as is described in this invention is recommended.

APAP, a well-known clinically proven analgesic and antipyretic, produces analgesia by elevating the pain threshold. APAP is indicated as an analgesic for both acute and chronic pain conditions, including arthritic and rheumatic conditions involving musculoskeletal pain, headache, dysmenorrhea, myalgias and neuralgias. APAP is an extremely

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safe analgesic, rarely producing side-effects and is especially well tolerated by aspirin-sensitive patients. (Seegers, A. J. M., L. P. Jager, and J. Van Noordwijk, "Effects of Phenacetin Parcetamol and Caffeine on the Erosive Activity of Acetylsalicylic Acid in the Rat Stomach: Dose-Response Relationships, Time Course of Erosion Development and Effects of Acid Secretion", J. Pharmacol , 31:840-848, 1979), have shown that APAP decreases the gastric erosive activity of a strongly ulcerogenic NSAID. (Stern, A. I., D. L. Hogan, L. H. Kahn, and J. 1. Isenberg, "Protective Effect of Acetaminophen Against Aspirin - and Ethanol-Induced Damage to the Human Gastric Mucosa", Gastroenterology , 86:728-733, 1984), have additionally shown that a single dose of APAP prevents a significant amount of gastric mucosal damage caused by both aspirin and alcohol. Further, APAP is particularly well suited as an analgesic in patients with hemostatic disturbances as well as in patients with upper gastrointestinal disorders including ulcers, gastritis and hiatus hernia.

Aspirin and other NSAIDs are commonly used for the treatment of pain and inf lammation of a variety of etiologies. The mechanism of action of this class of drugs is by inhibition of the enzyme of prostaglandin synthetase, both contrally and peripherally. The peripheral prostaglandin synthetase inhibiting activity of aspirin and other NSAIDs is responsible for the anti-inflammatory and analgesic activity as well as for many of the varied side-effects of these drugs. Aspirin is specifically excluded from this invention since aspirin, by itself, causes severe inflammation of the gastric mucosa. In the presence of alcohol, this effect of aspirin is enhanced. Similarly, prolongation of bleeding time induced by aspirin, is enhanced in the presence of alcohol (See Deykin, D., P. Janson and L. McMahon, "Ethanol Potentiation of Aspirin-Induced Prolongation of the Bleeding Time", New England Journal of Medicine , 306:852-854, 1982). For these reasons aspirin is not a rational choice either alone or in combination with other compositions for treating acid indigestion in general and as it relates to overindulgence. While other NSAIDs can by themselves lead to increased stomach upset, this effect is not as severe as with aspirin, and they are thus useful in treating the symptoms of overindulgence in accordance with the combination composition of the invention.

The presence of gastrin, acetylcholine and histamine in the stomach interacting with the histamine receptor on the parietal cell results in the increased secretion of hydrochloric acid. The activity of gastrin and acetylcholine are believed to be influenced by histamine. Inhibition of the histamine receptor prevents the attachment of histamine to the parietal cell and subsequently inhibits acid secretion. Omeprazole, a proton pump inhibitor, irreversibly inhibits the enzyme responsible for acid production.

The histamine receptors are differentiated by the class of inhibitor so that while the acid secreting histamine receptor is called an H_2 receptor with the inhibitors of this site being called the H_2 receptor blocker, the histamine H_1 receptor site blockers comprise another class of antihistamine drugs. The combination of H_1 and H_2 blockers can synergistically protect the gastrointestinal mucosa from the effects of chemically induced damage such as occurs in alcohol and food related overindulgence.

The composition of the present invention shall preferably contain a combination of the following compositions or their pharmaceutically acceptable salts either acetaminophen from 500 to 1000 mg per dose or one of several NSAIDs from the group of: propionic acid derivatives including ibuprofen (the term ibuprofen is meant to include administration of both the racemic mixture of R- and S-enantiomers and the substantially pure S-enantiomer which is the analgesic active form of ibuprofen) from 200 to 400 mg per dose; naproxen from 200 to 500 mg per dose; fenoprofen from 200 to 600 mg per dose; ketoprofen from 50 to 300 mg per dose, meclofenamate from 50 to 400 mg per dose, mefenamic acid from 250 to 500 mg per dose; piroxicam from 10 to 20 mg per dose; indomethacin from 25 to 200 mg per dose, sulindac from 150 to 400 mg per dose, tolmetin from 200 to 1200 mg per dose; in combination with the H_2 receptor blocking drugs including cimetidine from 150 to 800 mg per dose; ranitidine from 50 to 300 mg per dose; famotidine from 5 to 40 mg per dose; or in combination with the proton pump inhibitor drugs including omeprazole from 100 to 500 mg per dose; and/or an H_1 receptor blocking drug from the group ethanolamines including diphenhydramine 25 to 200 mg per dose; dimenhydrimate from 50 to 400 mg per dose, carbinoxamine from 4 to 8 mg per dose; from the group ethylenediamines including tripelennamine frog 25 to 300 mg per dose; pyrilamine from 25 to 300 mg per dose; from the group alkylamines including chorpheniramine from 2 to 24 mg per dose, from the group piperazines including hydroxyzine from 25 to 100 mg per dose, cyclizine from 50 to 300 mg per dose, meclizine from 8 to 400 mg per dose; and from the group phenothiazines including promethazine from 12.5 to 50 mg per dose.

The dosage ranges described above are preferred adult doses and may vary depending upon the age and weight of the patient as would be known by those skilled in the pharmaceutical arts. Further, if a combination of, for example an H_1 and H_2 blocker is used, the dosage for each may be reduced.

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To establish the efficacy of the composition of this invention in humans, patients suffering from the symptoms of overindulgence which will include any of the constellation of signs of indigestion, upper abdominal discomfort, bloating, heartburn or pyrosis and headache can be administered acetaminophen or a non-steroidal anti-inflammatory drug with and without histamine receptor blockers (H_1 and/or H_2 blocking agents). To determine efficacy, patients are asked to subjectively estimate onset of relief, duration of relief and time to maximum relief. Appropriate statistical methods are used to show that on the average, acetaminophen or non-steroidal anti-inflammatory agents with H_1 histamine and/or H_2 histamine receptor blocking drugs are more efficacious.

Since appropriate animal models for the evaluation of overindulgence are not available, studies will not be conducted involving laboratory animals.

Other ingredients both active and inactive can be added to the combination pharmaceutical compositions of the invention. For example, flavoring compositions are desirably added to chewable and liquid dosage forms. Further, antidiarrheal, antiflatulent, antispasmodic and/or anticholinergic compositions may be added to the compositions of the invention to reduce and relieve gastrointestinal distress, which may be associated with acid indigestion. Exzmples of antidiarrheals include loperamidc, attapulgite, bismuth subsalicylate, diphenoxylate HCl, polycarbophil, calcium polycarbophil and mixtures thereof. An example of an antiflatulent is simethicone. Examples of antispasmodics include phenobarbital dicyclomine HCl, belladonna alkaloids, and atropine.

Examples

The invention will now be illustrated by examples. The examples are not intended to be limiting of the scope of the present invention but read in conjunction with the detailed and general description above, provide further understanding of the present invention and an outline of a process for preparing the compositions of the invention. Example 1-14 disclose various formulations for preparing tablets or caplets in accordance with the invention. Various conventional techniques for preparing medicament tablets or caplets can be employed as would be known to those skilled in the art as is disclosed for example by Remington's Pharmaceutle Sciences , flack Publishing Co., Chapter 90, "Oral Solid Dosage Forms", pp. 1603-1632 (1985).

Example 1:

A tablet consisting of:
500 mg of acetaminophen;
150 mg of cimetidine; and
other auxiliary agents and coloring agents.

Example 2:

A tablet consisting of:
500 mg of acetaminophen;
mg of diphenhydramine; and
other auxiliary agents and coloring agents.

Example 3:

A tablet consisting of:
200 mg of ibuprofen;
150 mg of cimetidine; and
other auxiliary agents and coloring agents.

Example 4:

A tablet consisting of:
200 mg of ibuprofen;
mg of ranitidine; and
other auxiliary agents and coloring agents.

Example 5:

A tablet consisting of:
200 mg of ibuprofen;
mg of diphenhydramine; and
other auxiliary agents and coloring agents.

Example 6:

A tablet consisting of:
500 mg of acetaminophen;
50 mg of ranitidine; and
other auxiliary agents and coloring agents.

Example 7:

A tablet consisting of:
500 mg of acetaminophen;
150 mg of cimetidine;
25 mg of diphenhydramine; and

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other auxiliary agents and coloring agents.

Example 8:

A tablet consisting of:
200 mg of ibuprofen;
350 mg of cimetidine;
mg of diphenhydramine; and
other auxiliary agents and coloring agents.

Example 9:

A tablet consisting of:
500 mg of acetaminophen;
50 mg of ranitidine;
25 mg of diphenhydramine; and
other auxiliary agents and coloring agents.

Example 10:

A tablet consisting of:
200 mg of ibuprofen;
50 mg of ranitidine;
25 mg of diphenhydramine; and
other auxiliary agents and coloring agents.

Example 11:

A tablet consisting of:
500 mg of acetaminphen;
60 mg of omeprazole; and
other auxiliary agents and coloring agents.

Example 12:

A tablet consisting of:
200 mg ibuprofen;
mg omeprazole; and
other auxiliary agents and coloring agents.

Example 13:

A tablet consisting of:
500 mg acetaminophen;
60 mg omeprazole;
25 mg diphenhydramine; and
other auxiliary agents and coloring agents.

Example 14:

A tablet consisting of:
200 mg ibuprofen;
60 mg omeprazole;
25 mg diphenhydramine; and
other auxiliary agents and coloring agents.

Various other dosage forms can be applied herein such as a filled gelatin capsule, liquid emulsion/suspension or chewable tablet form employing the dosage actives provided above or other dosage amounts in accordance with the present invention. A liquid suspension of ibuprofen to which cimetidine, diphenhydramine, ranitidine or combinations thereof in the amounts provided above can be added to the ibuprofen suspension disclosed in EP-A-90307001.9.

Method of Treating Patients for the Symptoms of Overindulgence

A patient exhibiting the symptoms or suffering from the symptoms of overindulgence is treated by the oral administration of one tablet of the pharmaceutical composition in accordance with any of Examples 1-14.

The scope of the present invention is not limited by the description, examples and suggested uses herein and modifications can be made without departing from the spirit of the invention. For example, the pharmaceutical compositions of the invention may be provided in a sustained release formulation for prolonged and/or nightime treatment of the symptoms of overindulgence. Application of the compositions and methods of the present invention for medical and pharmaceutical uses can be accomplished by any clinical, medical and pharmaceutical methods and techniques as are presently or prospectively known to those skilled in the art. Thus it is intended that the presently claimed invention cover the modifications and variations of this invention provided that they come within the scope of the appended claims and their equivalents.

Claims

1. A pharmaceutical composition comprising:
an analgesic effective amount of acetaminophen or a non-steroidal anti-inflammatory drug; and
a gastric acid inhibiting effective amount of an H_1 or H_2 receptor blocker, a proton pump inhibitor or a

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combination thereof.

2. The composition of claim 1 wherein the non-steroidal anti-inflammatory drug is a propionic acid derivative, a fenamic acid derivative, an oxicam, an indole acetic acid or a pharmaceutically acceptable salt thereof.

3. The composition of claim 1 or claim 2 wherein the acetaminophen or non-steroidal anti-inflammatory drug, selected from ibuprofen, fenoprofen, naproxen, ketoprofen, meclofenamate, mefenamic acid, piroxicam, indomethacin, sulindac, tolmetin, or a pharmaceutically acceptable salt thereof, is combined with:

one of the H_2 receptor blocking drugs cimetidine, ranitidine and famotidine;

the proton pump inhibitor drug omeprazole; or one of the H_1 receptor blocking drugs diphenhydramine, dimenhydrimate, carbinoxamine, tripelennamine, pyrilamine, chorpheniramine, hydroxyzine, cyclizine, meclizine, promethazine;

or a pharmaceutically acceptable salt thereof.

4. The composition of any one of claims 1 to 3 which contains:

acetaminophen from 500 to 1000mg per dose, ibuprofen from 200 to 400 mg per dose, naproxen from 200 to 500 mg per dose, fenoprofen from 200 to 600 mg per dose, ketoprofen from 50 to 300 mg per dose, meclofenamate from 50 to 400 mg per dose, mefenamic acid from 250 to 500 mg per dose, piroxicam from 10 to 20 mg per dose, indomethacin from 25 to 200 mg per dose, sulindac from 150 to 400 mg per dose, tolmetin from 200 to 1200 mg per dose or a pharmaceutically acceptable salt thereof;

in combination with:

cimetidine from 150 to 800 mg per dose, ranitidine from 50 to 300 mg per dose, famotidine from 5 to 40 mg per dose, omeprazole from 100 to 500 mg per dose, diphenhydramine from 25 to 200 mg per dose, dimenhydrimate from 50 to 400 mg per dose, carbinoxamine from 4 to 8 mg per dose, tripelennamine from 25 to 300 mg per dose, pyrilamine from 25 to 100 mg per dose, chlorpheniramine from 2 to 24 mg per dose, hydroxyzine from 25 to 100 mg per dose, cyclizine from 50 to 300 mg per dose, meclizine from 8 to 400 mg per dose, promethazine from 12.5 to 50 mg per dose, a pharmaceutically acceptable salt thereof or a combination thereof.

5. The composition of any one of claims 1 to 4 comprising fenoprofen, ketoprofen, meclofenamate, mefenamic acid, piroxicam, indomethacin, sulindac, tolmetin or a pharmaceutically acceptable salt thereof, and

(a) cimetidine, ranitidine or famotidine; or

(b) diphenhydramine, dimenhydrimate, carbinoxamine, tripelennamine, pyrilamine, chlorpheniramine, hydroxyzine, cyclizine, meclizine or promethazine; or

(c) a combination of a drug from group (a) and a drug from group (b).

6. The composition of any one of claims 1 to 5 comprising:

a combination of acetaminophen and cimetidine;

a combination of ibuprofen and cimetidine; or

a combination of naproxen anddiphenhydramine.

7. The composition of any one of claims 1 to 6, in oral tablet, caplet, chewable or liquid dosage form.

8. The composition of any one of claims 1 to 7, for use in treating the symptoms of over indulgence.

9. A method for producing the composition of any one of claims 1 to 8 which comprises forming a pharmaceutical composition containing:

an analgesic effective amount of acetaminophen or a non-steroidal anti-inflammatory drug; and

a gastric acid inhibiting amount of an H_1 or H_2 receptor blocker, a proton pump inhibitor or a combination thereof.

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European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 90 31 1995

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	UNLISTED DRUGS, vol. 20, no. 11, November 1968, Chatnam, New Jersey, US * Page 167, paragraph e: "Infacete" *	1-9	A 61 K 31/415 A 61 K 31/34 A 61 K 31/165 A 61 K 31/19 A 61 K 31/44 // (A 61 K 31/415 A 61 K 31:19 A 61 K 31:165) (A 61 K 31/34 A 61 K 31:165) (A 61 K 31/165 A 61 K 31:135) (A 61 K 31/19 A 61 K 31:135) (A 61 K 31/44 A 61 K 31:19 A 61 K 31:165)
X	WO-A-8 503 443 (RICHARDSON-VICKS, INC.) * Pages 25-28, claims 1-27 *	1-9	
X	GB-A-2 105 193 (GLAXO GROUP LTD) * Page 3, lines 19-35, claims 1-7 *	1-9	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of search	Examiner
The Hague	28 January 91	BRINKMANN C.

CATEGORY OF CITED DOCUMENTS

X: particularly relevant if taken alone
Y: particularly relevant if combined with another document of the same catagory
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention

E: earlier patent document, but published on, or after the filing date
D: document cited in the application
L: document cited for other reasons

&: member of the same patent family, corresponding document

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(54) **Use of a composition for the manufacture of a medicament for curing the symptoms of overindulgence.**

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Description

This invention relates to pharmaceutical compositions for treating the symptoms of overindulgence. More particularly, the invention comprises treating the symptoms of overindulgence with a combination of non-steroidal anti-inflammatory drug or acetaminophen and a histamine receptor blocker and/or a proton pump inhibitor composition

Non-steroidal anti-inflammatory drugs (hereinafter referred to as "NSAID(S)") and acetaminophen (hereinafter referred to as "APAP") are known to be effective analgesics for the treatment of mild to moderate pain. Histamine receptor blockers (referred to generically herein as H_1 or H_2 blockers) are effective inhibitors of gastric acid production. Proton pump inhibitors have been recently introduced as effective gastric acid inhibitors.

The symptoms of overindulgence due to excessive or inappropriate intake of food and/or alcoholic beverage are well known and include headache as well as indigestion, upper abdominal discomfort, bloating, heartburn or pyrosis. These latter symptoms collectively are sometimes referred to as acid indigestion or sour stomach. Indigestion has been variously described and will be defined herein as encompassing one or more of the following symptoms: abdominal pain and/or pressure, heartburn, a sense of abdominal fullness or bloating, excessive belching or flatulence and a vague feeling that digestion has not proceeded naturally (See Friedman, L.S., and K. J. Isselbacher, "Indigestion", Harison's Principles of Internal Medicine, 11th Edition, McGraw Hill Book Company, N.Y., p 171-175, 1986).

The pathophysiology of indigestion is generally believed to be related to increased intraluminal acidity. The effects of alcohol and/or food on the gastrointestinal tract are influenced by a number of factors, including the mental state of the patient, the amount and type of food concurrently ingested, the individual subject's tolerance for alcohol and the presence or absence of disease. Gastric secretions stimulated by alcohol are rich in acid and normal in pepsin content. Stimulation of the antral mucosa by alcohol also leads to increased gastric secretion. Histamine has also been shown to be released in response to the alcohol-gestrin inter-relationship. (See Glass, G. B. J., B. L. Slomiany and A. Slomiany, "Biochemical and Pathological Derangements of the Gastrointestinal Tract following Acute and Chronic Ingestion of Ethanol", Biochemistry and Pharmacology of Ethanol, Vol 1, Plenum Press, N.Y., p 551-586, 1979.)

Alcohol in concentrations of about 10% in the stomach results in an acid rich secretion. Alcoholic drinks of 40% concentration and over are quite irritating to the gastric mucosa and cause congestive hyperemia and inflammation of the gastric mucosa and can produce erosive gastritis (See Ritchie, J. M., "The Aliphatic Alcohols", The Pharmacological Basis of Therapeutics, 7th Edition, MacMillan Publishing Co, N.Y., p 372-386, 1985). The irritation produced by alcohol stimulates sensitized visceral afferent nerves which accompany the abdominal sympathetic pathway and is responsible for the symptom of abdominal discomfort which accompanies overindulgence. Inflammation also generally lowers the threshold for pain from visceral distention or exaggerated muscular contraction (See Lorber, S. H., and V. P. Dimoso, Jr., "Diseases of the Gastrointestinal Tract", The Biology of Alcoholism, Vol 3, Clinical Pathology, Plenum Press, N.Y., p 339-357, 1974).

Heartburn or pyrosis is frequently associated with overindulgence and is the result of reflux of acidic gastric content into the lower esophagus after a large meal or excessive alcohol intake. Heartburn is described as a sensation of warmth or burning located substernally or high in the epigastrum with occasional radiation into the neck and occasionally to the arms.

Treatment of the gastric mucosal irritation and heartburn associated with overindulgence due to alcohol has traditionally been directed toward reducing gastric acidity with various oral antacids. Recent introduction of H_2 receptor blocking agents has added another dimension to the treatment regimen and has only lately been considered as a routine therapy for gastric mucosal irritation due to a variety of causes. Histamine is known to stimulate the release of gastric acid. Evidence is available that blocking the histamine gastric response is possible with agents which selectively block the H_1 receptor. Similarly, combinations of H_1 and H_2 receptor blocking agents have been shown to have a synergistic effect on protecting the gastric mucosa. An appropriate treatment of heartburn or pyrosis could encompass a composition containing an H_1 receptor blocking agent, an H_2 receptor blocking agent or a combination of the two depending upon the desired result or severity of the condition.

Headache due to excessive food or alcohol ingestion is a much more obscure subject. While the etiology of the common headache due to overindulgence may be related to the essential oils, metabolic by-products of ethyl alcohol metabolism or osmotic changes induced by the anhydrous nature of the alcohol itself, specific details of the mechanism are difficult to determine. Should etiologies and mechanisms of headache production be more precisely known, therapy can be more specifically oriented. Meanwhile, treatment has been directed at avoidance and symptomatic therapy with analgesic compositions, e.g. aspirin or APAP (See Adams, R.D. and J.B. Martin, "Headache", Harrison's Principles of Internal Medicine, 11th Edition, McGraw Hill Book Company, N.Y., p 26-33, 1986).

The treatment of the symptoms of overindulgence often requires the co-administration of an an-

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algesic to relieve the headache along with an agent to reduce gastric acidity which is generally believed to cause the indigestion and heartburn. For example, effervescent products comprising aspirin or APAP combined with an antacid such as sodium or calcium carbonates have been commercially available as treatments for the symptoms of overindulgence.

WO85/03443 (Richardson-Vicks, Inc.) discloses analgesic and anti-inflammatory compositions comprising a non-steroidal anti-inflammatory drug and diphenhydramine. It is disclosed that the diphenhydramine acts synergistically with the non-steroidal anti-inflammatory drug to provide enhanced analgesic and anti-inflammatory response.

GB-A-2105193 (Glaxo Group Limited) discloses pharmaceutical compositions comprising a non-steroidal anti-inflammatory drug and the histamine H_2-antagonist ranitidine. The ranitidine reduces the undesirable ulcerogenic side-effects of certain non-steroidal anti-inflammatory drugs and is especially useful when the medicament has to be administered over an extended period.

The concept of combining an agent to reduce or inhibit the production of gastric acid with an analgesic in a single composition has, however, heretofore been overlooked as a method of treating overindulgence. Such a combination would be significant advance and meet a long felt need for treating the symptoms of overindulgence, permitting a single composition to more effectively treat all the symptoms concurrently.

The foregoing object of fulfilling e long felt need for pharmaceutical compositions which can relieve the symptoms of overindulgence defined herein as headache and acid indigestion has now been accomplished in accordance with the compositions and methods of the present invention.

In accordance with the purposes of the invention, as embodied and fully described herein, the invention providas the use of a composition comprising:

an analgesic effective amount of acetaminophen or a non-steroidal anti-inflammatory drug; and

a gastric acid inhibiting effective amount of an H_1 or H_2 receptor blocker, a proton pump inhibitor or a combination thereof for the preparation of a medicament for use in the treatment of the effects of overindulgence.

In preferred embodiments the NSAID is selected from the group consisting of propionic acid derivatives including ibuprofen, fenoprofen, naproxen and ketoprofen; fenamic acid derivatives, including meclofenamate and mefenamic acids; oxicams, including piroxicam; indole acetic acids, including indomethacin, sulindac, tolmetin; and pharmaceutically acceptable salt thereof. The preferred H_1 or H_2 or proton pump inhibitors are selected from the group consisting of the H_2 receptor blocking drugs cimetidine, ranitidine and famotidine; the proton pump inhibitor drug omeprazole; and the H_1 receptor blocking drugs, from the group ethanolamines including diphenhydramine, dimenhydrinate, carbinoxamine, from the group ethylenediamines, including tripelennamine, pyrilamine, from the group alkylamines, including chorpheniramine, from the group piperazines, including hydroxyzine, cyclizine, meclizine, from the group phenothiazines, including promethazine. In more preferred embodiments the APAP or ibuprofen are used in combination with cimetidine.

As embodied and broadly described herein, the invention may be used in methods for treating the symptoms of overindulgence comprising administering a combination pharmaceutical composition to a patient comprising an analgesic effective amount of APAP or an NSAID and a gastric acid inhibiting effective amount of an H_1 or H_2 blocker, a proton pump inhibitor or a combination thereof as is described above.

Detailed Description of Preferred Embodiments of the Invention

Reference will now be made in detail to preferred embodiments of the invention, examples of which are illustrated in the following examples section.

To achieve the object of the invention of providing a pharmaceutical composition for treating the symptoms of overindulgence an analgesic effective amount of APAP or an NSAID is combined with a gastric acid inhibiting effective amount of an H_1 or H_2 blocker or a proton pump inhibitor or a combination thereof.

The treatment of overindulgence is directed to the symptomatic relief of the complaints of acid indigestion and headache. This requires the use of an agent which would treat the headache, abdominal discomfort and reduce the intraluminal gastric acidity. Since no single agent has been found to be capable of treating the multipla symptons of overindulgence, a composition such as is described in this invention is recommended.

APAP, a well-known clinically proven analgesic and antipyretic, produces analgesia by elevating the pain threshold. APAP is indicated as an analgesic for both acute and chronic pain conditions, including arthritic and rheumatic conditions involving musculoskeletal pain, headache, dysmenorrhea, myalgias and neuralgias. APAP is an extremely safe analgesic, rarely producing side-effects and is especially well tolerated by aspirin-sensitive patients. (Seegers, A. J. M., L. P. Jager, and J. Van Noordwijk, "Effects of Phenacetin Paracetamol and Caffeine on the Erosive Activity of Acetylsalicylic Acid in the Rat Stomach: Dose-Response Relationships, Time Course of Erosion Development and Effects of Acid Secretion", J. Pharmacol, 31:840-848, 1979), have shown that APAP decreases the gastric erosive activity of a strongly ulcerogenic NSAID. (Stern, A. I., D. L. Hogan, L. H. Kahn,

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and J. 1. Isenberg, "Protective Effect of Acetaminophen Against Aspirin - and Ethanol-Induced Damage to the Human Gastric Mucosa", Gastroenterology, 86:728-733, 1984), have additionally shown that a single dose of APAP prevents a significant amount of gastric mucosal damage caused by both aspirin and alcohol. Further, APAP is particularly well suited as an analgesic in patients with hemostatic disturbances as well as in patients with upper gastrointestinal disorders including ulcers, gastritis and hiatus hernia.

Aspirin and other NSAIDs are commonly used for the treatment of pain and inflammation of a variety of etiologies. The mechanism of action of this class of drugs is by inhibition of the enzyme of prostaglandin synthetase, both centrally and peripherally. The peripheral prostaglandin synthetase inhibiting activity of aspirin and other NSAIDs is responsible for the anti-inflammatory and analgesic activity as well as for many of the varied side-effects of these drugs. Aspirin is specifically excluded from this invention since aspirin, by itself, causes severe inflammation of the gastric mucosa. In the presence of alcohol, this effect of aspirin is enhanced. Similarly, prolongation of bleeding time induced by aspirin, is enhanced in the presence of alcohol (See Deykin, D., P. Janson and L. McMahon, "Ethanol Potentiation of Aspirin-Induced Prolongation of the Bleeding Time", New England Journal of Medicine, 306:852-854, 1982). For these reasons aspirin is not a rational choice either alone or in combination with other compositions for treating acid indigestion in general and as it relates to overindulgence. While other NSAIDs can by themselves lead to increased stomach upset, this effect is not as severe as with aspirin, and they are thus useful in treating the symptoms of overindulgence in accordance with the combination composition of the invention.

The presence of gastrin, acetylcholine and histamine in the stomach interacting with the histamine receptor on the parietal cell results in the increased secretion of hydrochloric acid. The activity of gastrin and acetylcholine are believed to be influenced by histamine. Inhibition of the histamine receptor prevents the attachment of histamine to the parietal cell and subsequently inhibits acid secretion. Omeprazole, a proton pump inhibitor, irreversibly inhibits the enzyme responsible for acid production.

The histamine receptors are differentiated by the class of inhibitor so that while the acid secreting histamine receptor is called an H_2 receptor with the inhibitors of this site being called the H_2 receptor blocker, the histamine H_1 receptor site blockers comprise another class of antihistamine drugs. The combination of H_1 and H_2 blockers can synergistically protect the gastrointestinal mucosa from the effects of chemicelly induced damage such as occurs in alcohol and food related overindulgence.

The composition of the present invention shall preferably contain a combination of the following compositions or their pharmaceutically acceptable salts either acetaminophen from 500 to 1000 mg per dose or one of several NSAIDs from the group of: propionic acid derivatives including ibuprofen (the term ibuprofen is meant to include administration of both the racemic mixture of R- and S-enantiomers and the substantially pure S-enantiomer which is the analgesic active form of ibuprofen) from 200 to 400 mg per dose; naproxen from 200 to 500 mg per dose; fenoprofen from 200 to 600 mg per dose; ketoprofen from 50 to 300 mg per dose, meclofenamate from 50 to 400 mg per dose, mefenamic acid from 250 to 500 mg per dose; piroxicam from 10 to 20 mg per dose; indomethacin from 25 to 200 mg per dose, sulindac from 150 to 400 mg per dose, tolmetin from 200 to 1200 mg per dose; in combination with the H_2 receptor blocking drugs including cimetidine from 150 to 800 mg per dose; ranitidine from 50 to 300 mg per dose; famotidine from 5 to 40 mg per dose; or in combination with the proton pump inhibitor drugs including omeprazole from 100 to 500 mg per dose; and/or an H_1 receptor blocking drug from the group ethanolamines including diphenhydramine 25 to 200 mg per dose; dimenhydrinate from 50 to 400 mg per dose, carbinoxamine from 4 to 8 mg per dose; from the group ethylenediamines including tripelennamine from 25 to 300 mg per dose; pyrilamine from 25 to 100 mg per dose; from the group alkylamines including chorpheniramine from 2 to 24 mg per dose, from the group piperazines including hydroxyzine from 25 to 100 mg per dose, cyclizine from 50 to 300 mg per dose, meclizine from 8 to 400 mg per dose; and from the group phenothiazines including promethazine from 12.5 to 50 mg per dose.

The dosage ranges described above are preferred adult doses and may vary depending upon the age and weight of the patient as would be known by those skilled in the pharmaceutical arts. Further, if a combination of, for example an H_1 and H_2 blocker is used, the dosage for each may be reduced.

To establish the efficacy of the composition of this invention in humans, patients suffering from the symptoms of overindulgence which will include any of the constellation of signs of indigestion, upper abdominal discomfort, bloating, heartburn or pyrosis and headache can be administered acetaminophen or a non-steroidal anti-inflammatory drug with and without histamine receptor blockers (H_1 and/or H_2 blocking agents). To determine efficacy, patients are asked to subjectively estimate onset of relief, duration of relief and time to maximum relief. Appropriate statistical methods are used to show that on the average, acetaminophen or non-steroidal anti-inflammatory agents with H_1 histamine and/or H_2 histamine receptor blocking drugs are more efficacious.

Since appropriate animal models for the evaluation of overindulgence are not available, studies will not be conducted involving laboratory animals.

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Other ingredients both active and inactive can be added to the combination pharmaceutical compositions of the invention. For example, flavoring compositions are desirably added to chewable and liquid dosage forms. Further, antidiarrheal, antiflatulent, antispasmodic and/or anticholinergic compositions may be added to the compositions of the invention to reduce and relieve gastrointestinal distress, which may be associeted with acid indigestion. Examples of antidiarrheals include loperamide, attapulgite, bismuth subsalicylate, diphenoxylate HCl, polycarbophil, calcium polycarbophil and mixtures thereof. An example of an antiflatulent is simethicone. Examples of antispasmodics include phenobarbital dicyclomine HCl, belladonna alkaloids, and atropine.

Examples

The invention will now be illustrated by examples. The examples are to be read in conjunction with the detailed and general description above, provide further understanding of the present invention and an outline of a process for preparing the compositions of the invention. Examples 1-14 disclose various formulations for preparing tablets or caplets in accordance with the invention. Various conventional techniques for preparing medicament tablets or caplets can be employed as would be known to those skilled in the art as is disclosed for example by Remington's Pharmaceutical Sciences, Mack Publishing Co., Chapter 90, "Oral Solid Dosage Forms", pp. 1603-1632 (1985).

Example 1:

A tablet consisting of:
500 mg of acetaminophen;
150 mg of cimetidine; and
other auxiliary agents and coloring agents.

Example 2:

A tablet consisting of:
500 mg of acetaminophen;
25 mg of diphenhydramine; and
other auxiliary agents and coloring agents.

Example 3:

A tablet consisting of:
200 mg of ibuprofen;
150 mg of cimetidine; and
other auxiliary agents and coloring agents.

Example 4:

A tablet consisting of:
200 mg of ibuprofen;
50 mg of ranitidine; and
other auxiliary agents and coloring agents.

Example 5:

A tablet consisting of:
200 mg of ibuprofen;
25 mg of diphenhydramine; and
other auxiliary agents and coloring agents.

Example 6:

A tablet consisting of:
500 mg of acetaminophen;
50 mg of renitidine; and
other auxiliary agents and coloring agents.

Example 7:

A tablet consisting of:
500 mg of acetaminophen;
150 mg of cimetidine;
25 mg of diphenhydramine; and
other auxiliary agents and coloring agents.

Example 8:

A tablet consisting of:
200 mg of ibuprofen;
350 mg of cimetidine;
25 mg of diphenhydramine; and
other auxiliary agents and coloring agents.

Example 9:

A tablet consisting of:
500 mg of acetaminophen;
50 mg of ranitidine;
25 mg of diphenhydramine; and
other auxiliary agents and coloring agents.

Example 10:

A tablet consisting of:
200 mg of ibuprofen;
50 mg of ranitidine;
25 mg of diphenhydramine; and
other auxiliary agents and coloring agents.

Example 11:

A tablet consisting of:
500 mg of acetaminphen;
60 mg of omeprazole; and
other auxiliary agents and coloring agents.

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Example 12:

A tablet consisting of:
200 mg ibuprofen;
60 mg omeprazole; and
other auxiliary agents and coloring agents.

Example 13:

A tablet consisting of:
500 mg acetaminophen;
60 mg omeprazole;
25 mg diphenhydramine; and
other auxiliary agents and coloring agents.

Example 14:

A tablet consisting of:
200 mg ibuprofen;
60 mg omeprazole;
25 mg diphenhydramine; and
other auxiliary agents and coloring agents.

Various other dosage forms can be applied herein such as a filled gelatin capsule, liquid emulsion/suspension or chewable tablet form employing the dosage actives provided above or other dosage amounts in accordance with the present invention. A liquid suspension of ibuprofen to which cimetidine, diphenhydramine, ranitidine or combinations thereof in the amounts provided above can be added to the ibuprofen suspension disclosed in EP-A-90307001.9.

Treating Patients for the Symptoms of Overindulgence

A patient exhibiting the symptoms or suffering from the symptoms of overindulgence is treated by the oral administration of one tablet of the pharmaceutical composition in accordance with any of Examples 1-14.

For example, the pharmaceutical use of the compositions of the invention may be provided in a sustained release formulation for prolonged and/or nighttime treatment of the symptoms of overindulgence. Medical and pharmaceutical uses of the present invention can be accomplished by any clinical, medical and pharmaceuticel methods and techniques as are presently or prospectively known to those skilled in the art.

Claims

1. Use of a composition comprising:
an analgesic effective amount of acetaminophen or a non-steroidal anti-inflammatory drug; and
a gastric acid inhibiting effective amount of an H_1 or H_2 receptor blocker, a proton pump inhibitor or a combination thereof for the preparation of a medicament for use in the treatment of the effects of over-indulgence.

2. Use of a composition according to claim 1 wherein the non-steroidal anti-inflammatory drug is a propionic acid derivative, a fenamic acid derivative, an oxicam, an indole acetic acid or a pharmaceutically acceptable salt thereof.

3. Use of a composition according to claim 1 or claim 2 wherein the acetaminophen or non-steroidal anti-inflammatory drug, selected from ibuprofen, fenoprofen, naproxen, ketoprofen, meclofenamate, mefenamic acid, piroxicam, indomethacin, sulindac, tolmetin, or a pharmaceutically acceptable salt thereof, is combined with:
one of the H_2 receptor blocking drugs cimetidine, ranitidine and famotidine;
the proton pump inhibitor drug omeprazole; or
one of the H_1 receptor blocking drugs diphenhydramine, dimenhydrinate, carbinoxamine, tripelennamine, pyrilamine, chlorpheniramine, hydroxyzine, cyclizine, meclizine, promethazine;
or a pharmaceutically acceptable salt thereof.

4. Use of a composition according to any one of claims 1 to 3 wherein the medicament contains:
acetaminophen from 500 to 1000 mg per dose, ibuprofen from 200 to 400 mg per dose, naproxen from 200 to 500 mg per dose, fenoprofen from 200 to 600 mg per dose, ketoprofen from 50 to 300 mg per dose, meclofenamate from 50 to 400 mg per dose, mefenamic acid from 250 to 500 mg per dose, piroxicam from 10 to 20 mg per dose, indomethacin from 25 to 200 mg per dose, sulindac from 150 to 400 mg per dose, tolmetin from 200 to 1200 mg per dose or a pharmaceutically acceptable salt thereof;
in combination with:
cimetidine from 150 to 800 mg per dose, ranitidine from 50 to 300 mg per dose, famotidine from 5 to 40 mg per dose, omeprazole from 100 to 500 mg per dose, diphenhydramine from 25 to 200 mg per dose, dimenhydrinate from 50 to 400 mg per dose, carbinoxamine from 4 to 8 mg per dose, tripelennamine from 25 to 300 mg per dose, pyrilamine from 25 to 100 mg per dose, chlorpheniramine from 2 to 24 mg per dose, hydroxyzine from 25 to 100 mg per dose, cyclizine from 50 to 300 mg per dose, meclizine from 8 to 400 mg per dose, promethazine from 12.5 to 50 mg per dose, a pharmaceutically acceptable salt thereof or a combination thereof.

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5. Use of a composition according to any one of claims 1 to 4 wherein the composition comprises fenoprofen, ketoprofen, meclofenamate, mefenamic acid, piroxicam, indomethacin, sulindac, tolmetin or a pharmaceutically acceptable salt thereof, and
   (a) cimetidine, ranitidine or famotidine; or
   (b) diphenhydramine, dimenhydrinate, carbinoxamine, tripelennamine, pyrilamine, chlorpheniramine, hydroxyzine, cyclizine, meclizine or promethazine; or
   (c) a combination of a drug from group (a) and a drug from group (b).

6. Use of a composition according to any one of claims 1 to 5 wherein the composition comprises:
   a combination of acetaminophen and cimetidine;
   a combination of ibuprofen and cimetidine; or
   a combination of naproxen and diphenhydramine.

7. Use of a composition according to any one of claims 1 to 6, wherein the medicament is in oral tablet, caplet, chewable or liquid dosage form.

Patentansprüche

1. Verwendung einer Zusammensetzung, umfassend:
   eine analgetisch wirksame Menge Acetaminophen oder eines nichtsteroiden, entzündurigshemmenden Arzneistoffes; und
   eine Magensäure inhibierende wirksame Menge eines H_1- oder H_2-Rezeptorblockers, eines Protonenpumpen-Inhibitors oder einer Kombination derselben zur Herstellung eines Medikaments zur Verwendung bei der Behandlung der Effekte von übermäßigem Genuß.

2. Verwendung einer Zusammensetzung nach Anspruch 1, wobei der nichtsteroide, entzündungsbemmende Arzneistoff ein Propionsäurederivat, ein Fenaminsäurederivat, ein Oxicam, eine Indoleessigsäure oder ein pharmazeutisch verträgliches Salz davon ist.

3. Verwendung einer Zusammensetzung nach Anspruch 1 oder nach Anspruch 2, wobei das Acetaminophen oder der nichtsteroide, entzündungshemmende Arzneistoff, ausgewählt aus Ibuprofen, Fenoprofen, Naproxen, Ketoprofen, Meclofenamat, Mefenaminsäure, Piroxicam, Indomethacin, Sulindac, Tolmetin, oder ein pharmazeutisch verträgliches Salz davon, kombiniert ist mit:
   einem der den H_2-Rezeptor blockierenden Arzneistoffe Cimetidin, Ranitidin und Famotidin;
   dem Protonenpumpen-Inhibitor-Arzneistoff Omeprazol; oder
   einem der den H_1-Rezeptor blockierenden Arzneistoffe Diphenhydramin, Dimenhydrinat, Carbinoxamin, Tripelennamin, Pyrilamin, Chlorpheniramin, Hydroxyzin, Cyclizin, Meclizin, Promethazin;
   oder einem pharmazeutisch verträglichen Salz davon.

4. Verwendung einer Zusammensetzung nach einem der Ansprüche 1 bis 3, wobei das Medikament enthält:
   Acetaminophen von 500 bis 1000 mg pro Dosis, Ibuprofen von 200 bis 400 mg pro Dosis, Naproxen von 200 bis 500 mg pro Dosis, Fenoprofen von 200 bis 600 mg pro Dosis, Ketoprofen von 50 bis 300 mg pro Dosis, Meclofenamat von 50 bis 400 mg pro Dosis, Mefenaminsäure von 250 bis 500 mg pro Dosis, Piroxicam von 10 bis 20 mg pro Dosis, Indomethacin von 25 bis 200 mg pro Dosis, Sulindac von 150 bis 400 mg pro Dosis, Tolmetin von 200 bis 1200 mg pro Dosis oder einem pharmazeutisch verträglichen Salz davon;
   in Kombination mit:
   Cimetidin von 150 bis 800 Mg pro Dosis, Ranitidin von 50 bis 300 mg pro Dosis, Famotidin von 5 bis 40 mg pro Dosis, Omeprazol von 100 bis 500 mg pro Dosis, Diphenhydramin von 25 bis 200 mg pro Dosis, Dimenhydrinat von 50 bis 400 mg pro Dosis, Carbinoxamin von 4 bis 8 mg pro Dosis, Tripelennamin von 25 bis 300 mg pro Dosis, Pyrilamin von 25 bis 100 mg pro Dosis, Chlorpheniramin von 2 bis 24 mg pro Dosis, Hydroxyzin von 25 bis 100 mg pro Dosis, Cyclizin von 50 bis 300 mg pro Dosis, Meclizin von 8 bis 100 mg pro Dosis, Promethazin von 12,5 bis 50 mg pro Dosis, einem pharmazeutisch verträglichen Salz davon oder einer Kombination davon.

5. Verwendung einer Zusammensetzung nach einem der Ansprüche 1 bis 4, wobei die Zusammensetzung Fenoprofen, Ketoprofen, Meclofenamat, Mefenaminsäure, Piroxicam, Indomethacin, Sulindac, Tolmetin oder ein pharmazeutisch verträgliches Salz davon und
   (a) Cimetidin, Ranitidin oder Famitidin; oder
   (b) Diphenhydramin, Dimenhydrinat, Carbinoxamin, Tripelennamin, Pyrilamin, Chlorpheniramin, Hydroxyzin, Cyclizin, Meclizin oder Promethazin; oder
   (c) eine Kombination der Arzneistoffe von Gruppe (a) und einen Arzneistoff von Gruppe (b) umfaßt.

6. Verwendung einer Zusammensetzung nach ei-

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nem der Ansprüche 1 bis 5, wobei die Zusammensetzung umfaßt:

eine Kombination von Acetaminophen und Cimetidin;

eine Kombination von Ibuprofen und Cimetidin; oder

eine Kombination von Naproxen und Diphenhydramin.

7. Verwendung einer Zusammensetzung nach einem der Ansprüche 1 bis 6, wobei das Arzneimittel in einer Dosierungsform als orale Tablette, Kaplette, zum Kauen oder flüssig vorliegt.

Revendications

1. Utilisation d'une composition comprenant :
   - une quantité efficace d'un analgésique et d'acétaminophène ou d'un médicament anti-inflammatoire non-stéroïdal ;
   - une quantité efficace inhibant l'acide gastrique d'un agent bloquant de récepteur H_1 ou H_2, un inhibiteur de pompe de protons ou une combinaison de ceux-ci pour la préparation d'un médicament pour utilisation dans le traitement des effets de l'intempérance.

2. Utilisation d'une composition selon la revendication 1, dans laquelle le médicament anti-inflammatoire non-stéroïdal est un dérivé d'acide propionique, un dérivé d'acide fénamique, un oxicame, un acide acétique indole ou un sel pharmaceutiquement acceptable de ceux-ci.

3. Utilisation d'une composition selon la revendication 1 ou 2, dans laquelle l'acétaminophène ou le médicament anti-inflammatoire non-stéroïdal, choisi parmi l'ibuprofène, le fenoprofène, le naproxène, le kétoprofène, le méclofénamate, l'acide méfénamique, le piroxicame, l'indométhacine, le sulindac, le tolmétine, ou un sel pharmaceutiquement acceptable de ceux-ci, est combiné avec :
   - un des médicaments bloquant les récepteurs H_2 cimétidine, ranitidine et famotidine ;
   - le médicament inhibiteur de pompe de protons oméprazole ; ou
   - un des médicaments bloquant les récepteurs H1 diphenhydramine, dimenhydrinate, carbinoxamine, tripélennamine, pyrilamine, chlorphéniramine, hydroxyzine, cyclizine, méclizine, prométhazine ;

   ou un sel pharmaceutiquement acceptable de ceux-ci.

4. Utilisation d'une composition selon l'une quelconque des revendications 1 à 3, dans laquelle le médicament contient :

de l'acétaminophène de 500 à 1000 mg per dose, de l'ibuprofène de 200 à 400 mg par dose, du naproxène de 200 à 500 mg par dose, du fénoprofène de 200 à 600 mg par dose, du kétoprofène de 50 à 300 mg par dose, du méclofénamate de 50 à 400 mg par dose, de l'acide méfénamique de 250 à 500 mg par dose, du piroxicame de 10 à 20 mg par dose, de l'indométhacine de 25 à 200 mg par dose, du sulindac de 150 à 400 mg par dose, du tolmétine de 200 à 1200 mg par dose ou un sel pharmaceutiquement acceptable de ceux-ci ;

en combinaison avec :

de la cimétidine de 150 à 800 mg par dose, de la ranitidine de 50 à 300 mg par dose, de la famotidine de 5 à 40 mg par dose, de l'oméprazole de 100 à 500 mg par dose, de la diphénhydramine de 25 à 200 mg par dose, de la dimenhydrinate de 50 à 400 mg par dose, du carbinoxamine de 4 à 8 mg par dose, du tripélennamine de 25 à 300 mg par dose, du pyrilamine de 25 à 100 mg par dose, du chlorphéniramine de 2 à 24 mg par dose, de l'hydroxyzine de 25 à 100 mg par dose, du cyclizine de 50 à 300 mg par dose, du méclizine de 8 à 400 mg par dose, du prométhazine de 12,5 à 50 mg par dose, un sel pharmaceutiquement acceptable de ceux-ci ou une combinaison de ceux-ci.

5. Utilisation d'une composition selon l'une quelconque des revendications 1 à 4, dans laquelle la composition comprend du fénoprofène, kétoprofène, méclofénamate, acide méfénamique, piroxicame, indométhacine, sulindac, tolmétine ou un sel pharmaceutiquement acceptable de ceux-ci, et
   (a) de la cimétidine, ranitidine ou famotidine ; ou
   (b) de la diphénhydramine, diménhydrinate, carbinoxamine, tripélennamine, pyrilamine, chlorphéniramine, hydroxyzine, cyclizine, méclizine ou prométhazine ; ou
   (c) une combinaison d'un médicament du groupe (a) et d'un médicament du groupe (b).

6. Utilisation d'une composition selon l'une quelconque des revendications 1 à 5, dans laquelle la composition comprend :

une combinaison d'acétaminophène et de cimétidine ;

une combinaison d'ibuprofène et de cimétidine ; ou

une combinaison de naproxène et de diphénhydramine.

7. Utilisation d'une composition selon l'une quelconque des revendications 1 à 6, dans laquelle le médicament est sous forme de dosage liquide ou à croquer, en comprimé oral .

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(54) **Medicaments for treating inflammatory conditions or for analgesia containing a NSAID and ranitidine bismuth citrate**

Zusammensetzungen zur Behandlung von entzündlichen Zuständen oder Analgesie, die Ranitidin Wismuth Citrat und einen NSAID enthalten

Médicaments pour le traitement de conditions inflammatoires ou pour l'analgésie contenants un NSAID et du citrate de bismuth-ranitidine

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EP-A- 0 426 479
GB-A- 2 105 193
GB-A- 2 220 937

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Description

[0001] The present invention relates to improvements in the treatment of inflammatory conditions and for analgesia. More particularly it relates to the co-administration of a non-steroidal anti-inflammatory drug with a salt formed between ranitidine and a complex of bismuth with a carboxylic acid.

[0002] Systemic non-steroidal anti-inflammatory drugs, such as aspirin, indomethacin, ibuprofen and piroxicam, are known to give rise to undesirable side effects. In particular, they are known to be ulcerogenic and can thus, for example, give rise to gastric and/or duodenal ulceration when administered orally. This side effect may be further enhanced in combination with other factors such as stress and smoking. Since in some treatments these compounds may have to be used for an extended period, such side effects can prove a serious disadvantage.

[0003] GB-A-2105193 relates to a pharmaceutical composition comprising a systemic non-steroidal anti-inflammatory drug together with the histamine H_2-antagonist ranitidine or physiologically acceptable salts thereof. The histamine H_2-antagonist reduces gastric mucosal lesions caused by the anti-inflammatory drug.

[0004] In our UK Patent Specification No. 2220937B we describe and claim salts formed between ranitidine and a complex of bismuth with a carboxylic acid, particularly tartaric acid and, more especially, citric acid. One such salt is N-[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine 2-hydroxy-1,2,3-propanetricarboxylate bismuth (3^+) complex, also known as ranitidine bismuth citrate.

[0005] The salts disclosed in UK Patent Specification No. 222937B possess the H_2-antagonist antisecretory properties associated with ranitidine, together with antibacterial activity against Helicobacter pylori (formerly Campylobacter pylori). In addition, such salts possess cytoprotective properties, and display activity against the human gastric pepsins with preferential inhibition of pepsin 1, a pepsin enzyme associated with peptic ulcer. The salts disclosed in UK Patent Specification No. 2220937B thus possess a particularly advantageous combination of properties for the treatment of gastrointestinal disorders, especially peptic ulcer disease (e.g. gastric and duodenal ulceration) and other gastroduodenal conditions, for example gastritis and non-ulcer dyspepsia.

[0006] Tests in animals and humans have now shown that mucosal lesions of the gastrointestinal tract caused by non-steroidal anti-inflammatory drugs are significantly reduced by administering ranitidine bismuth citrate. In particular, we have demonstrated in rats the ability of ranitidine bismuth citrate to prevent indomethacin induced gastric antral ulceration using a modification of the method of Satoh et al., Gastroenterology (1981), 81, 719-725. In this test ranitidine bismuth citrate was markedly more potent than both ranitidine hydrochloride and tripotassium dicitrato bismuthate as DeNol™. A recently published human clinical study (N. Hudson et al., Gut 1992, 33 supplement, s47) also demonstrates that ranitidine bismuth citrate confers substantial protection from aspirin-induced injury to the gastric mucosa.

[0007] The present invention thus provides, in one aspect, the use of (i) ranitidine bismuth citrate and (ii) a non-steroidal anti-inflammatory drug in the manufacture of medicaments for simultaneous, separate or sequential use in treating or preventing inflammatory conditions or for analgesia.

[0008] In a further, or alternative, aspect the present invention provides the use of ranitidine bismuth citrate in the manufacture of medicaments to prevent gastrointestinal damage caused by non-steroidal anti-inflammatory drugs.

[0009] Combination therapy according to the present invention may be used in the treatment of inflammatory conditions, particularly acute and chronic musculo-skeletal inflammatory conditions such as rheumatoid and osteo-arthritis and ankylosing spondylitis and for analgesia in conditions such as dysmenorrhoea, especially where the use of the anti-inflammatory drug is limited by gastrointestinal side effects. As stated above, co-administration of ranitidine bismuth citrate with a systematic non-steroidal anti-inflammatory drug may also be used to prevent gastrointestinal damage caused by non-steroidal anti-inflammatory drugs. Such gastrointestinal damage includes duodenal and/or gastric ulceration, non-steroidal anti-inflammatory drug associated gastritis and gastric erosions, and non-steroidal anti-inflammatory drug associated mucosal damage to the small intestine.

[0010] Suitable systemic non-steroidal anti-inflammatory drugs which may be employed in the invention generally also show analgesic activity and include, for example, aspirin, indomethacin, ibuprofen, piroxicam, fenoprofen, ketoprofen, naproxen, mefenamic acid, diflunisal, benorylate, azapropazone, diclofenac, fenbufen, feprazone, fenclofenac, flufenamic acid, flurbiprofen, oxyphenbutazone, phenylbutazone, sulindac and tolmetin.

[0011] The ranitidine bismuth citrate and the anti-inflammatory drug are preferably co-administered in the form of separate pharmaceutical compositions for simultaneous and/or sequential use. Alternatively the ranitidine bismuth citrate and the anti-inflammatory drug may be administered as a single pharmaceutical composition for oral use comprising effective amounts of the active ingredients.

[0012] Thus, according to a further aspect, the invention provides a product containing (i) ranitidine bismuth citrate and (ii) a non-steroidal antiinflammatory drug as a combined preparation for simultaneous, separate or sequential use in treating or preventing inflammatory conditions or for analgesia.

[0013] When the ranitidine bismuth citrate and the non-steroidal anti-inflammatory are administered as separate preparations, the anti-inflammatory may be provided in any convenient formulation, such as in the manner known in the art and/or commercially for the compound concerned. Administration of both the ranitidine bismuth citrate and the non-

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steroidal anti-inflammatory by the oral route is preferred, although the anti-inflammatory, where appropriate, may also be given by another route, for example parenterally (e.g. intravenously) or rectally (e.g. by suppository).

[0014] The ranitidine bismuth citrate may conveniently be formulated as tablets (including chewable tablets), capsules (of either the hard or soft type), or as a liquid preparation, as described for example in UK Patent Specification Nos. 2220937B and 2248185A. Tablets are generally preferred.

[0015] As stated hereinabove, ranitidine bismuth citrate and the non-steroidal anti-inflammatory drug may be administered as a single pharmaceutical composition for oral use. Thus, according to a further aspect the invention provides a pharmaceutical composition, for oral use in human or veterinary medicine, comprising ranitidine bismuth citrate and a non-steroidal anti-inflammatory drug, together, where appropriate, with a pharmaceutically acceptable carrier or excipient.

[0016] Suitable additional carriers or excipients include binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). An alkaline salt of the type described in UK Patent Specification No. 2248185A may be added to improve the rate of disintegration and/or dissolution of the composition.

[0017] The compositions may be prepared according to conventional techniques well known in the pharmaceutical industry. Thus, for example, the ranitidine bismuth citrate and the non-steroidal anti-inflammatory drug may be admixed together, if desired, with suitable carriers or excipients. Tablets may be prepared, for example, by direct compression or wet granulation of such a mixture. Capsules may be prepared by filling the blend along with suitable carriers or excipients into gelatin capsules, using a suitable filling machine. Tablets may be coated by methods well known in the art. The preparations may also contain flavouring, colouring and/or sweetening agents as appropriate.

[0018] When ranitidine bismuth citrate and the non-steroidal anti-inflammatory drug are administered as a single pharmaceutical composition for oral use the composition is preferably in the form of a capsule or, more particularly, a tablet.

[0019] The compositions for use according to the invention may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredients. The pack may for example comprise metal or plastic foil, such as a blister pack. Where the ranitidine bismuth citrate and the non-steroidal anti-inflammatory drug are intended for administration as separate compositions these may be presented in the form of, for example, a twin pack.

[0020] Thus, according to a further aspect the present invention provides a twin-container pack for use in treating or preventing inflammatory conditions or for analgesia, one of the containers containing ranitidine bismuth citrate and the other containing a non-steroidal anti-inflammatory drug.

[0021] The doses at which the ranitidine bismuth citrate and the non-steroidal anti-inflammatory may be administered to man (of approximately 70kg body weight) will depend on the route of administration of the anti-inflammatory and on the nature and severity of the condition being treated. It will also be appreciated that it may be necessary to make routine variations to the dosage depending on the age and weight of the patient.

[0022] A proposed dosage of ranitidine bismuth citrate for use according to the invention is 150mg to 1.5g, preferably 200 - 800mg per unit dose. The unit dose may be administered, for example, 1 to 4 times per day, preferably once or twice per day.

[0023] The non-steroidal anti-inflammatory may conveniently be administered at doses within the normal dosage range at which the compound is therapeutically effective, -for example 50mg-1g of aspirin, 10 -100 mg of indomethacin, 5 - 50 mg of piroxicam, 100-500mg of ibuprofen and 200-800mg of mefenamic acid per dosage unit taken one or more times daily in accordance with the normal dosage regime for the drug in question.

[0024] In a further aspect, the present invention provides a method of treating inflammatory conditions or for analgesia in a human or animal subject, which comprises administering to said subject effective amounts of ranitidine bismuth citrate and a non-steroidal anti-inflammatory drug.

[0025] In another, or alternative, aspect the present invention provides a method of treating gastrointestinal damage caused by non-steroidal anti-inflammatory drugs in a human or animal subject, which comprises administering to said subject an effective amount of ranitidine bismuth citrate.

[0026] References herein to treatment include prophylactic treatment as well as the alleviation of acute symptoms.

[0027] The methods of the present invention comprise administering the non-steroidal anti-inflammatory drug and ranitidine bismuth citrate either concurrently or non-concurrently. As used herein, concurrent administration means that the agents are given within 24 hours of each other, whereas non-concurrent administration means that the agents are given more than 24 hours apart. When the agents are administered concurrently, it may be preferable to administer the agents within about 1 hour of each other or, more preferably, within about 5 minutes of each other.

[0028] For the methods of the present invention, the duration of administration of the agents during either concurrent or non-concurrent dosing will vary according to the specific condition being treated.

[0029] The following examples illustrate pharmaceutical compositions for oral use containing both ranitidine bismuth

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citrate and a suitable non-steroidal anti-inflammatory drug.

Example 1

TABLETS

[0030]

		mg/tablet
(a)	Ranitidine bismuth citrate	400.00
	Ibuprofen	400.00
	Lactose	200.00
	Hydroxypropyl methylcellulose	5.00
	Sodium starch glycollate	30.00
	Magnesium stearate	10.00
	Compression weight	1045.00

[0031] The ranitidine bismuth citrate and ibuprofen are sieved through a 250 μm sieve and blended with the lactose. This mix is granulated with a solution of the hydroxypropyl methylcellulose. The granules are dried, screened and blended with the sodium starch glycollate and the magnesium stearate. The lubricated granules are compressed into tablets using 15.0mm punches.

		mg/tablet
(b)	Ranitidine bismuth citrate	400.00
	Indomethacin	50.00
	Microcrystalline cellulose	114.00
	Anhydrous sodium carbonate	30.00
	Magnesium stearate	6.00
	Compression weight	600.00

[0032] The ranitidine bismuth citrate and indomethacin are blended with the microcrystalline cellulose, sodium carbonate and magnesium stearate and compressed using 12.5mm punches.

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Example 2

CAPSULES

[0033]

		Capsule
(a)	Ranitidine bismuth citrate	200.00
	Ibuprofen	400.00
	Starch 1500**	196.00
	Magnesium stearate	4.00
	Fill weight	800.00

** A form of directly compressible starch supplied by Colorcon Ltd, Orpington, Kent.

[0034] The ranitidine bismuth citrate and ibuprofen are sieved through a 250 μm sieve and blended with the Starch 1500 and magnesium stearate. The resultant mix is filled into size 0 hard gelatin capsules using a suitable filling machine.

		mg/capsule
(b)	Ranitidine bismuth citrate	200.00
	Indomethacin	50.00
	Starch 1500	48.50
	Magnesium stearate	1.50
	Fill weight	300.00

[0035] The ranitidine bismuth citrate and indomethacin are sieved through a 250 μm sieve and blended with the Starch 1500 and magnesium stearate. The resultant mix is filled into size 2 hard gelatin capsules using a suitable filling machine.

Example 3

INHIBITION OF INDOMETHACIN-INDUCED GASTRIC LESIONS IN THE RAT

[0036] The ability of ranitidine bismuth citrate to prevent indomethacin-induced gastric antral ulceration was compared with that of ranitidine hydrochloride and De-Nol™.

[0037] Female rats, which had been fasted for 24 hours and then re-fed, received ranitidine bismuth citrate (1 to 100mg/kg), ranitidine hydrochloride (10 to 100mg/kg) or De-Nol™ (3 to 100mg/kg) by oral gavage. Ranitidine bismuth citrate was administered as a suspension and the other test compounds as solutions. Thirty minutes after dosing with the test compound, animals received indomethacin (60mg/kg sc) as an ulcerogenic stimulus and after a further 6 hours the animals were killed and the antral region assessed macroscopically for damage.

[0038] Results are presented in the table below. Ranitidine bismuth citrate produced a dose-related inhibition of indomethacin-induced lesions and was relatively potent, an ED_{50} value of 4.5mg/kg po being calculated. Ranitidine hydrochloride and De-Nol™ were markedly less potent.

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ED_{50} Values for Inhibition of Indomethacin - Induced Antral Ulceration			
Compound	Ranitidine Bismuth Citrate	Ranitidine Hydrochloride	De-Nol™
ED_{50} mg/kg p.o.	4.5	23.4	43.2
95% confidence limits	0.5 - 10.7	16.0 - 33.0	23.6 - 93.0

Claims

1. The use of (i) ranitidine bismuth citrate and (ii) a non-steroidal anti-inflammatory drug in the manufacture of medicaments for simultaneous, separate or sequential use in treating or preventing inflammatory conditions or for analgesia.

2. The use of ranitidine bismuth citrate in the manufacture of medicaments to prevent gastrointestinal damage caused by non-steroidal anti-inflammatory drugs.

3. The use according to Claim 1 in which the compounds (I) and (ii) are presented as separate compositions for said use.

4. A use according to any one of Claims 1 to 3 wherein the non-steroidal anti-inflammatory drug is selected from aspirin, indomethacin, ibuprofen, piroxicam, fenoprofen, ketoprofen, naproxen, mefenamic acid, diflunisal, benorylate, azapropazone, diclofenac, fenbufen, feprazone, fenclofenac, flufenamic acid, flurbiprofen, oxyphenbutazone, phenylbutazone, sulindac and tolmetin.

5. A use according to any preceding claim in which compounds (i) and (ii) are in forms suitable for oral administration.

6. A use according to any preceding claim in which compound (i) is formulated as a tablet.

7. A use according to claim 6 in which compound (i) is suitable for administration at a dosage of 200 - 800mg per unit dose.

8. A product containing compounds (i) and (ii) as defined in Claim 1 as a combined preparation for simultaneous, separate or sequential use in treating or preventing inflammatory conditions or for analgesia.

9. A pharmaceutical composition, for oral use, which comprises both a compound (i) and a compound (ii) as defined in Claim 1, optionally together with suitable pharmaceutical carriers or excipients.

10. A product as claimed in Claim 8 or a composition as claimed in Claim 9 in which the non-steroidal anti-inflammatory drug is as defined in Claim 4.

11. A product as claimed in Claim 8 or Claim 10 in which compounds (i) and (ii) are formulated as defined in any one of Claims 5 to 7.

12. A composition according to Claim 9 or Claim 10, in association with instructions for the use of both compound (i) and compound (ii) in treating or preventing inflammatory conditions or for analgesia.

13. A twin-container pack for use in treating or preventing inflammatory conditions or for analgesia, one of the containers containing compound (i) and the other containng compound (ii) as defined in any one of claims 1, 4, 5, 6 or 7.

14. A pack according to Claim 13, in association with instructions for the use of both compound (i) and compound (ii) in treating or preventing inflammatory conditions or for analgesia.

15. A method for the preparation of a composition according to Claim 9 or Claim 10 which comprises admixing compounds (i) and (ii) optionally together with suitable pharmaceutical carriers or excipients.

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Patentansprüche

1. Verwendung von (i) Ranitidin-Bismutcitrat und (ii) einem nicht-steroidalen entzündungshemmenden Arzneistoff zur Herstellung von Medikamenten zur gleichzeitigen, separaten oder aufeinanderfolgenden Verwendung bei der Behandlung oder Vorbeugung entzündlicher Zustände oder zur Analgesie.

2. Verwendung von Ranitidin-Bismutcitrat zur Herstellung von Medikamenten zur Vorbeugung gastrointestinaler Schädigung, verursacht durch nicht-steroidale entzündungshemmende Arzneistoffe.

3. Verwendung gemäß Arispruch 1, worin die Verbindungen (i) und (ii) als separate Zusammensetzungen für die Verwendung angeboten werden.

4. Verwendung gemäß einem der Ansprüche 1 bis 3, worin der nicht-steroidale entzündungshemmende Arzneistoff ausgewählt ist aus Aspirin, Indomethacin, Ibuprofen, Piroxicam, Fenopro£en, Ketoprofen, Naproxen, Mefenaminsäure, Diflunisal, Benorylat, Azapropazon, Diclofenac, Fenbufen, Feprazon, Fenclofenac, Flufenaminsäure, Flurbiprofen, Oxyphenbutazon, Phenylbutazon, Sulindac und Tolmetin.

5. Verwendung gemäß einem der vorhergehenden Ansprüche, worin die Verbindungen (i) und (ii) in zur oralen Verabreichung geeigneten Formen sind.

6. Verwendung gemäß einem der vorhergehenden Ansprüche, worin die Verbindung (i) als Tablette formuliert ist.

7. Verwendung gemäß Anspruch 6, worin die Verbindung (i) zur Verabreichung mit einer Dosierung von 200 bis 800 mg je Einheitsdosis geeignet ist.

8. Produkt, enthaltend die Verbindungen (i) und (ii), wie in Anspruch 1 definiert, als eine kombinierte Zubereitung zur gleichzeitigen, separaten oder aufeinanderfolgenden Verwendung zur Behandlung oder Vorbeugung entzündlicher Zustände oder zur Analgesie.

9. Pharmazeutische Zusammensetzung zur oralen Verwendung, die sowohl eine Verbindung (i) als auch eine Verbindung (ii) umfaßt, wie in Anspruch 1 definiert, gegebenenfalls zusammen mit geeigneten pharmazeutischen Trägern oder Arzneimittelzusatzstoffen.

10. Produkt gemäß Anspruch 8 oder Zusammensetzung gemäß Anspruch 9, worin der nicht-steroidale entzündungshemmende Arzneistoff wie in Anspruch 4 definiert ist.

11. Produkt gemäß Anspruch 8 oder Anspruch 10, worin die Verbindungen (i) und (ii) wie in einem der Ansprüche 5 bis 7 definiert formuliert sind.

12. Zusammensetzung gemäß Anspruch 9 oder 10 in Verbindung mit Anweisungen zur Verwendung sowohl der Verbindung (i) als auch der Verbindung (ii) zur Behandlung oder Vorbeugung entzündlicher Zustände oder zur Analgesie.

13. Paar-Behälterpackung zur Verwendung zur Behandlung oder Vorbeugung entzündlicher Zustände oder zur Analgesie, wobei einer der Behälter die Verbindung (i) enthält und der andere Behälter die Verbindung (ii) enthält, wie in einem der Ansprüche 1, 4, 5, 6 oder 7 definiert.

14. Packung gemäß Anspruch 13 in Verbindung mit Anweisungen zur Verwendung sowohl der Verbindung (i) als auch der Verbindung (ii) zur Behandlung oder Vorbeugung entzündlicher Zustände oder zur Analgesie.

15. Verfahren zur Herstellung einer Zusammensetzung gemäß Anspruch 9 oder 10, welches das Vermischen der Verbindungen (i) und (ii) umfaßt, gegebenenfalls zusammen mit geeigneten pharmazeutischen Trägern oder Arzneimittelzusatzstoffen.

Revendications

1. Utilisation de (i) citrate de ranitidine bismuth et (ii) d'un médicament anti-inflammatoire non stéroïde dans la fabrication de médicaments pour une utilisation simultanée, séparée ou séquentielle dans le traitement ou la prévention

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des états inflammatoires ou pour l'analgésie.

2. Utilisation de citrate de ranitidine bismuth dans la fabrication de médicaments pour empêcher les altérations gastrointestinales provoquées par les médicaments anti-inflammatoires non stéroïdes.

3. Utilisation suivant la revendication 1, dans laquelle les composés (i) et (ii) sont présentés sous la forme de compositions séparées pour ladite utilisation.

4. Utilisation suivant l'une quelconque des revendications 1 à 3, dans laquelle le médicament anti-inflammatoire non stéroïde est choisi parmi l'aspirine, l'indométhacine, l'ibuprofen, le piroxicam, le fénoprofen, le cétroprofen, le naproxène, l'acide méfénamique, le diflunisal, le benorylate, l'azapropazone, le diclofénac, le fenbufen, la féprazone, le fenclofénac, l'acide flufénamique, le flurbiprofen, l'oxyphenbutazone, la phénylbutazone, le sulindac et la tolmétine.

5. Utilisation suivant l'une quelconque des revendications précédentes, dans laquelle les composés (i) et (ii) sont sous des formes destinées à l'administration orale.

6. Utilisation suivant l'une quelconque des revendications précédentes, dans laquelle le composé (i) est formulé sous la forme d'un comprimé.

7. Utilisation suivant la revendication 6, dans laquelle le composé (i) est destiné à l'administration à un dosage de 200-800 mg par dose unitaire.

8. Produit contenant des composés (i) et (ii) tels que définis à la revendication 1 sous la forme d'une préparation combinée pour une utilisation simultanée, séparée ou séquentielle dans le traitement ou la prévention des états inflammatoires ou pour l'analgésie.

9. Composition pharmaceutique, pour l'utilisation orale, qui comprend à la fois un composé (i) et un composé (ii) tels que définis à la revendication 1, éventuellement en même temps qu'avec des supports ou excipients pharmaceutiques appropriés.

10. Produit suivant la revendication 8 ou composition suivant la revendication 9, dans lequel le médicament anti-inflammatoire non stéroïde est tel que défini à la revendication 4.

11. Produit suivant l'une ou l'autre des revendications 8 et 10, dans lequel les composés (i) et (ii) sont formulés tels que définis dans l'une quelconque des revendications 5 à 7.

12. Composition suivant l'une ou l'autre des revendications 9 et 10, en association à des instructions pour l'utilisation à la fois de composé (i) et de composé (ii) dans le traitement ou la prévention des états inflammatoires ou pour l'analgésie.

13. Emballage à deux récipients utilisable dans le traitement ou la prévention des états inflammatoires ou pour l'analgésie, l'un des récipients contenant le composé (i) et l'autre contenant le composé (ii) tels que définis dans l'une quelconque des revendications 1, 4, 5, 6 et 7.

14. Emballage suivant la revendication 13, en association à des instructions pour l'utilisation à la fois de composé (i) et de composé (ii) dans le traitement ou la prévention des états inflammatoires ou pour l'analgésie.

15. Procédé de préparation d'une composition suivant l'une ou l'autre des revendications 9 et 10, qui comprend le mélange des composés (i) et (ii) éventuellement en même temps qu'avec des supports ou excipients pharmaceutiques appropriés.

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Die folgenden Angaben sind den vom Anmelder eingereichten Unterlagen entnommen

Prüfungsantrag gem. § 44 PatG ist gestellt

(54) Pharmazeutische Zubereitung zur oralen Verabreichung

(57) Die Erfindung betrifft eine pharmazeutische Zubereitung zur oralen Verarbeitung, enthaltend als Wirkstoff wenigstens einen Protonenpumpeninhibitor und gegebenenfalls pharmazeutisch akzeptable Trägerstoffe, sowie übliche Zusatz- und Hilfssubstanzen, wobei die Zubereitung eine gefüllte, nahtlose Kapsel ist, enthaltend ein Kapselfüllmaterial umfassend den mindestens einen Wirkstoff, der in einem Lösungs- und/oder Suspendiermittel gelöst bzw. suspendiert ist, und mindestens eine Schicht bzw. einen Film zum Beschichten des Kapselfüllmaterials.

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Beschreibung

Die vorliegende Erfindung betrifft eine neue pharmazeutische Zubereitung zur oralen Verabreichung. Sie enthält als Wirkstoff wenigstens eine säurelabile heterozyklische Verbindung, wie einen Protonenpumpeninhibitor, wobei Omeprazol besonders bevorzugt ist. Die erfindungsgemäße pharmazeutische Zubereitung ist insbesondere bestimmt zur Behandlung von Störungen oder Krankheiten des Gastrointestinaltrakts. Weiterhin betrifft die vorliegende Erfindung ein Verfahren zur Herstellung dieser neuen pharmazeutischen Zubereitung.

Protonenpumpeninhibitoren werden allgemein zur Hemmung der Magensäuresekretion sowohl bei Säugetieren als auch bei Menschen eingesetzt.

Allgemein werden sie zur Prävention und Behandlung von Störungen oder Krankheiten, die bei der Magensäuresekretion auftreten, verwendet, einschließlich z. B. Ösophagitis, Gastritis, Duodenitis, gastrischem Ulkus und duodenalem Ulkus. Weiterhin können Protonenpumpeninhibitoren zur Behandlung von anderen gastrointestinalen Störungen eingesetzt werden, bei denen erwünscht ist, daß eine Sekretion der Magensäure unterbleibt, z. B. bei Patienten, die sich einer Therapie mit nichtsteroidalen Antiphlogistika (NSAID) unterziehen. Weiterhin sind Protonenpumpeninhibitoren nützlich bei der Behandlung von Heliobakter-Infektion und damit in Zusammenhang stehenden Krankheiten.

Bekannte Protonenpumpeninhibitoren, die unter ihrem INN Namen bekannt sind, sind z. B. Omeprazol, Lansoprazol, Pantoprazol, Pariprazol, Leminoprazol.

Geeignete Protonenpumpeninhibitoren sind z. B. in EP-A1-0005129, EP-A1-174 726, EP-A1-166 287, GB 2 163 747, WO 90/06925, WO91/19711, WO 91/19712 beschrieben.

Die unter dem generischen Namen Omeprazol bekannte Substanz (5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazol ist in EP-A1-0 005 129 beschrieben. Bestimmte Omeprazolsalze einschließlich alkalischer Omeprazolsalze sind in EP-A-0 124 495 und in WO 95/01977 beschrieben. Weiterhin sind Salze von einzelnen Omeprazolenantiomeren in WO 94/27988 beschrieben.

Protonenpumpeninhibitoren und insbesondere Omeprazol sind jedoch unter Feuchtigkeits- und Säureeinfluß extrem instabil. Z.B. liegt die Halbwertszeit des Abbaus von Omeprazol in wässerigen Lösungen, die ph-Werte von weniger als drei aufweisen, bei weniger als zehn Minuten. Der Abbau von Omeprazol wird von Säuren katalysiert, während alkalische Verbindungen zu einer Stabilisierung führen (siehe WO 96/24338). Die Stabilität von Omeprazol wird ebenfalls durch Wärme, organische Lösungsmittel und in gewisser Weise durch Tageslicht beeinflußt.

Aufgrund der vorgenannten Stabilitätsprobleme muß der Protonenpumpeninhibitor und insbesondere Omeprazol in Form von magensaftresistenten Zubereitungen verabreicht werden. Alle bisherigen Ansätze zur oralen Verabreichung von Protonenpumpeninhibitoren lösen dieses Problem über Darreichungsformen, bei denen der Protonenpumpeninhibitor bzw. das Omeprazol mit Feststoffen zu festen Arzneiformen verarbeitet wird. Beispielsweise seien hier US-4,853,230 sowie WO 96/24338 genannt. Ebenso wie in US-4,786,505, EP-0 277 741 und EP-A-0 342 522 werden in der Patentliteratur Zubereitungen beschrieben, die im wesentlichen aus einem festen Kern bestehen, in dem Omeprazol als stabilisiertes Alkalisalz formuliert ist. Dieser Omeprazol-Kern kann von mehreren Schichten geschützt werden.

WO 96/01623 beschreibt Omeprazoltabletten mit verzögerter Wirkstofffreisetzung, bestehend aus einem Omeprazol-Kernmaterial und darüberliegenden Beschichtungsschichten. Diese Hülle kann aus ein oder mehreren Schichten bestehen, wobei insbesondere eine Methacrylsäurecopolymer (L30D-55)-Schicht verwendet wird.

Daher ist es Aufgabe der Erfindung, eine neue pharmazeutische Zubereitungsform zur oralen Verabreichung, enthaltend als Wirkstoff wenigstens einen Protoneninhibitor und insbesondere Omeprazol, bereitzustellen, wobei der Protonenpumpeninhibitor bzw. Omeprazol nicht mehr mit Feststoffen zu festen Arzneimitteln verarbeitet werden muß. Weiterhin soll ein Verfahren zur Herstellung dieser neuen pharmazeutischen Zubereitung angegeben werden.

Diese Aufgabe wird durch die neue pharmazeutische Zubereitung zur oralen Verabreichung gem. Anspruch 1 gelöst. Die erfindungsgemäße Zubereitung besteht aus einer gefüllten nahtlosen Kapsel, die ein Kapselfüllmaterial d. h. einen Inhalt und einen Film zum Beschichten des Inhalts enthält. Der Inhalt des Kapselfüllmaterials besteht aus dem wenigstens einen Wirkstoff, der in einem Lösungs- und/oder Suspendiermittel gelöst bzw. suspendiert ist und ggf. pharmazeutisch akzeptablen Trägerstoffen sowie üblichen Zusatz- und Hilfssubstanzen. Die erfindungsgemäße gefüllte nahtlose Kapsel ist mit mindestens einem Film bzw. einer Schicht beschichtet, so daß die Kapseln die Magenpassage überstehen und erst im Dünndarm den Wirkstoff freisetzen.

Erfindungsgemäß wurde festgestellt, daß Omeprazol erstmals in Form von Lösungen bzw. Suspensionen ebenfalls zu stabilen oralen magensaftresistenten Arzneimitteln verarbeitet werden können.

Die erfindungsgemäße Aufgabe wird weiterhin durch das Verfahren gemäß Anspruch 13 gelöst.

In den Unteransprüchen sind vorteilhafte Ausführungsformen der Erfindung enthalten.

Die Erfindung betrifft daher eine neue pharmazeutische Zubereitungsform zur oralen Verabreichung, enthaltend als Wirkstoff wenigstens einen Protonenpumpeninhibitor und gegebenenfalls pharmazeutische akzeptable Trägerstoffe, sowie übliche Zusatz- und Hilfssubstanzen, wobei die erfindungsgemäße Zubereitung eine gefüllte, nahtlose Kapsel **1** ist, enthaltend ein Kapselfüllamterial **2**, umfassend den mindestens einen Wirkstoff, der in einem Lösungs- und/oder Suspendiermittel gelöst bzw. suspendiert ist, und mindestens eine Schicht bzw. einen Film **3** zum Beschichten des Kapselfüllmaterials **2**.

Weiterhin betrifft die vorliegende Erfindung ein Verfahren zur Herstellung der pharmazeutischen Zubereitung wobei man gleichzeitig eine Beschichtungsschicht oder Filmlösung für die nahtlose(n) Kapsel(n) und die Lösung und/oder Suspension des wenigstens einen Wirkstoffes in eine Kühllösung aus einer konzentrisch angeordneten Mehrfachdüse, die wenigstens aus zwei Düsen besteht, extrudiert, wobei die innere Düse einen kleineren Durchmesser als die äußere Düse aufweist, und wobei insbesondere die Kühlflüssigkeit im Bereich des Strahleintritts in diese in den Strahl umhüllende Schwingungen versetzt wird, und der Strahlstrom unter Anwendung der Grenzflächenspannung kontinuierlich in kleine sphärische nahtlose Kapseltropfen **1** überführt wird. In einer besonderen Ausführungsform des erfindungsgemäßen Verfahrens kann man eine Mehrfachdüse mit wenigstens drei Düsen einsetzen, bestehend aus einer Außendüse und einer Innendüse und wenigstens einer Zwischendüse, die sich in der Mittelstellung zwischen der Außen- und Innendüse befindet.

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Der Durchmesser der drei Düsen steigt graduell in der vorgenannten Reihenfolge an. Gemäß dem erfindungsgemäßen Verfahren wird gleichzeitig eine Filmlösung für die nahtlose Kapsel, die Lösung bzw. die Suspension der Wirksubstanz und eine weitere Filmlösung in eine Kühllösung extrudiert und der Strahlstrom der drei Flüssigkeiten unter Ausnutzung der Grenzflächenspannung kontinuierlich in kleine sphärische nahtlose Kapseltropfen **1** überführt.

Gemäß der Erfindung können die nahtlosen Kapseln **1** eine Größe von 0,3 mm bis 10,0 mm im Durchmesser, insbesondere eine Größe von 0,8 bis 3,0 mm im Durchmesser aufweisen.

Der Protonenpumpeninhibitor im Inneren der Kapsel **1** ist in einer besonderen Ausführungsform durch zwei Schichten **3** und **4** geschützt, einer enterischen Beschichtungsschicht **3** und einer Schicht, die die enterische Besichtungsschicht **4** von den Protonenpumpeninhibitor abtrennt. Erfindungsgemäß kann die vorgenannte Hülle aus einer oder mehreren Schichten bestehen. Die Hüllen sind so gestaltet, daß die Mikrokapseln die Magenpassage überstehen und erst im Dünndarm den Wirkstoff freisetzen. Die so hergestellten Mikrokapseln können in Dosen/Sachets oder Kapseln abgefüllt und/oder unter Zusatz üblicher pharmazeutischer Hilfsstoffe zu Tabletten verpreßt werden.

Als Protonenpumpeninhibitor kommen Stoffe wie Omeprazol, Lansoprazol, Pantoprazol, Pariprazol, Lemiprazol in Betracht, wobei Omeprazol bevorzugt ist. Als Wirkstoff kann gemäß einer besonderen Ausführungsform der Erfindung Omeprazol, ein alkalisches Salz von Omeprazol, ein einzelnes Enantiomer von Omeprazol oder ein alkalisches davon oder ein Magenesiumsalz von S-Omeprazol eingesetzt werden.

Bevor die erfindungsgemäßen nahtlosen Kapseln hergestellt werden, muß Omeprazol in einem geeigneten Lösungs- und/oder Suspendiermittel gelöst bzw. suspendiert werden. Als geeignetes Lösungs- und/oder Suspendiermittel kommen Parafinöl, mittelkettige Triglyceride, Isopropylmyristat, Pflanzenöle, niedrigschmelzende Wachse in Betracht. Diesen Lösungs- bzw. Suspendiermitteln können gegebenenfalls alkalisch reagierende Verbindungen zur Stabilisierung des Omeprazols zugesetzt werden. Derartig alkalisch reagierende Verbindungen sind z. B. Aminosäuren wie Lysin, Arginin, Ornitin, Histidin, puffernde Substanzen wie Trometamin, N-Aminozucker wie N-Methyl-D-glukamin (Meglumin), N-Ethyl-D-glukamin (Eglumin), Glukosamin, Dinatrium-N-stearoylglutamat, heterocyclische Aminderivate wie Piperazin, N-Methyl-piperazin, Morpholin, Alkalisalze von Zitronensäure, Weinsäure etc., oder Alkalisalze von Fettsäuren, oder Alkalimetallphosphate, Alkalisilikate oder Alkalikarbonate etc. Besonders bevorzugte alkalisch reagierende Verbindungen zur Stabilisierung sind Harnstoff, Natriumhydrogencarbonat, Natriumhydorgenphosphat und Natriumacetat.

Die Menge der alkalischen Verbindung sollte etwa 0,1 mmol/g Wirkstoff bis zu 15 mmol/g Wirkstoff betragen.

Die Hülle bzw. die Hüllen der erfindungsgemäßen nahtlosen Kapseln können aus Gelatine, Agar und/oder Kombinationen von Gelatine und/oder Agar mit Pektin und/oder Hydroxypropylmethylcellulose und/oder Chitosan und/oder Polyacrylaten bestehen, wobei Methacrylsäurecopolymere (z. B. L30D-55) bevorzugt sein können. Die Menge an verwendeter Gelatine und/oder Agar oder der vorbeschriebenen Gemische beträgt normalerweise 60 bis 90 Gewichtsprozent des Gesamtgewichtes des Kapselfilms. Geeignetes niederes Methoxypectin mit einem Molekulargewicht von nicht mehr als 200 000 und einem Methoxylierungsgrad von 1–6% liegt vorzugsweise in einer Menge von 5–20 Gew.-%, vorzugsweise in einer Menge von 10–15 Gew.-%, bezogen auf das Gesamtgewicht des Films, vor.

Die Beschichtungsschichten können ebenfalls pharmazeutisch akzeptable Weichmacher wie z. B. Phtalsäureestercetylalkohol, Polyethylenglykole etc. enthalten. Die Menge an Weichmacher beträgt üblicherweise 15-50 Gew.-%, bezogen auf das Gesamtgewicht der Beschichtung. Um die säurelabilen Substanzen zu schützen, beträgt die Schichtdicke der Beschichtung wenigstens 10 µm, vorzugsweise 20 µm.

Das Kapselfüllmaterial **2** kann neben dem Wirkstoff noch Bindemittel, oberflächenaktive Substanzen, Füllstoffe und andere bekannte Zusatz- und Hilfsstoffe enthalten. Bindemittel sind zum Beispiel Cellulosen wie Hydroxypropylmethylcellulosen, Hydroxypropylcellulose und Carboxymethylcellulose, Polyvinylpyrolidon, Stärken und andere Substanzen.

Der Protonenpumpeninhibitor kann in einer Menge von 5–80 mg, insbesondere in einer Menge von 10–50 mg in der Kapselfüllung **2** vorliegen. Als Protonenpumpeninhibitor wird Omeprazol besonders bevorzugt.

Neben den nahtlosen Kapseln mit dem Protonenpumpeninhibitor kann zusätzlich mindestens ein weiterer Wirkstoff aus der Gruppe der NSAID wie Ibuprofen, Diclofenac, Piroxicam, Naproxen, Indomethazin, Fenoprofen, Acemetacin, Flurbiprofen, Ketroprofen oder ein pharmazeutisches Salz davon oder ein Enantiomeres davon vorliegen. Vorzugsweise liegt der Wirkstoff aus der Gruppe NSAID in einer Dosierung von 20–1000 mg vor.

In einer anderen Ausführungsform der Erfindung kann neben den nahtlosen Kapseln mit dem Protonenpumpeninhibitor zusätzlich eine oder mehrere antimikrobiell wirksame Substanzen vorliegen.

Geeignete antibakteriell wirksame Substanzen schließen z. B. Antibiotika, Tetracycline, Nitroimidazole, Penicilline, Cephalosporine, Carbopenemene, Aminoglykoside, Macrolid-Antibiotika, Linkosamid-Antibiotika, 4-Quinolone, Rifamycine, Nitrofurnatoin ein. Beispiele sind: Ampicillin, Amoxicillin, Benzylpenicillin, Phenoxymethylpenicillin, Bacampicillin, Pivampicillin, Carbenicillin, Cloxacillin, Clyclacillin, Dicloxacillin, Methicillin, Oxacillin, p-Peracillin, Ticarcilin, Flucloxacillin, Cefuroxime, Cefetamet, Cefetram, Cefixim, Cefoxitin, Ceftazidim, Ceftizoxim, Latamoxef, Cefoperazon, Ceftriaxon, Cefsulodin, Cefotaxim, Cephalexin, Cefaclor, Cefadroxil, Cefalothin, Cefazolin, Cefpodoxim, Ceftibuten, Aztreonam, Tigemonam, Erythromycin, Dirithromycin, Roxithromycin, Azithromycin, Clarithromycin, Clindamycin, Paldimycin, Lincomycin, Vancomycin, Spectinomycin, Tobramycin, Paromomycin, Metronidazol, Tinidazol, Ornidazol, Amifloxacin, Cinoxacin, Ciprofloxacin, Difloxacin, Enoxacin, Fleroxadin, Norfloxacin, Ofloxacin, Temafloxacin, Doxycyclin, Minoclyclin, Tetracyclin, Chlortetracyclin, Oxytetracyclin, Methacyclin, Rolitracyclin, Nitrofurantoin, Nalidixinsäure, Gentamicin, Rifampicin, Amikacin, Netilmicin, Imipenem, Cilastatin, Chloramphenicol, Furazolidone, Nifuroxazide, Sulfadiazin, Sulfametoxazol, Wismutsubsalizylat, kolloidales Wismutsubcitrat, Granicidin, Mecillinam, Cloxiquin, Chlorhexidin, Dichlorobenzylalkohol, Methyl-2-pentylphenol, wobei Clarithromycin, Erythromycin, Roxithromycin, Azithromycin, Amoxicillin, Metronidazol, Tinidazol und Tretracylin bevorzugt sind.

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Erfindungsgemäß bevorzugt sind folgende Wirkstoffkombinationen:

Omeprazol	20 mg
Clarithormycin	250 bzw. 500 mg
Metronidazol	400 mg

In einer anderen Ausführungsform der Erfindung ist eine Kombination von:

Omeprazol	20 mg
Amoxicillin	1000 mg
Clarithromycin	500 mg

als Füllmaterial **2** bevorzugt. In einer weiteren Ausführungsform der Erfindung wird folgende Kombination als Wirkstoff in die nahtlosen Kapseln eingefüllt:

Omeprazol	20 mg
Clarithromycin	1000 mg
Metronidazol	400 mg

Gemäß einer besonders bevorzugten Ausführungsform der Erfindung, können die nahtlosen Kapseln **1** in Hartgelatinekapseln eingefüllt und konfektioniert werden. In einer anderen Form kann die erfindungsgemäße pharmazeutische Zubereitung die Form einer Tablette aufweisen, die den Protonenpumpeninhibitor in Form von einzelnen, enterisch beschichteten gefüllten nahtlosen Kapseln enthält, wobei die enterisch Beschichtungsschicht **3** die einzelnen nahtlosen Kapseln beschichtet, um ihnen mechanische Festigkeit zu verleihen, so daß beim Tablettieren der gefüllten nahtlosen Kapseln **1** die Säurebeständigkeit der enterischbeschichteten gefüllten nahtlosen Kapseln **1** nicht beeinträchtigt wird.

Die nahtlosen Kapseln mit den Protoneninhibitoren können aber auch als solche oder zusammen mit weiteren Pulvergranulaten, Pellets in Beuteln oder Dosen bzw. Sachets eingefüllt sein.

Die Herstellung der erfindungsgemäßen Kapseln (vergleiche **Fig.** 1 bzw. **Fig.** 2) erfolgt über Zwei- bzw. Dreistoffdüsen, wobei gleichzeitig eine Beschichtungs- oder Filmlösung für die nahtlosen Kapseln und die Lösung und der Suspension des Wirkstoffes in eine Kühllösung aus einer konzentrisch angeordneten Mehrfachdüse extrudiert wird, wobei die innere Düse einen kleineren Durchmesser als die der äußeren Düse aufweist. Die Kühlflüssigkeit wird gegebenenfalls im Bereich des Strahleintritts in diese in umhüllende Schwingungen versetzt und der Strahlstrom wird unter Ausnutzung der Grenzflächenspannung kontinuierlich in kleine sphärische nahtlose Kapseltropfen **1** überführt.

Fig. 1 ist eine schematische Darstellung der erfindungsgemäßen Mikrokapsel **1** mit einer Hülle **3**. Omeprazol befindet sich in Lösung oder Suspension als Kapselfilmmaterial. **Fig.** 2 zeigt eine Omeprazolmikrokapsel **1** mit einer inerten oder magensaftresistenten Hülle **1** (Schicht **3**) oder sowie einer zweiten magensaftresitenten Hülle **2** (Schicht **4**).

Die Herstellung der erfindungsgemäßen nahtlosen Kapsel erfolgt über eine spezielle Technologie. Dabei wird die Lösung des Wirkstoffes **2** in den Düsenteil einer Zwei- bzw. Dreistoffdüse geleitet und aus der inneren Düse extrudiert und eine viskose Flüssigkeit **3** mit einer Hüllsubstanz, die in Wasser unlöslich ist, aus einer ringförmigen zweiten Düse extrudiert. Gleichzeitig wird eine weitere Lösung für die Hülle **4** aus der äußeren dritten Düse extrudiert und der Strahl in eine Kühlflüssigkeit eingedüst, so daß die nahtlosen Kapseln **1** der Erfindung erhalten werden.

Die nahtlosen Kapseln **1** können dann gegebenenfalls getrocknet und gewaschen werden.

Im allgemeinen können Gelatine und/oder Kombinationen von Gelatine mit Pektin usw. als Hüllsubstanzen verwendet werden.

Beispiele

Die folgenden Beispiele sollen die Erfindung näher erläutern, ohne sie einzuschränken.

Beispiel 1

Im folgenden soll die Herstellung der Omeprazolmikrokapseln gemäß **Fig.** 1 beschrieben werden. Die Mikrokapsel hat folgende Zusammensetzung:

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Zusammensetzung einer Mikrokapsel

Ausführungsbeispiel zu **Fig.** 1

Füllung: (Lösung (a))	Omeprazol	0,40 mg	Verhältnis 70 %
	Natriumlaurylsulfat	0,001 mg	
	Paraffinöl	8,00 mg	
Hülle: (Lösung (b))	Gelatine	1,823 mg	20 %
	Gummiarab.	0,351 mg	
	Pektin	0,687 mg	
		= 11,262 mg	

50 dieser Mikrokapseln werden in konventionelle Hartgelatinekapseln abgefüllt.

Unter Verwendung einer konzentrischen Doppeldüse wurde eine Omeprazollösung, die Parafinöl und Natriumlaurylsulfat enthielt (Lösung (a)), aus der inneren Düse extrudiert und eine Gelatine/Gummi-Arabikum/Pektinlösung auf 80°C erhitzt (Lösung (b)) und aus einer äußeren Düse zur gleichen Zeit in einem Verhältnis von 70% zu 20% ein Kühlmittel: in Pflanzenöl extrudiert, das eine Temperatur von etwa 12°C aufwies und eine Strömungsgeschwindigkeit von 0,3 m/Sekunde hatte. Die erhaltenen Kapseln wurden getrocknet.

Beispiel 2

Im folgenden wird die Herstellung der in **Fig.** 2 beschriebenen gecoateten Mikrokapseln beschrieben. Die Mikrokapseln hatten folgende Zusammensetzung.

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Füllung: (Lösung (a))	Omeprazol	0,44 mg	Verhältnis 65%
	Cetiol HE	1,25 mg	
	Paraffinöl	7,00 mg	
	Dinatriummonohydrogenphosphat	0,05 mg	
	Natriumlaurylsulfat	0,002 mg	
		= 8,742 mg	
Hülle 1: (Lösung (b))	Gelatine	1,537 mg	20%
	Gummiarab.	0,374 mg	
	Pectin	0,483 mg	
		= 2,394 mg	
Hülle 2: (Lösung (c))	Eudragit L100	1,038 mg	15%
	Triethylcitrat	0,085 mg	
	Talkum	0,256 mg	
	Titandioxid	0,132 mg	

Die Mikrokapseln wurden in Hartgelatinekapseln oder Sachets abgefüllt. Im Unterschied zu **Fig.** 1 wurde hier eine Dreistoffdüse verwendet und Lösungen der Hüllen (Lösung (b)), Lösung (c)) sowie Lösungen mit den Wirkstoffen (Lösung (a)) in einem Verhältnis von 65% : 20% :15% gleichzeitig in Pflanzenöl mit einer Temperatur von 12°C extrudiert. Die Mikrogelatinekapseln wurden wie oben beschrieben getrocknet und in Hartgelatinekapseln oder Sachets abgefüllt.

Beispiel 3

Es wurde eine gecoatete Mikrokapsel mit einer Dreistoffdüse, wie dies in Beispiel 2 beschrieben ist, mit den folgenden Zusammensetzungen hergestellt.

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Zusammensetzung einer gecoateten Mikrokapsel

Füllung: (Lösung (a))	Omeprazol	0,50 mg	Verhältnis 65%
	Mittelkettige Triglyceride	6,03 mg	
	Natriumhydorgenphosphat	0,0025 mg	
	Natriumlautylsulfat	0,002 mg	
		= 6,5345 mg	
Hülle: (Lösung (b))	Gelatine	1,625 mg	20%
	Gummiarab.	0,234 mg	
	Pectin	0,526 mg	
		= 2,385 mg	
Hülle 2: (Lösung (c))	HPMC phthalat	0,938 mg	15%
	Diethyl phthalat	0,023 mg	
		0,961 mg	
		= 9,8805 mg	

Die Mikrokapseln wurden dann weiter zu einer Tablette weiterverarbeitet mit der folgenden Tablettiermischung:

Omeprazol	
Mikrokapseln 40 Stück	395,22 mg
Maisstärke	225,00 mg
Mikrokristalline Cellulose	375,00 mg
Aerosil 200	5,00 mg
Magnesiumstearat	10,00 mg
	= 1010,22 mg

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Bezugszeichenliste

1 nahtlose Kapsel
2 Kapselfüllmaterial
3 Hülle **1** (inert) und/oder magensaftresistent
4 Hülle **2** magensaftresistent
※ Omeprazol in Suspension oder Lösung

Patentansprüche

1. Pharmazeutische Zubereitung zur oralen Verabreichung, enthaltend als Wirkstoff wenigstens einen Protonenpumpeninhibitor und gegebenenfalls pharmazeutisch akzeptable Trägerstoffe, sowie übliche Zusatz- und Hilfssubstanzen, **dadurch gekennzeichnet**, daß die Zubereitung eine gefüllte, nahtlose Kapsel (**1**) ist, enthaltend ein Kapselfüllmaterial (**2**) umfassend den mindestens einen Wirkstoff, der in einem Lösungs- und/oder Suspendiermittel gelöst bzw. suspendiert ist, und mindestens eine Schicht bzw. einen Film (**3**) zum Beschichten des Kapselfüllmaterials (**2**).

2. Pharmazeutische Zubereitung zur oralen Verabreichung gemäß Anspruch 1, dadurch gekennzeichnet, daß die Kapseln eine Größe von 0,3 mm bis 10 mm im Durchmesser aufweisen.

3. Pharmazeutische Zubereitung zur oralen Verabreichung nach Anspruch 1, dadurch gekennzeichnet, daß die Kapseln eine Größe von 0,8 mm bis 3 mm im Durchmesser aufweisen.

4. Pharmazeutische Zubereitung zur oralen Verabreichung nach einem der vorhergehenden Ansprüche 1 bis 3, dadurch gekennzeichnet, daß der Protonenpumpeninhibitor durch zwei Schichten (**3**, **4**) geschützt ist, eine enterische Beschichtungsschicht (**4**) und einen Film bzw. eine Schicht (**3**), die die enterische Beschichtungsschicht (**4**) von dem Protonenpumpeninhibitor abtrennt.

5. Pharmazeutische Zubereitung zur oralen Verabreichung gemäß einem der vorhergehenden Ansprüche 1 bis 4, dadurch gekennzeichnet, daß der Protonenpumpeninhibitor Omeprazol, ein alkalisches Salz von Omeprazol, ein einzelnes Enantiomer von Omeprazol oder ein alkalisches Salz davon oder das Magnesiumsalz von S-Omeprazol ist.

6. Pharmazeutische Zubereitung zur oralen Verabreichung gemäß einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß der Protonenpumpeninhibitor in einer Menge von 5 mg bis 80 mg, insbesondere in einer Menge von 10 mg bis 50 mg in der Kapselfüllung (**2**) vorliegt.

7. Pharmazeutische Zubereitung zur oralen Verabreichung gemäß einem der vorhergehenden Ansprüche 1 bis 6, dadurch gekennzeichnet, daß das Lösungs- und/oder Suspendiermittel eine alkalisch reagierende Verbindung zur Stabilisierung des Protonenpumpeninhibitors enthält.

8. Pharmazeutische Zubereitung einer oralen Verabreichung gemäß einem der vorhergehenden Ansprüche 1 bis 7, dadurch gekennzeichnet, daß sie neben den nahtlosen Kapseln mit dem Protonenpumpeninhibitor zusätzlich einen oder mehrere Wirkstoffe aus der Gruppe der NSAID wie Ibuprofen, Diclofenac, Piroxicam, Naproxen, Indomethazin, Fenoprofen, Acemetacin, Flurbiprofen, Uetroprofen oder pharmazeutisches Salz oder ein Enantiomeres davon enthält.

9. Pharmazeutische Zubereitung zur oralen Verabreichung gemäß einem der vorhergehenden Ansprüche 1 bis 8, daß sie die neben den nahtlosen Kapseln mit dem Protonenpumpeninhibitor zusätzlich ein oder mehrere Antibiotika enthält.

10. Pharmazeutische Zubereitung zur oralen Verabreichung gemäß einem der vorhergehenden Ansprüche 1 bis 9, dadurch gekennzeichnet, daß sie in Form einer Hartgelatinekapsel vorliegt, in der die nahtlosen Kapseln (**1**) gemäß einem der vorhergehenden Ansprüche 1 bis 9 enthalten sind.

11. Pharmazeutische Zubereitung zur oralen Verabreichung gemäß einem der vorhergehenden Ansprüche 1 bis 9, dadurch gekennzeichnet, daß sie in Form einer Tablette vorliegt, die den Protonenpumpeninhibitor in Form von einzelnen, enterisch beschichteten, gefüllten nahtlosen Kapseln (**1**) enthält, wobei die enterische Beschichtungsschicht (**3**) die einzelnen nahtlosen Kapseln beschichtet, um ihnen mechanische Festigkeit zu verleihen, so daß beim Tablettieren der gefüllten nahtlosen Kapseln (**1**), die Säurebeständigkeit der enterisch beschichteten, gefüllten nahtlosen Kapseln (**1**) nicht beeinträchtigt wird.

12. Pharmazeutische Zubereitung zur oralen Verabreichung gemäß einem der vorhergehenden Ansprüche 1 bis 8, dadurch gekennzeichnet daß die nathlosen Kapseln mit dem Protonenpumpeninhibitor als solche oder zusammen mit weiterem Pulvergranulat oder Pellets in Beuteln oder Dosen bzw. Sachets gefüllt sind.

13. Verfahren zum Herstellen der pharmazeutischen Zubereitung gemäß einem der vorhergehenden Ansprüche 1 bis 9, dadurch gekennzeichnet, daß man gleichzeitig eine Beschichtungs- oder Filmlösung für die nahtlose(n) Kapsel(n) (**1**) und die Lösung und/oder Suspension des wenigstens einen Wirkstoffes in eine Kühllösung aus einer konzentrisch angeordneten Mehrfachdüse, die aus wenigstens zwei Düsen besteht, extrudiert, wobei die innere Düse einen kleineren Durchmesser als die äußere Düse aufweist, wobei insbesondere die Kühlflüssigkeit im Bereich des Strahleintritts in diese in den Strahl umhüllende Schwingungen versetzt wird, und der Strahlstrom unter Ausnutzung der Grenzflächenspannung kontinuierlich in kleine sphärische nahtlose Kapseltropfen (**1**) überführt wird.

14. Verfahren nach Anspruch 13, dadurch gekennzeichnet, daß die zunächst einfach mikroverkapselte Wirkstofflösung bzw. -suspension im nächsten Schritt in einer Wirbelschicht mit einem weiteren magensaftresistenten Überzug (**4**) versehen wird.

15. Verfahren nach Anspruch 13, dadurch gekennzeichnet, daß man eine Mehrfachdüse mit wenigstens drei Düsen einsetzt, bestehend aus einer Außendüse und einer Innendüse und wenigstens einer Zwischendüse, die sich in der Mittelstellung zwischen der Außen- und Innendüse befindet, wobei der Durchmesser der drei Düsen graduell in dieser Reihenfolge ansteigt, und gleichzeitig eine Filmlösung für die nahtlose Kapsel, die Lösung bzw. die Suspension

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der Wirksubstanz und eine weitere Filmlösung in eine Kühllösung extrudiert und der Strahlstrom der drei Flüssigkeiten unter Ausnutzung der Grenzflächenspannung kontinuierlich in kleine sphärische, nahtlose Kapseltropfen (1) überführt wird.

Hierzu 1 Seite(n) Zeichnungen

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Nummer: DE 198 01 811 A1
Int. Cl.[6]: A 61 K 9/50
Offenlegungstag: 22. Juli 1999

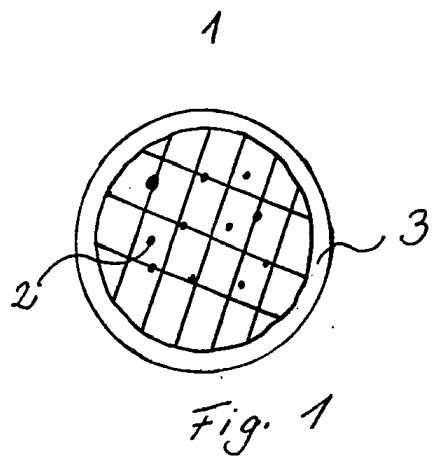


Fig. 1

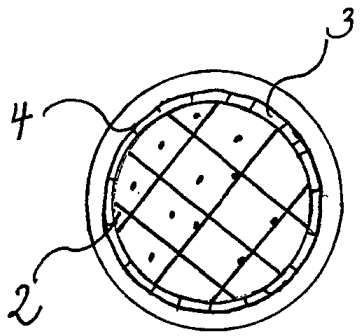


Fig. 2

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of:

Plachetka, John R.

Appl. No.: 10/158,216

Filed: May 31, 2002

For: **Pharmaceutical Compositions for the Coordinated Delivery of NSAIDs**

Art Unit: to be assigned

Examiner: to be assigned

Atty. Dkt.: 7569/73281
(Formerly 71896/284951)

CHANGE OF ADDRESS NOTICE

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FITCH, EVEN, TABIN & FLANNERY

By Michael A. Sanzo
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*ADMITTED TO D.C. BAR; D.C. PRACTICE OF ALL OTHERS LIMITED TO FEDERAL COURTS AND AGENCIES

April 24, 2003

Assistant Commissioner for Patents
Washington, DC 20231

Re: Information Disclosure Statement
Appl. No.: 10/158,216
Filed: May 31, 2002
Title: **Pharmaceutical Compositions for the Coordinated Delivery of NSAIDs**
Inventor(s): Plachetka, John R.
Atty. Dkt.: 7569/73281 (formerly 71896/284951)

Dear Sir:

The following documents are being forwarded herewith for appropriate action by the U.S. Patent and Trademark Office:

1. Information Disclosure Statement;
2. PTO Form 1449 - List of References Cited by Applicant;
3. References AA1-AF2, AG1-AH1, and AK1-AM3;
4. Change of Address Notice; and
5. One return postcard.

Applicant does not believe that any fee is due for the filing of this IDS. However, the Commissioner is hereby authorized to charge any fee deficiency to our Deposit Account No. 06-1135 under Order No. 7569/73281.

It is respectfully requested that the enclosed postcard be stamped with the date the enclosed documents are received by the PTO and that it be returned as soon as possible.

Very truly yours,

FITCH, EVEN, TABIN & FLANNERY

Michael A. Sanzo
Reg. No. 36,912
Attorney for Applicant

MAS:ct
Enclosures

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of:

Plachetka, John R.

Appl. No.: 10/158,216

Filed: May 31, 2002

For: **Pharmaceutical Compositions for the Coordinated Delivery of NSAIDs**

Art Unit: to be assigned

Examiner: to be assigned

Atty. Dkt.: 7569/73281
(Formerly 71896/284951)

Information Disclosure Statement

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Submitted herewith is a listing of documents known to Applicant and/or his attorney in compliance with the requirements of 37 C.F.R. § 1.56. One of these documents was cited in the International Search Report for counterpart international application no. PCT/US02/17105, dated March 14, 2003, a copy of which is enclosed. Copies of the listed documents are also enclosed.

Applicant does not waive any rights to appropriate action to establish patentability over any of the listed documents should they be applied as references against the claims of the present application. This statement should not be construed as a representation that more material information does not exist or that an exhaustive search of the relevant art has been made.

Consideration of the cited documents and making the same of record in the prosecution of the above-captioned application are respectfully requested.

Applicant does not believe that any fee is due for the filing of this IDS. However, the Commissioner is hereby authorized to charge any fee deficiency to our Deposit Account No. 06-1135 under Order No. 7569/73281.

Respectfully submitted,

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LIST OF REFERENCES CITED BY APPLICANT (Use several sheets if necessary)	Atty. Docket No.: 7569/73281	Appl No.: 10/158,216
	Applicant(s) Plachetka, John R.	
	Filing Date: May 31, 2002	Group: to be assigned

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U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date If Appropriate
	AA 1	4,554,276	Nov. 19, 1985	LaMattina	514	272	Oct. 3, 1983
	AB 1	4,676,984	Jun. 30, 1987	Wu, *et al.*	424	157	Aug. 14, 1985
	AC 1	4,704,278	Nov. 3, 1987	Wu, *et al.*	424	157	Aug. 8, 1986
	AD 1	4,757,060	Jul. 12, 1988	Lukacsko, *et al.*	514	160	Apr. 29, 1986
	AE 1	4,766,117	Aug. 23, 1988	Crawford, *et al.*	514	219	Dec. 12, 1986
	AF 1	4,786,505	Nov. 22, 1988	Lovgren, *et al.*	424	468	Apr. 20, 1987

FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	Subclass	Translation Yes	Translation No
	AG 1	WO 85/03443	15 August 1985	WIPO	A61K	45/06		
	AH 1	GB 2 105 193	23 March 1983	United Kingdom	A61K	31/34		
	AI							
	AJ							

OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)

	AK 1	Bigard, *et al.*, "Complete Prevention by Omeprazole of Aspirin Induced Gastric Lesions in Healthy Subjects," *GUT 29(5)*:A712, T49 (1988).
	AL 1	Bombardier, *et al.*, "Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis," *N. Engl. J. Med. 343*:1520-1528 (2000).
	AM1	Brown, *et al.*, "Prevention of the Gastrointestinal Adverse Effects of Nonsteroidal Anti-Inflammatory Drugs," *Pract. Drug Safety 21*:503-512 (1999).
	AN 1	Cullen, *et al.*, "Primary Gastroduodenal Prophylaxis with Omeprazole for Non-Steroidal Anti-Inflammatory Drug Users," *Aliment. Pharmacol. Ther. 12*:135-140 (1998).
	AO 1	Hawkey, "Progress in Prophylaxis Against Nonsteroidal Anti-Inflammatory Drug-Associated Ulcers and Erosions," *Am. J. Med. 104*:67S-74S (1998).
	AP 1	Hawkey, *et al.*, "Omeprazole Compared with Misoprostol for Ulcers Associated with Nonsteroidal Anti-Inflammatory Drugs," *N. Engl. J. Med. 338*:727-734 (1998).
	AQ 1	Howden, "Clinical Pharmacology of Omeprazole," *Clin. Pharmacokinet. 20*:38-49 (1991).
	AR 1	Katz, *et al.*, "Gastric Acidity and Acid Breakthrough with Twice-Daily Omeprazole or Iansoprazole," *Aliment. Pharmacol. Ther 14*:709-714 (2000).

Examiner	Date Considered

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Page 553 of 613

LIST OF REFERENCES CITED BY APPLICANT *(Use several sheets if necessary)*	Atty. Docket No.: 7569/73281	Appl No.: 10/158,216
	Applicant(s) Plachetka, John R.	
	Filing Date: May 31, 2002	Group: to be assigned

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U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date If Appropriate
	AA 2	5,037,815	Aug. 6, 1991	Lukacsko, *et al.*	514	162	Sep. 8, 1988
	AB 2	5,204,118	Apr. 20, 1993	Goldman, *et al.*	424	489	Apr. 29, 1992
	AC 2	5,417,980	May 23, 1995	Goldman, *et al.*	424	464	Jun. 29, 1994
	AD 2	5,466,436	Nov. 14, 1995	Stables	514	161	Dec. 17, 1993
	AE 2	5,716,648	Feb. 10, 1998	Halskov, *et al.*	424	682	Dec. 21, 1995
	AF 2	6,365,184 B1	Apr. 2, 2002	Depui, *et al.*	424	469	Dec. 23, 1999

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		Document Number	Date	Country	Class	Subclass	Translation	
							Yes	No
	AG							
	AH							
	AI							
	AJ							

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	AK 2	Kephart, *et al.*, "Coprescribing of Nonsteroidal Anti-Inflammatory Drugs and Cytoprotective and Antiulcer Drugs in Nova Scotia's Senior Population," *Clin. Ther. 17*:1159-1173 (1995).
	AL 2	Lad, *et al.*, "Management of Nonsteroidal Anti-Inflammatory Drug-Induced Gastroduodenal Disease by Acid Suppression," *Can. J. Gastroenterol 13*:135-142 (1999).
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	AO 2	Scheiman, "NSAID-Induced Peptic Ulcer Disease: A Critical Rview of Pathogenesis and Management," *Dig. Dis. 12*:210-222 (1994).
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	AQ 2	Silverstein, *et al.*, "Gastrointestinal Toxicity with Celecoxib vs. Nonsteroidal Anti-Inflammatory Drugs for Osteoarthritis and Rheumatoid Arthritis; The CLASS Study: A Randomized Controlled Trial," *JAMA 284*:1247-1255 (2000).
	AR 2	Tronstad, *et al.*, "Gastroscopic Findings after Treatment with Enteric-Coated and Plain Naproxen Tablets in Healthy Subjects," *Scand. J. Gastroenterol. 20*:239-242 (1985).

Examiner	Date Considered

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Page 554 of 613

LIST OF REFERENCES CITED BY APPLICANT *(Use several sheets if necessary)*	Atty. Docket No.: 7569/73281	Appl No.: 10/158,216
	Applicant(s) Plachetka, John R.	
	Filing Date: May 31, 2002	Group: to be assigned

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	AA						
	AB						
	AC						
	AD						
	AE						
	AF						

FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	Subclass	Translation	
							Yes	No
	AG							
	AH							
	AI							
	AJ							

OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)

	AK 3	Wolfe, *et al.*, "Gastrointestinal Toxicity of Nonsteroidal Anti-Inflammatory Drugs," *N. Engl. J. Med. 340*:1888-1899 (1999).
	AL 3	Yeomans, *et al.*, "A Comparison of Omeprazole with Ranitidine for Ulcers Associated with Nonsteroidal Anti-Inflammatory Drugs," *N. Engl. J. Med. 338*:719-726 (1998).
	AM3	Yeomans, *et al.*, "New Data on Healing of Nonsteroidal Anti-Inflammatory Drug-Associated Ulcers and Erosions," *Am. J. Med. 104*:56S-61S (1998).
	AN	
	AO	
	AP	
	AQ	
	AR	

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Page 555 of 613

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In re patent application of:

Plachetka, John R.	Art Unit: to be assigned
Appl. No.: 10/158,216	Examiner: to be assigned
Filed: May 31, 2002	Atty. Dkt.: 7569/73281 (Formerly 71896/284951)
For: **Pharmaceutical Compositions for the Coordinated Delivery of NSAIDs**	

CHANGE OF ADDRESS NOTICE

Effective immediately, please change the address for the above-captioned application to:

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OIPE AUG 0 3 2002 PATENT & TRADEMARK OFFICE
MAIL DATE CANCELLED

#3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	John R. Plachetka
Appl. No.:	10/158,216
Filed:	May 31, 2002
For:	**Pharmaceutical Compositions for the Coordinated Delivery of NSAIDs**

All

Commissioner of Patents and Trademarks
Washington, D.C. 20231

DECLARATION (37 C.F.R. § 1.63) AND POWER OF ATTORNEY

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name, and

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the application identified above.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with 37 C.F.R. § 1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119, of any United States provisional applications or foreign application(s) for patent or inventor's certificate or of any PCT International Application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application for patent or inventor's certificate or any PCT International Application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application on which priority is claimed:

Patent Owner Ex. 2005
IPR2015-01344
Page 557 of 613

Application Serial No.	Country	Filing Date (Day/Month/Year)	Priority Claimed (Yes/No)
60/294,588	United States	June 1, 2001	Yes

I hereby claim the benefit under Title 35, United States Code, Section 120, of any United States application(s) or PCT International Application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application(s) in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56, which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status (Patented, Pending, Abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I hereby appoint Romi N. Bose, Reg. No. 43,322; Kendrew H. Colton, Reg. No. 30,368; Francis A. Even, Reg. No. 16,880; Stephen S. Favakeh, Reg. No. 36,798; Karl R. Fink, Reg. No. 34,161; Morgan L. Fitch, Jr., Reg. No. 17,023; John F. Flannery, Reg. No. 19,759; Robert J. Fox, Reg. No. 27,635; James J. Hamill, Reg. No. 19,958; Mark W. Hetzler, Reg. No. 38,183; Ramon R. Hoch, Reg. No. 34,108; Perry J. Hoffman, Reg. No. 37,150; Robert B. Jones, Reg. No. 20,135; Richard A. Kaba, Reg. No. 30,562; James P. Kreuger, Reg. No. 35,234; Timothy E. Levstik, Reg. No. 30,192; Timothy P. Maloney, Reg. No. 38,233; Bruce R. Mansfield, Reg. No. 29,086; Steven G. Parmelee, Reg. No. 28,790; Philip T. Petti, Reg. No. 31,651; Kathleen A. Ranney, Reg. No. 37,702; Kenneth H. Samples, Reg. No. 25,747; Michael A. Sanzo, Reg. No. 36,912; Joseph E. Shipley, Reg. No. 31,137; James J. Schumann, Reg. No. 20,856; Julius Tabin, Reg. No. 16,754; all registered to practice before the Patent and Trademark Office, as my attorneys with full power of substitution and revocation to prosecute this application and all divisions and continuations thereof and to transact all business in the Patent and Trademark Office connected therewith and request that all correspondence and telephone communications be directed to the following person(s) at the mailing address and telephone number hereafter given:

Patent Owner Ex. 2005
IPR2015-01344
Page 558 of 613

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Signature of Inventor John R. Plachetka Date July 22, 2002

Residence: 321 Silver Creek Trail
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Citizenship: United States

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Patent Owner Ex. 2005
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#3

UNITED STATES PATENT AND TRADEMARK OFFICE

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WASHINGTON, D.C. 20231
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APPLICATION NUMBER	FILING/RECEIPT DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
10/158,216	05/31/2002	John R. Plachetka	71896/284951

CONFIRMATION NO. 5014

PILLSBURY WINTHROP LLP
1600 TYSONS BOULEVARD
MCLEAN, VA 22102

FORMALITIES LETTER

OC000000008390808

Date Mailed: 07/02/2002

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
  Applicant must submit $ **740** *to complete the basic filing fee for a non-small entity. If appropriate, applicant may make a written assertion of entitlement to small entity status and pay the small entity filing fee (37 CFR 1.27).*
- The oath or declaration is unsigned.
- To avoid abandonment, a late filing fee or oath or declaration surcharge as set forth in 37 CFR 1.16(l) of $130 for a non-small entity, must be submitted with the missing items identified in this letter.

Items Required To Avoid Processing Delays:

The item(s) indicated below are also required and should be submitted with any reply to this notice to avoid further processing delays.

Adjustment date: 09/04/2002 YTEKLEMI
09/04/2002 MBERHE 00000064 061135 10158216
04 FC:202 84.00 CR

- Additional claim fees of **$2116** as a non-small entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.

09/04/2002 MBERHE 00000064 061135 10158216
01 FC:201 370.00 CH
02 FC:205 65.00 CH
03 FC:203 918.00 CH
04 FC:202 84.00 CH
05 FC:204 140.00 CH

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is **$2986** for a Large Entity

- **$740** Statutory basic filing fee.
- **$130** Late oath or declaration Surcharge.
- Total additional claim fee(s) for this application is **$2116**
  - **$1836** for **102** total claims over 20.

- $280 for multiple dependent claim surcharge.

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*A copy of this notice **MUST** be returned with the reply.*

Customer Service Center
Initial Patent Examination Division (703) 308-1202
PART 2 - COPY TO BE RETURNED WITH RESPONSE

OIPE JC168 SEP 03 2002 PATENT & TRADEMARK OFFICE

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OIPE JC34 AUG 03 2002 PATENT & TRADEMARK OFFICE

September 3, 2002

Assistant Commissioner for Patents
Washington, DC 20231

Adjustment Date: 09/19/2002 MTEKLEMI
09/04/2002 MBERHE 00000064 061135 10158216
04 FC:202 84.00 CR

Re: Response to Notice to File Missing Parts

Appl. No.:	10/158,216
Filed:	May 31, 2002
Title:	**Pharmaceutical Compositions for the Coordinated Delivery of NSAIDs**
Inventor(s):	Plachetka, John R.
Atty. Dkt.:	7569/73281 (formerly 71896/284951)

Dear Sir:

The following documents are being forwarded herewith for appropriate action by the U.S. Patent and Trademark Office:

1. A copy of the Notice to File Missing Parts of Nonprovisional Application - Filing Date Granted;

2. Declaration Under 37 C.F.R. § 1.63 and Power of Attorney, executed by inventor John R. Plachetka (3 pages);

3. Assignment to POZEN Inc., executed by inventor John R. Plachetka (2 pages), the recordation of which is respectfully requested;

4. Form PTO-1594, Recordation Form Cover Sheet;

5. The Commissioner is hereby authorized to charge the following fees in the amount of $1,617.00 **(Small Entity Status is claimed)** to our Deposit Account No. 06-1135 under Order No. 7569/73281:

$ 370.00	Basic Filing Fee (37 C.F.R. 1.16(a)),
84.00	2 Independent Claims in excess of 3 (37 C.F.R. 1.16(b)),
918.00	102 Claims in excess of 20 (37 C.F.R. 1.16(c)),
140.00	Multiple Dependent Claim Fee (37 C.F.R. 1.16(d)),
65.00	Surcharge for late filing of Declaration (37 C.F.R. 1.16(e)),
40.00	Assignment recordation fee (37 C.F.R. 1.21(h)); and

6. One return postcard.

The Commissioner is hereby authorized to charge any fee deficiency or credit any overpayment to our Deposit Account No. 06-1135 under Order No. 7569/73281.

It is respectfully requested that the enclosed postcard be stamped with the date the enclosed documents are received by the PTO and that it be returned as soon as possible.

Very truly yours,

FITCH, EVEN, TABIN & FLANNERY

Michael A. Sanzo

Michael A. Sanzo
Reg. No. 36,912
Attorney for Applicant

MAS:ct
Enclosures

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
www.uspto.gov

APPLICATION NUMBER	FILING/RECEIPT DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
10/158,216	05/31/2002	John R. Plachetka	71896/284951

CONFIRMATION NO. 5014

PILLSBURY WINTHROP LLP
1600 TYSONS BOULEVARD
MCLEAN, VA 22102

FORMALITIES LETTER

OC000000008390808

Date Mailed: 07/02/2002

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
  Applicant must submit $ **740** *to complete the basic filing fee for a non-small entity. If appropriate, applicant may make a written assertion of entitlement to small entity status and pay the small entity filing fee (37 CFR 1.27).*
- The oath or declaration is unsigned.
- To avoid abandonment, a late filing fee or oath or declaration surcharge as set forth in 37 CFR 1.16(l) of $130 for a non-small entity, must be submitted with the missing items identified in this letter.

Items Required To Avoid Processing Delays:

The item(s) indicated below are also required and should be submitted with any reply to this notice to avoid further processing delays.

- Additional claim fees of **$2116** as a non-small entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is **$2986** for a Large Entity

- **$740** Statutory basic filing fee.
- **$130** Late oath or declaration Surcharge.
- Total additional claim fee(s) for this application is **$2116**
  - **$1836** for **102** total claims over 20.

- **$280**for multiple dependent claim surcharge.

A copy of this notice MUST be returned with the reply.

Customer Service Center
Initial Patent Examination Division (703) 308-1202

PART 3 - OFFICE COPY

J1051 U.S. PTO
05/31/02

PILLSBURY WINTHROP LLP

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JC857 U.S. PTO
10/158216
05/31/02

May 31, 2002

Assistant Commissioner for Patents
BOX: Patent Application
Washington, DC 20231

Re: New U.S. Patent Application
(Claiming Priority to Provisional Appl. No. 60/294,588)

Appl. No.	to be assigned
Filed:	herewith
Title:	**Pharmaceutical Compositions for the Coordinated Delivery of NSAIDs**
Inventor(s):	Plachetka, John R.
Atty. Dkt.:	71896/284951

Sir:

The following documents are being forwarded herewith for appropriate action by the U.S. Patent and Trademark Office:

1. U.S. Patent Application entitled:

   PHARMACEUTICAL COMPOSITIONS FOR THE COORDINATED DELIVERY OF NSAIDS

   and naming as inventor(s): John R. Plachetka

   the application comprising:

   29 pages of Specification (numbered as pages 1-29);
   6 pages of Claims (numbered as pages 30-35);
   a one-page Abstract (numbered as page 36); and
   2 sheets of formal drawings (labeled as Fig. 1-Fig. 3);

2. Declaration (37 C.F.R. § 1.63) and Power of Attorney of inventor John R. Plachetka, unexecuted (3 pages);

3. Assignment to POZEN Inc. of inventor John R. Plachetka, unexecuted (2 pages); and

4. Two (2) return postcards.

This application claims priority to provisional application no. 60/294,588, filed June 1, 2001. The application is being filed under 37 C.F.R. § 1.53 without Declaration and without filing fee.

It is respectfully requested that the attached postpaid postcards be stamped with the serial number of the above-named application and that these postcards be returned as soon as possible.

Very truly yours,

PILLSBURY WINTHROP LLP

Michael A. Sanzo
Attorney for Applicant
Reg. No. 36,912

MAS:ct
Enclosures

30290492V1

Pharmaceutical Compositions for the Coordinated Delivery of NSAIDs

Field of the Invention

The present invention is directed to pharmaceutical compositions that provide for the coordinated release of an acid inhibitor and a non-steroidal anti-inflammatory drug (NSAID). These compositions have a reduced likelihood of causing unwanted side effects, especially gastrointestinal side effects, when administered as a treatment for pain, arthritis and other conditions amenable to treatment with NSAIDs.

Background of the Invention

Although non-steroidal anti-inflammatory drugs are widely accepted as effective agents for controlling pain, their administration can lead to the development of gastroduodenal lesions, *e.g.*, ulcers and erosions, in susceptible individuals. It appears that a major factor contributing to the development of these lesions is the presence of acid in the stomach and upper small intestine of patients. This view is supported by clinical studies demonstrating an improvement in NSAID tolerability when patients are also taking independent doses of acid inhibitors (*Dig. Dis. 12*:210-222 (1994); *Drug Safety 21*:503-512 (1999); *Aliment. Pharmacol. Ther. 12*:135-140 (1998); *Am. J. Med. 104(3A)*:67S-74S (1998); *Clin. Ther. 17*:1159-1173 (1995)). Other major factors contributing to NSAID-associated gastropathy include a local toxic effect of NSAIDs and inhibition of protective prostaglandins (*Can. J. Gastroenterol. 13*: 135-142 (1999) and *Pract. Drug Safety 21*:503-512, (1999)), which may also make some patients more susceptible to the ulcerogenic effects of other noxious stimuli.

In general, more potent and longer lasting acid inhibitors, such as proton pump inhibitors, are thought to be more protective during chronic administration of NSAIDs than shorter acting agents, *e.g.*, histamine H_2 receptor antagonists (H-2 blockers) (*N. Eng. J. Med. 338*:719-726 (1998); *Am. J. Med. 104(3A)*:56S-61S (1998)). The most likely explanation for this is that gastric pH fluctuates widely throughout the dosing interval with short acting acid inhibitors leaving the mucosa vulnerable for significant periods of time. In particular, the pH is at its lowest point, and hence the mucosa is most vulnerable, at the end of the dosing interval (least amount of acid inhibition) and for some time after the subsequent dose of acid inhibitor. In general, it appears that when a short acting acid inhibitor and an NSAID are

administered simultaneously, NSAID-related mucosal damage occurs before the pH of the gastrointestinal tract can be raised and after the acid inhibiting effect of the short acting acid inhibitor dissipates.

Although longer lasting agents, such as proton pump inhibitors (PPIs), usually maintain a consistently higher gastroduodenal pH throughout the day, after several days dosing, their antisecretory effect may be delayed for several hours and may not take full effect for several days (*Clin. Pharmacokinet. 20*:38-49 (1991)). Their effect may be diminished toward the end of the usual dosing interval. Intragastric pH rises particularly slowly with the first dose in a course of treatment since this class of drugs is enteric coated to avoid destruction by stomach acid. As a result, absorption is delayed for several hours. Even then, some patients fail to respond consistently to drugs of this type and suffer from "acid breakthrough" which again leaves them vulnerable to NSAID-associated gastroduodenaldamage (*Aliment. Pharmacol. Ther. 14*:709-714 (2000)). Despite a significant reduction in gastroduodenal lesions with the concomitant administration of a proton pump inhibitor during six months of NSAID therapy, up to 16% of patients still develop ulcers, indicating that there remains substantial room for improvement (*N. Eng. J. Med. 338*:727-734 (1998)). Thus, the addition of a pH sensitive enteric coating to an NSAID could provide additional protection against gastroduodenal damage not provided by the H2 blocker or PPI alone. In addition, although long acting acid inhibitors may reduce the risk of GI lesions in chronic NSAID users, there are questions about the safety of maintaining an abnormally elevated pH in a patient's GI tract for a prolonged period of time (*Scand. J. Gastroenterol. Suppl. 178*:85-92 (1990)).

Recognizing the potential benefits of PPIs for the prevention of NSAID-induced gastroduodenal damage, others have disclosed strategies for combining the two active agents for therapeutic purposes. However, these suggestions do not provide for coordinated drug release or for reducing intragastric acid levels to a non-toxic level prior to the release of NSAID (U.S. 5,204,118; U.S. 5,417,980; U.S. 5,466,436; and U.S. 5,037,815). In certain cases, suggested means of delivery would expose the gastrointestinal tract to NSAIDs prior to onset of PPI activity (U.S. 6,365,184).

Attempts to develop NSAIDs that are inherently less toxic to the gastrointestinal tract have met with only limited success. For example, the recently developed cyclooxygenase-2

(COX-2) inhibitors show a reduced tendency to produce gastrointestinal ulcers and erosions, but a significant risk is still present, especially if the patient is exposed to other ulcerogens (*JAMA 284*:1247-1255 (2000); *N. Eng. J. Med. 343*:1520-1528 (2000)). In this regard, it appears that even low doses of aspirin will negate most of the benefit relating to lower gastrointestinal lesions. In addition, the COX-2 inhibitors may not be as effective as other NSAIDs at relieving some types of pain and have been associated with significant cardiovascular problems (*JADA 131*:1729-1737 (2000); *SCRIP 2617*, pg. 19, Feb. 14, 2001); NY Times, May 22, 2001, pg. C1)).

Other attempts to produce an NSAID therapy with less gastrointestinal toxicity have involved the concomitant administration of a cytoprotective agent. In 1998, Searle began marketing Arthrotec™ for the treatment of arthritis in patients at risk for developing GI ulcers. This product contains misopristol (a cytoprotective prostaglandin) and the NSAID diclofenac. Although patients administered Arthrotec™ do have a lower risk of developing ulcers, they may experience a number of other serious side effects such as diarrhea, severe cramping and, in the case of pregnant women, potential damage to the fetus.

Another approach has been to produce enteric coated NSAID products. However, even though these have shown modest reductions in gastroduodenal damage in short term studies (*Scand. J. Gastroenterol. 20*: 239–242 (1985) and *Scand. J. Gastroenterol. 25*:231–234 (1990)), there is no consistent evidence of a long term benefit during chronic treatment.

Overall, it may be concluded that the risk of inducing GI ulcers is a recognized problem associated with the administration of NSAIDs and that, despite considerable effort, an ideal solution has not yet been found.

Summary of the Invention

The present invention is based upon the discovery of a new method for reducing the risk of gastrointestinal side effects in people taking NSAIDs for pain relief and for other conditions, particularly during chronic treatment. The method involves the administration of a single, coordinated, unit-dose product that combines: a) an agent that actively raises intragastric pH to levels associated with less risk of NSAID-induced ulcers; and b) an NSAID that is specially formulated to be released in a coordinated way that minimizes the adverse effects of the NSAID on the gastroduodenal mucosa. Either short or long acting acid

inhibitors can be effectively used in the dosage forms. This method has the added benefit of being able to protect patients from other gastrointestinal ulcerogens whose effect may otherwise be enhanced by the disruption of gastroprotective prostaglandins due to NSAID therapy.

In its first aspect, the invention is directed to a pharmaceutical composition in unit dosage form suitable for oral administration to a patient. The composition contains an acid inhibitor present in an amount effective to raise the gastric pH of a patient to at least 3.5, preferably to at least 4, and more preferably to at least 5, when one or more unit dosage forms are administered. The gastric pH should not exceed 7.5 and preferably should not exceed 7.0. The term "acid inhibitor" refers to agents that inhibit gastric acid secretion and increase gastric pH. In contrast to art teaching against the use of H2 blockers for the prevention of NSAID-associated ulcers (*N. Eng. J. Med. 340*: 1888–1899 (1999)), these agents are preferred compounds in the current invention. Specific, H2 blockers that may be used include cimetidine, ranitidine, ebrotidine, pabutidine, lafutidine, loxtidine or famotidine. The most preferred acid inhibitor is famotidine present in dosage forms in an amount of between 5 mg and 100 mg. Other agents that may be effectively used include proton pump inhibitors such as omeprazole, esomeprazole, pantoprazole, lansoprazole or rabeprazole.

The pharmaceutical composition also contains a non-steroidal anti-inflammatory drug in an amount effective to reduce or eliminate pain or inflammation. The NSAID may be a COX-2 inhibitor such as celecoxib, rofecoxib, meloxicam, piroxicam, valdecoxib, parecoxib, etoricoxib, CS-502, JTE-522, L-745,337 or NS398. Alternatively, the NSAID may be aspirin, acetaminophen, ibuprofen, flurbiprofen, ketoprofen, naproxen, oxaprozin, etodolac, indomethacin, ketorolac, lornoxicam, nabumetone, or diclofenac. The most preferred NSAID is naproxen in an amount of between 50 mg and 1500 mg, and more preferably, in an amount of between 200 mg and 600 mg. It will be understood that, for the purposes of the present invention, reference to an acid inhibitor, NSAID, or analgesic agent will include all of the common forms of these compounds and, in particular, their pharmaceutically acceptable salts. The amounts of NSAIDs which are therapeutically effective may be lower in the current invention than otherwise found in practice due to potential positive kinetic interaction and NSAID absorption in the presence of an acid inhibitor.

The term "unit dosage form" as used herein refers to a single entity for drug administration. For example, a single tablet or capsule combining both an acid inhibitor and an NSAID would be a unit dosage form. A unit dosage form of the present invention preferably provides for coordinated drug release, in a way that elevates gastric pH and reduces the deleterious effects of the NSAID on the gastroduodenal mucosa, *i.e.*, the acid inhibitor is released first and the release of NSAID is delayed until after the pH in the GI tract has risen. In a preferred embodiment, the unit dosage form is a multilayer tablet, having an outer layer comprising the acid inhibitor and an inner core which comprises the NSAID. In the most preferred form, coordinated delivery is accomplished by having the inner core surrounded by a polymeric barrier coating that does not dissolve unless the surrounding medium is at a pH of at least 3.5, preferably at least 4 and more preferably, at least 5. Alternatively, a barrier coating may be employed which controls the release of NSAID by time, as opposed to pH, with the rate adjusted so that NSAID is not released until after the pH of the gastrointestinal tract has risen to at least 3.5, preferably at least 4, and more preferably at least 5. Thus, a time-release formulation may be used to prevent the gastric presence of NSAID until mucosal tissue is no longer exposed to the damage enhancing effect of very low pH.

The invention includes methods of treating a patient for pain, inflammation and/or other conditions by administering the pharmaceutical compositions described above. Although the method may be used for any condition in which an NSAID is effective, it is expected that it will be particularly useful in patients with osteoarthritis or rheumatoid arthritis. Other conditions that may be treated include, but are not limited to: all form of headache, including migraine headache; acute musculoskeletal pain; ankylosing spondylitis; dysmenorrhoea; myalgias; and neuralgias.

In a more general sense, the invention includes methods of treating pain, inflammation and/or other conditions by orally administering an acid inhibitor at a dose effective to raise a patient's gastric pH to at least 3.5, preferably to at least 4 or and more preferably to at least 5. The patient is also administered an NSAID, for example in a coordinated dosage form, that has been coated in a polymer that only dissolves at a pH of least 3.5, preferably at least 4 and, more preferably, 5 or greater or which dissolves at a rate that is slow enough to prevent NSAID release until after the pH has been raised. When acid inhibitor and NSAID are administered in separate doses, *e.g.*, in two separate tablets, they

should be given concomitantly (*i.e.*, so that their biological effects overlap) and may be given concurrently, *i.e.*, NSAID is given within one hour after the acid inhibitor. Preferably, the acid inhibitor is an H2 blocker and, in the most preferred embodiment, it is famotidine at a dosage of between 5 mg and 100 mg. Any of the NSAIDs described above may be used in the method but naproxen at a dosage of between 200 and 600 mg is most preferred. It is expected that the inhibitor and analgesic will be typically delivered as part of a single unit dosage form which provides for the coordinated release of therapeutic agents. The most preferred dosage form is a multilayer tablet having an outer layer comprising an H2 blocker and an inner core comprising an NSAID.

The invention also provides a method for increasing compliance in a patient requiring frequent daily dosing of NSAIDs by providing both an acid inhibitor and NSAID in a single convenient, preferably coordinated, unit dosage form, thereby reducing the number of individual doses to be administered during any given period.

Brief Description of the Drawings

Figure 1 is a schematic diagram of a four layer tablet dosage form. There is a naproxen core layer surrounded by a barrier layer. A third, enteric coating, layer delays the release of naproxen sodium until the pH is at a specific level, *e.g.*, above 4. Finally, there is an outer layer that releases an acid inhibitor such as famotidine.

Figure 2 illustrates a three layer dosage form. An acid inhibitor, *e.g.*, famotidine, is released immediately after ingestion by a patient in order to raise the pH of the gastrointestinal tract to above a specific pH, *e.g.*, above 4. The innermost layer contains naproxen. Thus, the dosage form has a naproxen core, an enteric film coat and an acid inhibitor film coat.

Figure 3 illustrates a naproxen sodium pellet which contains a subcoat or barrier coat prior to the enteric film coat.

Detailed Description of the Invention

The present invention is based upon the discovery of improved pharmaceutical compositions for administering NSAIDs to patients. In addition to containing one or more NSAIDs, the compositions include acid inhibitors that are capable of raising the pH of the GI tract of patients. All of the dosage forms are designed for oral delivery and provide for the

coordinated release of therapeutic agents, *i.e.*, for the sequential release of acid inhibitor followed by analgesic.

The NSAIDs used in preparations may be either short or long acting. As used herein, the term "long acting" refers to an NSAID having a pharmacokinetic half-life of at least 2 hours, preferably at least 4 hours and more preferably, at least 8-14 hours. In general, its duration of action will equal or exceed about 6-8 hours. Examples of long-acting NSAIDs are: flurbiprofen with a half-life of about 6 hours; ketoprofen with a half-life of about 2 to 4 hours; naproxen or naproxen sodium with half-lives of about 12 to 15 hours and about 12 to 13 hours respectively; oxaprozin with a half life of about 42 to 50 hours; etodolac with a half-life of about 7 hours; indomethacin with a half life of about 4 to 6 hours; ketorolac with a half-life of up to about 8-9 hours, nabumetone with a half-life of about 22 to 30 hours; mefenamic acid with a half-life of up to about 4 hours; and piroxicam with a half-life of about 4 to 6 hours. If an NSAID does not naturally have a half-life sufficient to be long acting, it can, if desired, be made long acting by the way in which it is formulated. For example, NSAIDs such as acetaminophen and aspirin may be formulated in a manner to increase their half-life or duration of action. Methods for making appropriate formulations are well known in the art (see *e.g.* Remington's Pharmaceutical Sciences, 16th ed., A. Oslo editor, Easton, PA (1980)).

It is expected that a skilled pharmacologist may adjust the amount of drug in a pharmaceutical composition or administered to a patient based upon standard techniques well known in the art. Nevertheless, the following general guidelines are provided:

Indomethacin is particularly useful when contained in tablets or capsules in an amount from about 25 to 75 mg. A typical daily oral dosage of indomethacin is three 25 mg doses taken at intervals during the day. However, daily dosages of up to about 150 mg are useful in some patients.

Aspirin will typically be present in tablets or capsules in an amount of between about 250 mg and 1000 mg. Typical daily dosages will be in an amount ranging from 500 mg to about 10 g.

Ibuprofen may be provided in tablets or capsules of 50, 100, 200, 300, 400, 600, or 800 mg. Daily doses should not exceed 3200 mg. 200 mg - 800 mg may be particularly useful when given 3 or 4 times daily.

Flurbiprofen is useful when in tablets at about from 50 to 100 mg. Daily doses of about 100 to 500 mg, and particularly from about 200 to 300 mg, are usually effective.

Ketoprofen is useful when contained in tablets or capsules in an amount of about 25 to 75 mg. Daily doses of from 100 to 500 mg and particularly of about 100 to 300 mg are typical as is about 25 to 50 mg every six to eight hours.

Naproxen is particularly useful when contained in tablets or capsules in an amount of from 250 to 500 mg. For naproxen sodium, tablets of about 275 or about 550 mg are typically used. Initial doses of from 100 to 1250 mg, and particularly 350 to 800 mg are also used, with doses of about 550 mg being generally preferred.

Oxaprozin may be used in tablets or capsules in the range of roughly 200 mg to 1200 mg, with about 600 mg being preferred. Daily doses of 1200 mg have been found to be particularly useful and daily doses should not exceed 1800 mg or 26 mg/kg.

Etodolac is useful when provided in capsules of 200 mg to 300 mg or in tablets of about 400 mg. Useful doses for acute pain are 200-400 mg every six-eight hours, not to exceed 1200 mg/day. Patients weighing less than 60 kg are advised not to exceed doses of 20 mg/kg. Doses for other uses are also limited to 1200 mg/day in divided doses, particularly 2, 3 or 4 times daily.

Ketorolac is usefully provided in tablets of 1-50 mg, with about 10 mg being typical. Oral doses of up to 40 mg, and particularly 10-30 mg/day have been useful in the alleviation of pain.

Patent Owner Ex. 2005
IPR2015-01344
Page 575 of 613

Nabumetone may be provided in tablets or capsules of between 500 mg and 750 mg. Daily doses of 1500-2000 mg, after an initial dose of 100 mg, are of particular use.

Mefenamic acid is particularly useful when contained in tablets or capsules of 50 mg to 500 mg, with 250 mg being typical. For acute pain, an initial dosage of 1-1000 mg, and particularly about 500 mg, is useful, although other doses may be required for certain patients.

Lornoxicam is provided in tablets of 4 mg or 8 mg. Useful doses for acute pain are 8 mg or 16 mg daily, and for arthritis are 12 mg daily.

One particular group of long acting NSAIDs that may be used are the cyclooxygenase-2 inhibitors. These include: celecoxib, rofecoxib, meloxicam, piroxicam, valdecoxib, parecoxib, etoricoxib, CS-502, JTE-522, L-745,337, or NS398. JTE-522, L-745,337 and NS398 as described, *inter alia*, in Wakatani, *et al.* (*Jpn. J. Pharmacol. 78*:365-371 (1998)) and Panara, *et al.* (*Br. J. Pharmacol. 116*:2429-2434 (1995)). The amount present in a tablet or administered to a patient will depend upon the particular COX-2 inhibitor being used. For example:

Celecoxib may be administered in a tablet or capsule containing from about 100 mg to about 500 mg or, preferably, from about 100 mg to about 200 mg.

Piroxicam may be used in tablets or capsules containing from about 10 to 20 mg.

Rofecoxib will typically be provided in tablets or capsules in an amount of 12.5, 25 or 50 mg. The recommended initial daily dosage for the management of acute pain is 50 mg.

Meloxicam is provided in tablets of 7.5 mg, with a recommended daily dose of 7.5 or 15 mg for the management of osteoarthritis.

Valdecoxib is provided in tablets of 10 or 20 mg, with a recommended daily dose of 10 mg for arthritis or 40 mg for dysmenorrhea.

With respect to acid inhibitors, tablets or capsules may contain anywhere from 1 mg to as much as 1g. Typical amounts for H2 blockers are: cimetidine, 100 to 800 mg/unit dose; ranitidine, 50-300 mg/unit dose; famotidine, 5-100 mg/unit dose; ebrotidine 400 – 800 mg/unit dose; pabutidine 40 mg/unit dose; lafutidine 5–20 mg/unit dose; and nizatidine, 50-600 mg/unit dose. Proton pump inhibitors will typically be present at about 5 mg to 600 mg per unit dose. For example, the proton pump inhibitor omeprazole should be present in tablets or capsules in an amount from 5 to 50 mg, with about 20 mg per unit dosage form being preferred. Other typical amounts are: esomeprazole, 5–100 mg, with about 40 mg per unit dosage form being preferred; lansoprazole, 15-150 mg, with about 30 mg per unit dosage form being preferred; pantoprazole, 10-200 mg, with about 40 mg per unit dosage form being preferred; and rabeprazole, 5-100 mg, with about 20 mg per unit dosage form being preferred.

Making of Pharmaceutical Preparations

The pharmaceutical compositions of the invention include tablets, dragees, liquids and capsules and can be made in accordance with methods that are standard in the art (see, *e.g.*, Remington's Pharmaceutical Sciences, 16th ed., A Oslo editor, Easton, Pa. (1980)). Drugs and drug combinations will typically be prepared in admixture with conventional excipients. Suitable carriers include, but are not limited to: water; salt solutions; alcohols; gum arabic; vegetable oils; benzyl alcohols; polyethylene glycols; gelatin; carbohydrates such as lactose, amylose or starch; magnesium stearate; talc; silicic acid; paraffin; perfume oil; fatty acid esters; hydroxymethylcellulose; polyvinyl pyrrolidone; etc. The pharmaceutical preparations can be sterilized and, if desired, mixed with auxiliary agents such as: lubricants, preservatives, disintegrants; stabilizers; wetting agents; emulsifiers; salts; buffers; coloring agents; flavoring agents; or aromatic substances.

Enteric coating layer(s) may be applied onto the core or onto the barrier layer of the core using standard coating techniques. The enteric coating materials may be dissolved or dispersed in organic or aqueous solvents and may include one or more of the following materials: methacrylic acid copolymers, shellac, hydroxypropylmethcellulose phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose trimellitate, carboxymethylethyl-cellulose, cellulose acetate phthalate or other suitable enteric coating polymer(s). The pH at which the enteric coat will dissolve can be controlled by the polymer or combination of polymers selected and/or ratio of pendant groups. For example, dissolution characteristics of

the polymer film can be altered by the ratio of free carboxyl groups to ester groups. Enteric coating layers also contain pharmaceutically acceptable plasticizers such as triethyl citrate, dibutyl phthalate, triacetin, polyethylene glycols, polysorbates or other plasticizers. Additives such as dispersants, colorants, anti-adhering and anti-foaming agents may also be included.

The Making of Tablet Dosage Forms

Preferably, the combination of an acid inhibitor and an NSAID will be in the form of a bi- or multi-layer tablet. In a bilayer configuration, one portion of the tablet contains the acid inhibitor in the required dose along with appropriate excipients, agents to aid dissolution, lubricants, fillers, etc. The second portion of the tablet will contain the NSAID, preferably naproxen, in the required dose along with other excipients, dissolution agents, lubricants, fillers, etc. In the most preferred embodiment, the NSAID layer is surrounded by a polymeric coating which does not dissolve at a pH of less than 4. The naproxen may be granulated by methods such as slugging, low- or high- shear granulation, wet granulation, or fluidized-bed granulation. Of these processes, slugging generally produces tablets of less hardness and greater friability. Low-shear granulation, high-shear granulation, wet granulation and fluidized-bed granulation generally produce harder, less friable tablets.

Examples

Example 1: Enteric Coated Naproxen Sodium Core and Famotidine Immediate Release

A schematic diagram of a four layer tablet dosage form is shown in Figure 1. The first layer contains naproxen sodium distributed throughout a matrix of pharmaceutically acceptable fillers, excipients, binding agents, disintegrants, and lubricants.

The second layer is a barrier layer which protects the first layer containing naproxen sodium. The barrier film coat is applied by conventional pan coating technology and the weight of the barrier coat may vary from 1% to 3% of the core tablet weight. In particular embodiments, the core naproxen sodium tablet is coated with coating ingredients such as Opaspray® K-1-4210A or Opadry® YS-1-7006 (Colorcon, West Point, PA). Polymer film coating ingredients such as hydroxypropylmethylcellulose 2910 and polyethylene glycol 8000 in a coating suspension may also be used.

The function of the third layer is to prevent the release of naproxen sodium until the dosage form reaches an environment where the pH is above about 4 or 5. The enteric coating does not dissolve in areas of the GI tract where the pH may be below about 4 or 5 such as in an unprotected stomach. Methacrylic acid copolymers are used as the enteric coating ingredient, triethyl citrate and dibutyl phthalate are plasticisers, and ammonium hydroxide is used to adjust the pH of the dispersion. The coating dissolves only when the local pH is above, for example, 5.5 and, as a result, naproxen sodium is released.

The outermost layer contains an "acid inhibitor" in an effective amount which is released from the dosage form immediately after administration to the patient. The acid inhibitor in the present example is a proton pump inhibitor or, preferably the H2 blocker famotidine, which raises the pH of the gastrointestinal tract to above 4. The typical effective amount of famotidine in the dosage form will vary from 5 mg to 100 mg. A typical film coating formulation contains Opadry Clear® YS-1-7006 which helps in the formation of the film and in uniformly distributing famotidine within the fourth layer without tablets sticking to the coating pan or to each other during application of the film coat. Other ingredients may include: plasticisers such as triethyl citrate, dibutyl phthalate, and polyethylene glycol; anti-adhering agents such as talc; lubricating ingredients such as magnesium stearate; and opacifiers such as titanium dioxide. In addition, the pH of the film coating solution can be adjusted to aid in dissolution of the famotidine. The film coating is thin and rapidly releases famotidine for absorption.

Core Tablet Ingredients	**% W/W**	**mg/Tablet**
Naproxen sodium, USP	74.074	500.00
Microcrystalline cellulose, NF (Avicel PH 200)	17.166	115.87
Povidone (K29/32), USP	3.450	23.29
Talc, USP	4.350	29.36
Magnesium Stearate, NF	0.960	6.48
Total	100.00	675.00

Barrier Film Coating Ingredients	% W/W
Opadry Clear® YS-1-7006	5.00
Purified water USP	95.00
Total	100.00

Enteric Coating Dispersion Ingredients	% W/W
Methacrylic Acid Copolymer, NF (Eudragit L-100-55)	7.30
Methacrylic Acid Copolymer, NF (Eudragit L-100)	7.30
Triethyl Citrate, NF	2.95
Dibutyl Phthalate, NF	1.17
Ammonium Hydroxide (30%), NF	0.87
Purified water, USP	80.41
Total	100.00

Famotidine Coating Dispersion Ingredients	% W/W
Famotidine, USP	3.0
Opadry Clear® (YS-1-7006)	5.0
Talc, USP	3.0
Purified Water, USP	89.0
Total	100.0

Example 2: Enteric Coated Naproxen Core and Famotidine Immediate Release

Figure 2 illustrates a three layered dosage form which releases famotidine immediately after ingestion by the patient in order to raise the pH of the gastrointestinal tract to above about 4. The innermost layer contains naproxen uniformly distributed throughout a matrix of pharmaceutically acceptable excipients. These excipients perform specific functions and may serve as binders, disintegrants, or lubricants. A pharmaceutically acceptable enteric coating surrounds the naproxen core. The function of the enteric coat is to delay the release of naproxen until the dosage form reaches an environment where the pH is above about 4. The

coating does not dissolve in the harshly acidic pH of the unprotected stomach. It contains methacrylic acid copolymers which prevent the release of naproxen in the unprotected stomach. Also included are: triethyl citrate, a plasticiser; simethicone emulsion, an anti-foaming agent; and sodium hydroxide which is used to adjust the pH of the dispersion.

The outermost layer contains an "acid inhibitor" in an effective amount which is released from the dosage form immediately after administration to the patient. The acid inhibitor in this example is a proton pump inhibitor or, preferably, the H2 blocker famotidine which raises the pH of the stomach to above 4. A typical film coating formulation contains Opadry Clear® YS-1-7006 which helps in the formation of the film and in uniformly distributing famotidine in the fourth layer without tablets sticking to the coating pan or sticking to each other during application of the film coat. Other ingredients are: plasticisers such as polyethylene glycol 8000; anti-adhering agents such as talc; lubricating ingredients such as magnesium stearate;, and opacifiers such as titanium dioxide. In addition, the pH of the film coating solution can be adjusted to aid in dissolution of the famotidine. The film coating is thin and rapidly releases famotidine for absorption.

Core Tablet Ingredients	**% W/W**	**mg /Tablet**
Naproxen, USP	90.91	500.00
Povidone K-90, USP	2.00	11.00
Starch, USP	2.59	14.25
Croscarmellose Sodium, USP	4.00	22.00
Magnesium Stearate, NF	0.50	2.75
Total	100.00	550.00
Purified Water, USP qs		

Enteric Coating Dispersion Ingredients	**% W/W**
Methacrylic Acid Copolymer Type C, NF (Eudragit L-100-55)	14.5
Talc, USP	3.8
Sodium Hydroxide, NF	0.2
Triethyl Citrate, NF	1.7

Simethicone Emulsion, USP	0.02
Purified Water, USP	79.78
Total	100.00

Famotidine Coating Dispersion Ingredients	**% W/W**
Famotidine, USP	3.0
Opadry Clear® (YS-1-7006)	5.0
Talc, USP	3.0
Purified Water, USP	89.0
Total	100.0

Example 3: Naproxen Controlled Release Core and Famotidine Immediate Release

A trilayer tablet which separates famotidine contained in the film coat from controlled-release naproxen may be used in the present invention. The core tablet of naproxen is formulated using excipients which control the drug release for therapeutic relief from pain and inflammation for 24 hours. Figure 2 shows an example of an appropriate trilayer tablet. In this particular example, naproxen is mixed with a polymeric material, hydroxypropyl-methylcellulose and granulated with water. The granules are dried, milled, and blended with a lubricant, such as magnesium stearate. They are then compacted into tablets.

The controlled-release core tablet of naproxen is film coated with a pharmaceutically acceptable enteric coating. The function of the enteric coat is to delay the release of naproxen until the dosage form reaches an environment where the pH is above about 4. The coating does not dissolve in the extremely acidic pH of the unprotected stomach. The function of methacrylic acid copolymers is to prevent the release of naproxen until the pH of the stomach rises. Triethyl citrate is a plasticiser, simethicone emulsion is a anti-foaming agent, and sodium hydroxide is used to adjust the pH of the dispersion.

The outermost layer contains an "acid inhibitor" which is released from the dosage form immediately after administration to the patient. The acid inhibitor in the present example is a proton pump inhibitor or, preferably, the H2 blocker famotidine which consistently raises the pH of the stomach to above 4. The typical effective amount of

famotidine in the dosage will vary from 5 mg to 100 mg. A typical film coating formulation contains Opadry Blue® YS-1-4215 which is essential for film formation and for the uniform application of famotidine to the core tablet. Polymer film coating ingredients, hydroxypropylmethylcellulose or Opaspray® K-1-4210A (Colorcon, West Point, PA) may also be used. Other ingredients which help in the formation of the film and in the uniform application of famotidine to the core tablet are: plasticisers such as triethyl citrate and dibutyl phthalate; anti-adhering agents such as talc; lubricating ingredients such as magnesium stearate; and opacifiers such as titanium dioxide. In addition, the pH of the film coating solution can be adjusted to aid in dissolution of the famotidine. The film coating is thin and rapidly releases famotidine for absorption.

Core Tablet Ingredients	**% W/W**	**mg/Tablet**
Naproxen, USP	94.00	750
Hydroxypropyl methylcellulose 2208, USP (viscosity 15000 cps)	5.00	39.9
Magnesium Stearate, NF	1.00	7.95
Total	100.00	797.85

Enteric Coating Dispersion Ingredients	**% W/W**
Methacrylic Acid Copolymer Type C, NF (Eudragit L-100-55)	14.5
Talc, USP	3.8
Sodium Hydroxide, NF	0.2
Triethyl Citrate, NF	1.7
Simethicone Emulsion, USP	0.02
Purified Water, USP	79.78
Total	100.00

Famotidine Coating Dispersion Ingredients	**% W/W**
Famotidine, USP	2.0
Opadry Blue® (YS-1-4215)	10.0
Talc, USP	9.0
Purified Water, USP	79.0
Total	100.0

Example 4: Naproxen and Famotidine Controlled Release Core and Famotidine Immediate Release

A trilayer tablet which separates famotidine contained in the film coat from controlled-release naproxen and famotidine may be used in the present invention. The core tablet of naproxen and famotidine is formulated using excipients which control the drug release for therapeutic relief from pain and inflammation for 24 hours. Figure 2 is an example of an appropriate trilayer tablet. In this particular example, naproxen and famotidine are mixed with a polymeric material, hydroxypropylmethylcellulose and granulated with water. The granules are dried, milled, and blended with a lubricant, such as magnesium stearate. They are then compacted into tablets.

The controlled-release core tablet of naproxen and famotidine is film coated with a pharmaceutically acceptable enteric coating. The function of the enteric coat is to delay the release of naproxen until the dosage form reaches an environment where the pH is above about 4. The coating does not dissolve in the extrememly acidic pH of the unprotected stomach. The function of methacrylic acid copolymers is to prevent the release of naproxen in the pH of the stomach rises. Triethyl citrate is a plasticiser, simethicone emulsion is a anti-foaming agent, and sodium hydroxide is used to adjust the pH of the dispersion.

The outermost later contains an "acid inhibitor" which is released from the dosage form immediately after administration to the patient. The acid inhibitor in the present example is a proton pump inhibitor or, preferably, the H2 blocker famotidine which consistently raises the pH of the stomach to above 4. The typical effective amount of famotidine in the dosage will vary from 5 mg to 100 mg. A typical film coating formulation contains Opadry Blue® YS-1-4215 which is essential for film formation and for the uniform application of famotidine to the core tablet. Polymer film coating ingredients, hydroxypropylmethylcellulose or Opaspray® K-1-4210A (Colorcon, West Point, PA) may also be used. Other ingredients which help in the formation of the film and in the uniform application of famotidine to the core tablet are: plasticisers such as triethyl citrate and dibutyl phthalate; anti-adhering agents such as talc; lubricating ingredients such as magnesium stearate; and opacifiers such as titanium dioxide. In addition, the pH of the film coating solution can be adjusted to aid in dissolution of the famotidine. The film coating is thin and rapidly releases famotidine for absorption.

Core Tablet Ingredients	% W/W	mg/Tablet
Naproxen, USP	88.05	500
Famotidine, USP	3.52	20.0
Hydroxypropyl methylcellulose 2208, USP (viscosity 15000 cps)	7.03	39.9
Magnesium Stearate, NF	1.40	7.95
Total	100.00	567.85

Enteric Coating Dispersion Ingredients	% W/W
Methacrylic Acid Copolymer Type C, NF (Eudragit L-100-55)	14.5
Talc, USP	3.8
Sodium Hydroxide, NF	0.2
Triethyl Citrate, NF	1.7
Simethicone Emulsion, USP	0.02
Purified Water, USP	79.78
Total	100.00

Famotidine Coating Dispersion Ingredients	% W/W
Famotidine, USP	2.0
Opadry Blue® (YS-1-4215)	10.0
Talc, USP	9.0
Purified Water, USP	79.0
Total	100.0

Example 5: Enteric Coated Naproxen Sodium Core and Pantoprazole Immediate Release in Film Coat

A schematic diagram of a four layer tablet dosage form is shown in Figure 1. The first layer contains naproxen sodium distributed throughout a matrix of pharmaceutically acceptable fillers, excipients, binding agents, disintegrants, and lubricants.

The second layer is a barrier layer which protects the first layer containing naproxen sodium. The barrier film coat is applied by conventional pan coating technology and the weight of the barrier coat may vary from 1% to 3% of the core tablet weight. In particular

embodiments, the core naproxen sodium tablet is coated with coating ingredients such as Opaspray® K-1-4210A or Opadry® YS-1-7006 (Colorcon, West Point, PA). Polymer film coating ingredients such as hydroxypropylmethylcellulose 2910 and polyethylene glycol 8000 in a coating suspension may also be used.

The third layer is an enteric film coat. It does not dissolve in areas of the GI tract where the pH may be below 4 such as in an unprotected stomach but it dissolves only when the local pH is above about 4. Therefore, the function of the third layer is to prevent the release of naproxen sodium until the dosage form reaches an environment where the pH is above 4. In this example, hydroxypropylmethylcellulose phthalate is the enteric coating ingredient, cetyl alcohol is a plasticiser and acetone and alcohol are solvents.

The fourth layer contains an "acid inhibitor" in an effective amount which is released from the dosage form as soon as the film coat dissolves. The acid inhibitor in this example is a proton pump inhibitor, pantoprazole which raises the pH of the gastrointestinal tract to above 4. The typical effective amount of pantoprazole in the dosage form may vary from 10 mg to 200 mg. The film coat is applied by conventional pan coating technology and the weight of film coat may vary from 4% to 8% of the core tablet weight. Other ingredients are, plasticisers such as triethyl citrate, dibutyl phthalate, anti-adhering agents such as talc, lubricating ingredients such as magnesium stearate, opacifiers such as, titanium dioxide, and ammonium hydroxide to adjust the pH of the dispersion. The film coating is thin and rapidly releases pantoprazole for absorption. Therefore, pantoprazole releases first and then the core erodes and releases naproxen sodium.

Core Tablet Ingredients	**% W/W**	**mg/tablet**
Naproxen sodium, USP	74.075	500.00
Microcrystalline cellulose, NF (Avicel PH 200)	17.165	115.87
Povidone (K29/32), USP	3.450	23.29
Talc, USP	4.350	29.36
Magnesium Stearate, NF	0.960	6.48
Total	100.00	675.00

Naproxen sodium, 50% microcrystalline cellulose and povidone are dry mixed and wet granulated in an appropriate granulator with sufficient purified water. The wet granules are dried, milled, and blended with the remaining 50% microcrystalline cellulose, talc and magnesium stearate. The final granule blend is compressed into tablets.

Barrier Film Coating Ingredients	**%W/W**
Opadry® Clear YS-1-7006	5.00
Purified Water, USP	95.00
Total	100.00

Opadry clear is added slowly to purified water and mixing is continued until Opadry is fully dispersed. The solution is sprayed on to the tablet cores in a conventional coating pan until proper amount of Opadry clear is deposited on the tablets.

Enteric Coating Ingredients	**%W/W**
Hydroxypropyl methylcellulose phthalate, NF	5.5
Cetyl alcohol, NF	0.3
Acetone, NF	66.3
Alcohol, USP	27.9
Total	100.00

Hydroxypropylmethylcellulose phthalate and cetyl alcohol are dissolved in a mixture of alcohol and acetone. The solution is then sprayed on to the tablet bed in proper coating equipment. A sample of the tablets is tested for gastric resistance and the coating stopped if the tablets pass the test.

Pantoprazole Film Coating Ingredients	**%W/W**
Pantoprazole sodium, USP	5.00
Opadry® Clear YS-1-7006	5.00
Sodium carbonate, NF	1.20
Purified Water, USP	88.80
Total	100.00

Pantoprazole sodium is dissolved in purified water containing sodium carbonate in solution. After thorough mixing, Opadry clear is added slowly and mixing is continued until Opadry is fully dispersed. The suspension is sprayed on to the tablet cores in a conventional coating pan until the proper amount of pantoprazole sodium is deposited.

Example 6: Enteric Coated Naproxen Sodium Core and Omeprazole Immediate Release in Film Coat

A schematic diagram of a four layer tablet dosage form is shown in Figure 1. The first layer contains naproxen sodium distributed throughout a matrix of pharmaceutically acceptable fillers, excipients, binding agents, disintegrants, and lubricants.

The second layer is a barrier layer which protects the first layer containing naproxen sodium. The barrier film coat is applied by conventional pan coating technology and the weight of the barrier coat may vary from 1% to 3% of the core tablet weight. In particular embodiments, the core naproxen sodium tablet is coated with coating ingredients such as Opaspray® K-1-4210A or Opadry® YS-1-7006 (Colorcon, West Point, PA). Polymer film coating ingredients such as hydroxypropylmethylcellulose 2910 and polyethylene glycol 8000 in a coating suspension may also be used.

The third layer is an enteric film coat. It does not dissolve in areas of the GI tract where the pH is below 4 such as in an unprotected stomach but it dissolves only when the local pH is above 4. Therefore, the function of the third layer is to prevent the release of naproxen sodium until the dosage form reaches an environment where the pH is above about 4. In this example, hydroxypropylmethylcellulose phthalate is the enteric coating ingredient, cetyl alcohol is a plasticiser and acetone and alcohol are solvents.

The fourth layer contains an "acid inhibitor" in an effective amount which is released from the dosage form as soon as the film coat dissolves. The acid inhibitor in this example is a proton pump inhibitor, omeprazole, which raises the pH of the gastrointestinal tract to above 4. The typical effective amount of omeprazole in the dosage form may vary from 5 mg to 50 mg. The film coat is applied by conventional pan coating technology and the weight of film coat may vary from 4% to 8% of the core tablet weight. Other ingredients are, plasticisers such as triethyl citrate, dibutyl phthalate, anti-adhering agents such as talc, lubricating ingredients such as magnesium stearate, opacifiers such as, titanium dioxide, and

ammonium hydroxide to adjust the pH of the dispersion. The film coating is thin and rapidly releases omeprazole for absorption. Therefore, omeprazole is released first and then the core erodes and releases naproxen sodium.

Core Tablet Ingredients	**% W/W**	**mg/tablet**
Naproxen sodium, USP	74.075	500.00
Microcrystalline cellulose, NF (Avicel PH 200)	17.165	115.87
Povidone (K29/32), USP	3.450	23.29
Talc, USP	4.350	29.36
Magnesium Stearate, NF	0.960	6.48
Total	100.00	675.00

Naproxen sodium, 50% microcrystalline cellulose and povidone are dry mixed and wet granulated in an appropriate granulator with sufficient purified water. The wet granules are dried, milled, and blended with the remaining 50% microcrystalline cellulose, talc and magnesium stearate. The final granule blend is compressed into tablets.

Barrier Film Coating Ingredients	**%W/W**
Opadry® Clear YS-1-7006	5.00
Purified Water, USP	95.00
Total	100.00

Opadry clear is added slowly to purified water and mixing is continued until Opadry is fully dispersed. The solution is sprayed on to the tablet cores in a conventional coating pan until the proper amount of Opadry clear is deposited on the tablets.

Enteric Coating Ingredients	**%W/W**
Methacrylic Acid Copolymer, NF (Eudragit L-100-55)	6.0
Triethyl Citrate, NF	0.6
Talc, USP	3.0
Purified Water, USP	5.0

Isopropyl Alcohol, USP	85.40
Total	100.00

Methacrylic acid copolymer, triethyl citrate, and talc are dissolved in a mixture of isopropyl alcohol and water. The solution is then sprayed on to the tablet bed in a proper coating equipment. A sample of the tablets is tested for gastric resistance and the coating is stopped if the tablets pass the test.

Omeprazole Film Coating Ingredients	**%W/W**
Omeprazole, USP	5.00
Opadry® Clear YS-1-7006	5.00
Purified Water, USP	10.00
Isopropyl Alcohol, USP	80.00
Total	100.00

Omeprazole is dissolved in a purified water and isopropyl alcohol mixture. After thorough mixing, Opadry clear is added slowly and mixing is continued until Opadry is fully dispersed. The suspension is sprayed on to the tablet cores in a conventional coating pan until proper amount of omeprazole is deposited on the tablets.

Example 7: Naproxen Sodium Delayed Release and Omeprazole Immediate Release Capsule

A coordinated delivery dosage may be used to provide fast release of an acid inhibitor, a proton pump inhibitor, omeprazole which raises the pH of the gastrointestinal tract to above 4, and the delayed release of a non-steroidal anti-inflammatory drug, naproxen sodium. Omeprazole granules modify the pH of the stomach such that the drug readily dissolves and is absorbed in the stomach without significant degradation. The typical effective amount of omeprazole in the dosage form may vary from 5 mg to 50 mg. The release of naproxen sodium is delayed by enteric coating.

Omeprazole granules contain an alkalizing excipient such as sodium bicarbonate. Other soluble alkalizing agents such as potassium bicarbonate, sodium carbonate, sodium hydroxide, or their combinations may also be used. The alkalizing agent helps solubilize and protect omeprazole from degradation before its absorption. Sodium lauryl sulfate helps in the wetting of omeprazole. Other surfactants may be used to perform the same function. In the

present example, hydroxypropyl methylcellulose helps in granule formation, sodium starch glycolate is a disintegrant, and magnesium stearate is a lubricant. Other excipients may also be used to perform these functions.

Naproxen sodium pellets as shown in Figure 3 are prepared by the wet massing technique and the conventional extrusion and spheronization process. The excipients used in the formulation are microcrystalline cellulose, and povidone. The pellets after drying and classification are coated with a protective subcoating containing povidone. Other coating ingredients may also be used such as Opaspray K-1-4210A or Opadry YS-1-7006 (trademarks of Colorcon, West Point, PA). Polymer film coating ingredients such as hydroxypropylmethylcellulose 2910 and polyethylene glycol 8000 in a subcoating suspension are also alternatives. Other ingredients are, plasticisers such as triethyl citrate, dibutyl phthalate, anti-adhering agents such as talc, lubricating ingredients such as magnesium stearate, opacifiers such as, titanium dioxide.

The subcoated pellets are enteric coated using enteric coating polymers. In this example, the enteric coating polymer is methacrylic acid copolymer and the plasticizer is dibutyl phthalate which are dissolved in a mixture of acetone and alcohol. The enteric film does not dissolve in the acidic pH but dissolves when the pH in the gut is above about pH 6 and releases naproxen sodium.

Omeprazole Granules	**% W/W**	**mg/capsule**
Omeprazole, USP	12.9	20.00
Sodium Bicarbonate, USP	82.40	127.72
Hydroxypropyl methylcellulose, USP	2.00	3.10
Sodium lauryl sulfate, NF	0.20	0.31
Sodium starch glycolate, NF	2.00	3.10
Magnesium stearate, NF	0.50	0.77
Total	100	100

Hydroxypropylmethylcellulose is dissolved in water, then sodium lauryl sulfate is added and the solution is mixed. Omeprazole, microcrystalline cellulose, and sodium bicarbonate are dry mixed together and granulated with the granulating solution. The

granulation is mixed until proper granule formation is reached. The granulation is then dried, milled, and blended with magnesium stearate.

Pellet Ingredients	**% W/W**	**mg/tablet**
Naproxen sodium, USP	86.80	250.00
Microcrystalline cellulose, NF (Avicel PH 200)	11.10	32.00
Povidone (K90), USP	2.10	6.00
Total	100.00	288.00

Povidone is dissolved in water. Naproxen sodium and microcrystalline cellulose are dry mixed and granulated with povidone solution. The wet mass is mixed until proper consistency is reached. The wet mass is then pressed through an extruder and spheronized to form pellets. The pellets are then dried and classified into suitable particle size range.

Subcoat Ingredients	**% W/W**
Povidone (K29-32), USP	10.00
Alcohol, USP	90.00
Total	100.00

The pellet cores are coated using povidone solution by a conventional coating pan method to a weight gain of 1-2%.

Enteric Coating Ingredients	**% W/W**
Methacrylic Acid Copolymer, NF (Eudragit L-100)	8.20
Diethyl Phthalate, NF	1.70
Acetone, NF	33.30
Isopropyl Alcohol, USP	56.80
Total	100.0

Eudragit L-100 is dissolved in isopropanol and acetone and diethyl phthalate is dissolved. The solution is sprayed on the pellet cores using proper film coating equipment. A sample of the pellets is tested for gastric resistance before stopping the coating process.

Omeprazole fast release granules and naproxen sodium delayed release pellets are blended together and filled into appropriate size capsules to contain 250 mg naproxen sodium and 20 mg omeprazole per capsule.

Example 8: Naproxen Delayed Release and Omeprazole Immediate Release Capsule

The present Example is directed to a coordinated delivery dosage form containing omeprazole and naproxen. The formulation contains 10 mg omeprazole and uses methylcellulose as a binder and croscarmellose sodium as a disintegrant. Naproxen pellets as shown in Figure 3 do not need a subcoating layer and are enteric coated with an aqueous dispersion of methacrylic acid copolymer. Optionally, these pellets could be compressed into a core and film coated with an acid inhibitor and thereby form a bilayer tablet.

Omeprazole Granules	**% W/W**	**mg/capsule**
Omeprazole, USP	6.45	10.00
Sodium Bicarbonate, USP	88.85	137.71
Methylcellulose, USP	2.00	3.10
Sodium lauryl sulfate, NF	0.20	0.31
Croscarmellose sodium, NF	2.00	3.10
Magnesium stearate, NF	0.50	0.78
Total	100	100

Methylcellulose is dissolved in water, then sodium lauryl sulfate is added to the solution and mixed. Omeprazole, microcrystalline cellulose, and sodium bicarbonate are dry mixed together and granulated with the granulating solution. The granulation is mixed until proper granule formation is reached. The granulation is then dried, milled, and blended with magnesium stearate.

Pellet Ingredients	% W/W	mg/tablet
Naproxen, USP	76.22	250.00
Microcrystalline cellulose, NF (Avicel PH 200)	21.78	71.44
Povidone (K90), USP	2.00	6.56
Total	100.00	328.00

Povidone is dissolved in water. Naproxen and microcrystalline cellulose are dry mixed and granulated with povidone solution. The wet mass is mixed until proper consistency is reached. The wet mass is then pressed through an extruder and spheronized to form pellets. The pellets are then dried and classified into a suitable particle size range.

Enteric Coating Ingredients	% W/W
Methacrylic Acid Copolymer, NF (Eudragit L30D 30% dispersion)	15.60
Talc, USP	7.60
Triethyl citrate, NF	1.60
Simethicone Emulsion, USP (Silicone antifoam emulsion SE 2)	0.20
Purified Water, USP	74.80

Eudragit 30D is dispersed in purified water and simethicone emulsion. Talc and triethyl citrate are then dispersed. The suspension is sprayed on the pellet cores using proper film coating equipment. A sample of the pellets is tested for gastric resistance before stopping the coating process. Omeprazole fast release granules and naproxen sodium delayed release pellets are blended together and filled into appropriate size capsules to contain 250 mg naproxen and 10 mg omeprazole per capsule.

Example 9: Clinical Study of the Relationship of Gastric pH to NSAID-induced Gastric Ulcers

Sixty-two subjects were enrolled in a clinical study and randomly assigned to three groups. The following three groups were administered study medication twice daily for five days: (a) 550 mg naproxen sodium (n=10), (b) 40 mg famotidine given with 550 mg of

naproxen or famotidine followed 90 minutes later by 550 mg naproxen, (n=39) or (c) 20 mg omeprazole followed by 550 mg naproxen sodium (n=13). Gastric pH was measured hourly beginning at the time of dosing of the final daily dose of study medication and for 8 – 10 hours thereafter. Subjects had a gastric endoscopy performed at the beginning and on Day 5 prior to the morning dose of study medication to identify gastric and duodenal irritation; no subjects were admitted to the study if gastric irritation was present at the time of initial endoscopy.

Five patients, three (33%) in the naproxen alone group and two (5%) in the famotidine/naproxen group, presented with gastroduodenal ulcers at the end of the study. In the naproxen alone group, the pH was greater than 4 only 4% of the time, and in the famotidine/naproxen group the pH was greater than 4 forty-nine percent of the time during the 8 – 10 hours following naproxen sodium dosing. Additionally, Lanza grade 3 or 4 damage was present in 28% (n=11) of the subjects receiving famotidine/naproxen sodium, and present 100% (n=10) in the naproxen sodium treatment group. Monitoring of gastric acidity on day 5 indicated that patients with Lanza scores of greater than 2 had integrated gastric acidity of greater than 100 mmol-hr./L. Only 20 – 40% of patients with integrated gastric acidity of less than 100 mmol-hr/L had gastric pathology, whereas all patients with integrated gastric acidity greater than 100 mmol-hr/L had pathology.

Example 10. Famotidine and Enteric Coated Naproxen Reduce Gastroduodenal Damage Due to NSAID Therapy

Forty patients are randomized to two groups for a one week study of twice-daily dosing of: 500mg enteric coated naproxen, and 500mg enteric coated naproxen preceded by 40mg famotidine. Endoscopies are conducted on all patients prior to first dosing and on the final day of the study. No subjects have any evidence of gastroduodenal damage at the beginning of the study (at first endoscopy).

At the second endoscopy, Lanza scores for gastroduodenal damage are assessed for all subjects. Subjects in the enteric coated naproxen 500mg group have a lower incidence of grade 3-4 gastroduodenal damage than subjects previously treated with non-enteric coated naproxen 500mg. Importantly, subjects administered 500mg enteric coated naproxen and 40mg famotidine have substantially lower incidence of grade 3 – 4 gastroduodenal damage than subjects who had previously taken naproxen alone (either naked or enteric coated)

which demonstrates the need for and the value of combining acid inhibition with enteric coating to minimize the gastrointestinal damage of NSAID.

All references cited herein are fully incorporated by reference. Having now fully described the invention, it will be understood by those of skill in the art that the invention may be performed within a wide and equivalent range of conditions, parameters and the like, without affecting the spirit or scope of the invention or any embodiment thereof.

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What is Claimed is:

1. A pharmaceutical composition in unit dose form suitable for oral administration to a patient, comprising:

(a) an acid inhibitor present in an amount effective to raise the gastric pH of said patient to at least 3.5 upon the administration of one or more of said unit dosage forms;

(b) a non-steroidal anti-inflammatory drug (NSAID) in an amount effective to reduce or eliminate pain or inflammation in said patient upon administration of one or more of said unit dosage forms;

and wherein said unit dosage form provides for the coordinated release of said acid inhibitor followed by said NSAID.

2. The pharmaceutical composition of claim 1, wherein said acid inhibitor is selected from: a proton pump inhibitor and an H2 blocker.

3. The pharmaceutical composition of claim 2, wherein said acid inhibitor is an H2 blocker selected from the group consisting of: cimetidine; ranitidine; ebrotidine; pabutidine; lafutidine; loxtidine and famotidine.

4. The pharmaceutical composition of claim 3, wherein said H2 blocker is famotidine, present in said unit dosage form in an amount of between 5 mg and 100 mg.

5. The pharmaceutical composition of claim 1, wherein said acid inhibitor is a proton pump inhibitor selected from the group consisting of: omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole.

6. The pharmaceutical composition of claim 5, wherein said proton pump inhibitor is pantoprazole, present in said unit dosage form in an amount of between 10 mg and 200 mg.

7. The pharmaceutical composition of claim 1, wherein said NSAID is a cyclooxygenese-2 (COX-2) inhibitor.

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8. The pharmaceutical composition of claim 7, wherein said COX-2 inhibitor is selected from the group consisting of celecoxib; rofecoxib; meloxicam; piroxicam; valdecoxib, parecoxib, etoricoxib, CS-502, JTE-522; L-745,337; and NS398.

9. The pharmaceutical composition of claim 1, wherein said NSAID is selected from the group consisting of: aspirin; acetaminophen; ibuprofen; flurbiprofen; ketoprofen; lornoxicam; naproxen; oxaprozin; etodolac; indomethacin; ketorolac; and nabumetone.

10. The pharmaceutical composition of claim 9, wherein said NSAID is naproxen present in an amount of between 50 mg and 1500 mg.

11. The pharmaceutical composition of claim 10, wherein said naproxen is present in an amount of between 200 mg and 600 mg.

12. The pharmaceutical composition of claim 1, wherein said unit dosage form is a multilayer tablet.

13. The pharmaceutical composition of claim 12, wherein said unit dosage form is a trilayer tablet having an outer layer of said acid inhibitor and an inner core of said NSAID.

14. The pharmaceutical composition of claim 12, wherein said unit dosage form is a bilayer tablet having an outer layer of said acid inhibitor and an inner core of said NSAID.

15. The pharmaceutical composition of any one of claims 12-14, wherein said tablet has an inner core of said NSAID surrounded by a barrier coating that does not dissolve unless the pH of the surrounding medium is 3.5 or greater.

16. The pharmaceutical composition of any one of claims 12-14, wherein said tablet has an inner core of said NSAID surrounded by a barrier coating that does not dissolve unless the pH of the surrounding medium is 4 or greater.

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17. The pharmaceutical composition of any one of claims 12-14, wherein said tablet has an inner core of said NSAID surrounded by a barrier coating that does not dissolve unless the pH of the surrounding medium is 5 or greater.

18. The pharmaceutical composition of any one of claims 12-14, wherein said tablet has an inner core of said NSAID surrounded by a barrier coating that dissolves at a rate such that said NSAID is not released until the pH of the surrounding medium is 3.5 or greater.

19. The pharmaceutical composition of any one of claims 12-14, wherein said tablet has an inner core of said NSAID surrounded by a barrier coating that dissolves at a rate such that said NSAID is not released until the pH of the surrounding medium is 4 or greater.

20. The pharmaceutical composition of any one of claims 12-14, wherein said tablet has an inner core of said NSAID surrounded by a barrier coating that dissolves at a rate such that said NSAID is not not released until the pH of the surrounding medium is 5 or greater.

21. The phamaceutical composition of claim 1, wherein said unit dosage form is a capsule.

22. A method of treating a patient for pain or inflammation, comprising administering to said patient the pharmaceutical composition of any one of claims 1-14.

23. The method of claim 22, wherein said patient is treated for either osteoarthritis or rheumatoid arthritis.

24. A method of treating a patient for pain or inflammation, comprising:

(a) orally administering to said patient an acid inhibitor at a dose effective to raise the gastric pH of said patient to at least 3.5; and

(b) orally administering to said patient an NSAID that is coated in a polymer that only dissolves at a pH of 3.5 or greater.

25. The method of claim 24, wherein said acid inhibitor is an H2 blocker.

26. The method of claim 25, wherein said H-2 blocker is selected from the group consisting of: cimetidine; ranitidine; ebrotidine; pabutidine; lafutidine; loxtidine and famotidine.

27. The method of claim 26, wherein said H2 blocker is famotidine administered at a dose of between 5 mg and 100 mg.

28. The method of claim 24, wherein said acid inhibitor is a proton pump inhibitor.

29. The method of claim 28, wherein said proton pump inhibitor is selected from the group consisting of: omeprazole, esomeprazole, lansoprazole, rabeprazole and pantoprazole.

30. The method of claim 29, wherein said proton pump inhibitor is pantoprazole administered at a dose of between10 mg and 200 mg.

31. The method of any one of claims 24 - 30, wherein said NSAID is a COX-2 inhibitor selected from the group consisting of: celecoxib; rofecoxib; meloxicam; piroxicam; valdecoxib, parecoxib, etoricoxib, CS-502, JTE-522; L-745,337; and NS398.

32. The method of any one of claims 24 – 30, wherein said NSAID is selected from the group consisting of: aspirin; acetaminophen; ibuprofen; flurbiprofen; ketoprofen; lornoxicam; naproxen; oxaprozin; etodolac; indomethacin; ketorolac; and nabumetone.

33. The method of claim 32, wherein said NSAID is naproxen administered at a dose of between 50 mg and 1500 mg.

34. The method of claim 33, wherein said naproxen is administered at a dose of between 200 mg and 600 mg.

35. The method of claim 24, wherein said acid inhibitor and said NSAID are delivered as part of a single dosage form providing for the coordinated release of therapeutic agents.

36. The method of claim 35, wherein said single dosage form is a bilayer tablet with an outer layer comprising an H2 blocker and an inner core comprising an NSAID.

37. A method of treating a patient for pain or inflammation, comprising:

(a) orally administering to said patient an acid inhibitor at a dose effective to raise the gastric pH of said patient to at least 3.5; and

(b) concurrently administering to said patient an NSAID that is coated in a polymer that dissolves at a rate such that said NSAID is not released until said gastric pH is at 3.5 or higher.

38. The method of claim 37, wherein said acid inhibitor is an H2 blocker.

39. The method of claim 38, wherein said H-2 blocker is selected from the group consisting of: cimetidine; ranitidine; ebrotidine; pabutidine; lafutidine; loxtidine and famotidine.

40. The method of claim 39, wherein said H2 blocker is famotidine administered at a dose of between 5 mg and 100 mg.

41. The method of claim 37, wherein said acid inhibitor is a proton pump inhibitor.

42. The method of claim 41, wherein said proton pump inhibitor is selected from the group consisting of: omeprazole, esomeprazole, lansoprazole, rabeprazole and pantoprazole.

43. The method of claim 42, wherein said proton pump inhibitor is pantoprazole administered at a dose of between 10 mg and 200 mg.

44. The method of any one of claims 37 - 43, wherein said NSAID is a COX-2 inhibitor selected from the group consisting of: celecoxib; rofecoxib; meloxicam; piroxicam; valdecoxib, parecoxib, etoricoxib, CS-502, JTE-522; L-745,337; and NS398.

45. The method of any one of claims 37 – 43, wherein said NSAID is selected from the group consisting of: aspirin; acetaminophen; ibuprofen; flurbiprofen; ketoprofen; lornoxicam; naproxen; oxaprozin; etodolac; indomethacin; ketorolac; and nabumetone.

46. The method of claim 45, wherein said NSAID is naproxen administered at a dose of between 50 mg and 1500 mg.

47. The method of claim 46, wherein said naproxen is administered at a dose of between 200 mg and 600 mg.

48. The method of claim 47, wherein said acid inhibitor and said NSAID are delivered as part of a single dosage form providing for the coordinated release of therapeutic agents.

49. The method of claim 48, wherein said single dosage form is a bilayer tablet with an outer layer comprising an H2 blocker and an inner core comprising an NSAID.

50. A method of improving compliance in patients requiring frequent daily dosages of an acid inhibitor and an NSAID comprising administering said dosages in a coordinated unit dosage form in accordance with claim 1.

Abstract

The present invention is directed to drug dosage forms that release an agent that raises the pH of a patient's gastrointestinal tract, followed by a non-steroidal anti-inflammatory drug. The dosage form is designed so that the NSAID is not released until the intragastric pH has been raised to a safe level. The invention also encompasses methods of treating patients by administering this coordinated release, gastroprotective, antiarthritic/analgesic combination unit dosage form to achieve pain and symptom relief with a reduced risk of developing gastrointestinal damage such as ulcers, erosions and hemorrhages.

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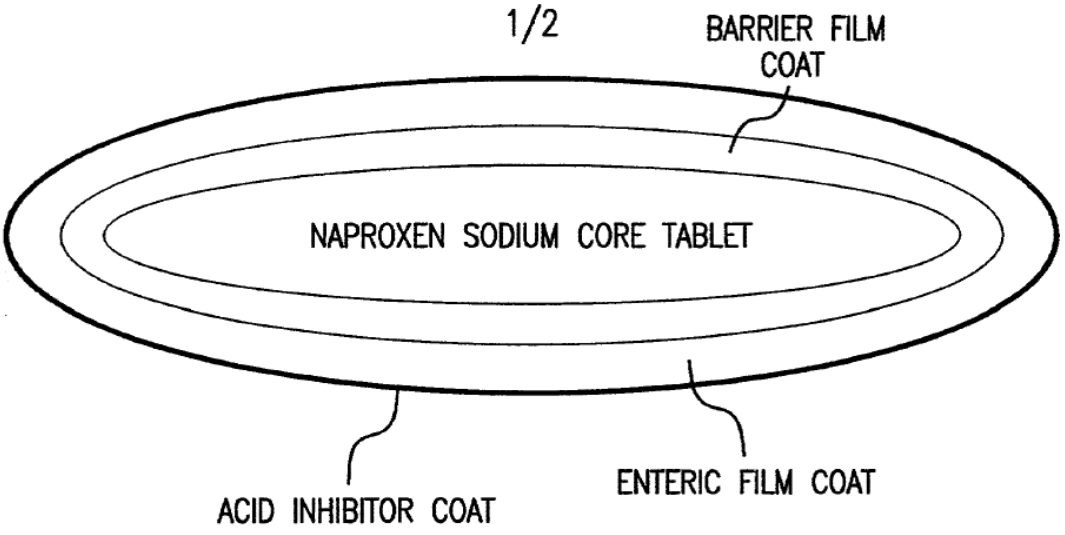

BARRIER FILM COAT
NAPROXEN SODIUM CORE TABLET
ACID INHIBITOR COAT
ENTERIC FILM COAT

FIG.1

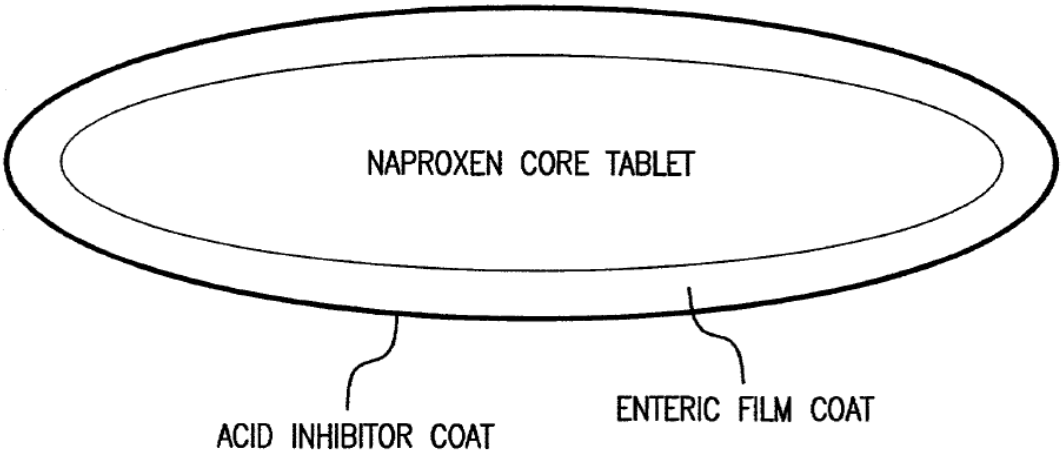

NAPROXEN CORE TABLET
ACID INHIBITOR COAT
ENTERIC FILM COAT

FIG.2

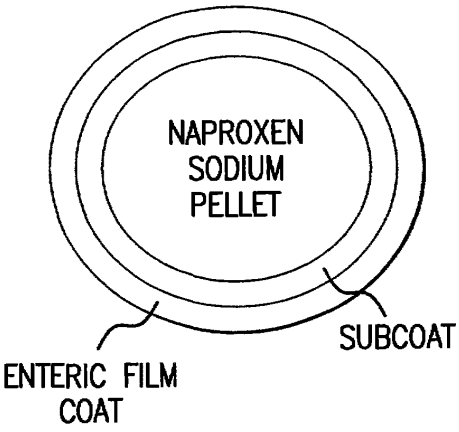


FIG.3

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	John R. Plachetka
Appl. No.:	to be assigned
Filed:	herewith
For:	**Pharmaceutical Compositions for the Coordinated Delivery of NSAIDs**

Commissioner of Patents and Trademarks
Washington, D.C. 20231

DECLARATION (37 C.F.R. § 1.63) AND POWER OF ATTORNEY

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name, and

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the application identified above.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with 37 C.F.R. § 1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119, of any United States provisional applications or foreign application(s) for patent or inventor's certificate or of any PCT International Application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application for patent or inventor's certificate or any PCT International Application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application on which priority is claimed:

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Application Serial No.	Country	Filing Date (Day/Month/Year)	Priority Claimed (Yes/No)
60/294,588	United States	June 1, 2001	Yes

I hereby claim the benefit under Title 35, United States Code, Section 120, of any United States application(s) or PCT International Application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application(s) in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56, which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status (Patented, Pending, Abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I hereby appoint William P. Atkins, Reg. No. 38,821; Guillermo Baeza, Reg. No. 35,056; Jack S. Barufka, Reg. No. 37,087; Paul T. Bowen, Reg.No. 38,009; Brian P. Collins, Reg.No. 43,560; Mark Danielson, Reg.No. 40,580; Henry J. Daley, Reg. No. 42,459; John P. Darling, Reg. No. 44,482; Caroline D. Dennison, Reg. No. 34,494; Samir Elamrfani, Reg. No. 43,601; Stephen C. Glazier, Reg. No. 31,361; Kerry T. Hartman, Reg.No. 41,818; Eric Hernandez, Reg.No. 47,641; Adam R. Hess, Reg. No. 41,835; Thomas P. Hilliard, Reg.No. 40,330; David A. Jakopin, Reg. No. 32,995; Jefffey D. Karceski, Reg. No. 35,914; G. Lloyd Knight, Reg. No. 17,698; Dale S. Lazar, Reg. No. 28,872; Christine H. McCarthy, Reg. No. 41,844; Anthony L. Miele, Reg. No. 34,393; Mark G. Paulson, Reg. No. 30,793; Glenn J. Perry, Reg. No. 28,458; Michael A. Sanzo, Reg. No. 36,912; Brian Siritzky, reg. No. 37,497; Paul L. Sharer, Reg. No. 36,004; George M. Sirilla, Reg. No. 18,221; Robin L. Teskin, Reg.No. 35,030; Roger R. Wise, Reg. No. 31,204; Richard H. Zaitlen, Reg. No. 27,248, all registered to practice before the Patent and Trademark Office, as my attorneys with full power of substitution and revocation to prosecute this application and all divisions and continuations thereof and to transact all business in the Patent and Trademark Office connected therewith and request that all correspondence and telephone communications be directed to the following person(s) at the mailing address and telephone number hereafter given:

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Name: Michael A. Sanzo

Registration No.: 36,912

Address: Pillsbury Winthrop LLP
1600 Tysons Boulevard
McLean, VA 22102

Telephone No.: (703) 905-2173

Signature of Inventor John R. Plachetka _____ Date _____

Residence: 321 Silver Creek Trail
Chapel Hill, North Carolina 27514

Citizenship: United States

Post Office Address: 321 Silver Creek Trail
Chapel Hill, North Carolina 27514

Patent Owner Ex. 2005
IPR2015-01344
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Assignment to POZEN Inc.

Applicant(s):	John R. Plachetka
Appl. No.:	to be assigned
Filed:	herewith
For:	**Pharmaceutical Compositions for the Coordinated Delivery of NSAIDs**

As a below-named inventor, I hereby declare that:

My post office address is as stated below under my signature and I am named as inventor of the inventions or discoveries (herein INVENTIONS) as described in the patent application (herein APPLICATION) identified above. In view of valuable consideration, receipt of which is hereby acknowledged, I do hereby assign and transfer unto POZEN Inc. (hereinafter "POZEN"), a corporation organized under the laws of the State of Delaware, its successors and assigns, my entire interest in and the full and exclusive right to the INVENTIONS, the APPLICATION and all related applications (including all divisions, reissues, continuations, and extensions thereof) and all counterparts in other countries, and any and all Letters Patent (and certificates of invention or similar certificates) (herein PATENTS) which may be granted based upon the INVENTIONS or the APPLICATION or related applications or counterparts in other countries; said transfer and assignment being applicable throughout the world. I hereby authorize and request officials of patent offices in any and all countries of the world to issue any and all of the PATENTS, when granted, to POZEN, its successors and assigns, as the assignee of my entire right, title, and interest in and to the same. I agree that I will communicate to POZEN, or its representatives, any facts known to me respecting the invention; testify in any legal proceedings; sign all lawful papers; execute all divisional, continuation, substitution, renewal, and reissue applications; execute all necessary assignment papers to cause any and all of the PATENTS to be issued to POZEN; make all rightful oaths; and generally do everything possible to aid POZEN,

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its successors and assigns, to obtain and enforce proper protection for the INVENTION in any and all countries throughout the world.

Signature of Inventor John R. Plachetka _____ Date _____

Address: 321 Silver Creek Trail
Chapel Hill, North Carolina 27514

EFS Web 2.2.5

PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 1, 2001

Application or Docket Number: 10158214

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS	50	
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	122 minus 20=	* 92
INDEPENDENT CLAIMS	3 minus 3 =	*
MULTIPLE DEPENDENT CLAIM PRESENT		☒

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐		OR	OTHER THAN SMALL ENTITY	
RATE	FEE		RATE	FEE
BASIC FEE	370.00	OR	BASIC FEE	740.00
X$ 9=		OR	X$18=	1656.00
X42=		OR	X84=	
+140=		OR	+280=	280
TOTAL		OR	TOTAL	2676.00

CLAIMS AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
***If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

FORM PTO-875 (Rev. 8/01) *U.S Government Printing Office: 2001 — 484-484/59268 Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 1, 2001

Application or Docket Number

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS		
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	minus 20=	*
INDEPENDENT CLAIMS	minus 3 =	*
MULTIPLE DEPENDENT CLAIM PRESENT		☐

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐		OR	OTHER THAN SMALL ENTITY	
RATE	FEE		RATE	FEE
BASIC FEE	370.00	OR	BASIC FEE	740.00
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL		OR	TOTAL	

CLAIMS AS AMENDED - PART II

AMENDMENT A	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
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TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
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X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
***If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

FORM PTO-875 (Rev. 6/01) *U.S. Government Printing Office: 2001 — 484-484/59268 Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

CLAIMS ONLY

SERIAL NO. 10/858,216 | FILING DATE

APPLICANT(S)

CLAIMS

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
1	1					
2		1				
3		1				
4		1				
5		1				
6		1				
7		1				
8		1				
9		1				
10		1				
11		1				
12		1				
13		1				
14		1				
15		3				
16		3				
17		3				
18		3				
19		3				
20		3				
21		1				
22		0				
23		0				
24	1					
25		1				
26		1				
27		1				
28		1				
29		1				
30		1				
31		1				
32		1				
33		1				
34		1				
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37	1					
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41		1				
42		1				
43		1				
44		1				
45		1				
46		1				
47		1				
48		1				
49		1				
50		1				
TOTAL IND.	3					
TOTAL DEP.	119					
TOTAL CLAIMS	122					

	*		*		*	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
51						
52						
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96						
97						
98						
99						
100						
TOTAL IND.						
TOTAL DEP.						
TOTAL CLAIMS						

* MAY BE USED FOR ADDITIONAL CLAIMS OR AMENDMENTS

FORM PTO-2022 (1-96)

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

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