

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE  
PROVISIONAL APPLICATION COVER SHEET

The Assistant Commissioner for Patents  
Washington, DC 20231

Sir:

This is a request for filing a PROVISIONAL APPLICATION under 37 C.F.R. § 1.53(b)(2).

[X] This application is being hand-delivered to the U.S. PTO. Please date stamp the enclosed prepaid postcards and return as soon as possible.

DOCKET NUMBER: 71896/279336

INVENTOR(s)/APPLICANT(s):

Last Name: Plachetka  
First Name: John  
Middle Initial: R.  
Residence: 321 Silver Creek Trail  
Chapel Hill, North Carolina 27514  
Citizenship: United States

TITLE OF THE INVENTION: **Pharmaceutical Compositions for the Coordinated  
Delivery of NSAIDs**

CORRESPONDENCE ADDRESS: Michael A. Sanzo  
PILLSBURY WINTHROP LLP  
1100 New York Avenue, N.W.  
Ninth Floor – East Tower  
Washington, DC 20005-3918  
Telephone: (202) 861-3020; Fax: (202) 822-0944

ENCLOSED APPLICATION PARTS:

1.	Specification	Number of Pages: 15 (Numbered as pages 1-15)
2.	Claims	Number of Pages: 3 (Numbered as pages 16-18)
3.	Abstract	Number of Pages: 1 (Numbered as page 19)
4.	Drawings	Number of Sheets: 3 (Labeled as Figures 1-4)

**Small Entity Status is claimed. Our check in the amount of \$75.00 representing the filing fee for this application is attached. The Commissioner is hereby authorized to charge any fee deficiency or credit any overpayment to our Deposit Account No. 03-3975.**

The invention was not made by an agency of the United States Government or under a contract with an agency of the United States Government.

Respectfully submitted,

PILLSBURY WINTHROP LLP

Date:

June 1, 2001

Michael A. Sanzo  
Michael A. Sanzo  
Reg. No. 36,912

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**  
**PROVISIONAL APPLICATION COVER SHEET**



The Assistant Commissioner for Patents  
 Washington, DC 20231

Sir:

This is a request for filing a PROVISIONAL APPLICATION under 37 C.F.R. § 1.53(b)(2).

[X] This application is being hand-delivered to the U.S. PTO. Please date stamp the enclosed prepaid postcards and return as soon as possible.

DOCKET NUMBER: 71896/279336

INVENTOR(s)/APPLICANT(s):

Last Name: Plachetka  
 First Name: John  
 Middle Initial: R.  
 Residence: 321 Silver Creek Trail  
 Chapel Hill, North Carolina 27514  
 Citizenship: United States

TITLE OF THE INVENTION: **Pharmaceutical Compositions for the Coordinated  
 Delivery of NSAIDs**

CORRESPONDENCE ADDRESS: Michael A. Sanzo  
 PILLSBURY WINTHROP LLP  
 1100 New York Avenue, N.W.  
 Ninth Floor – East Tower  
 Washington, DC 20005-3918  
 Telephone: (202) 861-3020; Fax: (202) 822-0944

ENCLOSED APPLICATION PARTS:

1.	Specification	Number of Pages: 15 (Numbered as pages 1-15)
2.	Claims	Number of Pages: 3 (Numbered as pages 16-18)
3.	Abstract	Number of Pages: 1 (Numbered as page 19)
4.	Drawings	Number of Sheets: 3 (Labeled as Figures 1-4)

Small Entity Status is claimed. Our check in the amount of \$75.00 representing the filing fee for this application is attached. The Commissioner is hereby authorized to charge any fee deficiency or credit any overpayment to our Deposit Account No. 03-3975.

The invention was not made by an agency of the United States Government or under a contract with an agency of the United States Government.

Respectfully submitted,

PILLSBURY WINTHROP LLP

Date: June 1, 2001

Michael A. Sanzo  
 Michael A. Sanzo  
 Reg. No. 36,912

## Pharmaceutical Compositions for the Coordinated Delivery of NSAIDs

### 5 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  
10 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 the 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 co-administered 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); U.S. 5,204,118; U.S. 5,417,980; U.S. 5,466,436; and U.S. 5,037,815).  
15  
20

In general, more potent and longer lasting acid inhibitors, such as proton pump inhibitors, have been found to be more protective during chronic administration than shorter acting agents, *e.g.*, 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 the mucosa is most vulnerable, at the end of the dosing interval (least amount of acid inhibition)  
25 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.  
30

Although longer lasting agents, such as proton pump inhibitors, 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)). Intragastric pH rises particularly slowly with the first dose in a course of treatment since this class of drugs must be enteric coated to avoid destruction by stomach acid. (*Aliment. Pharmacol. Ther.* 14:963-978 (2000)). As a result absorption is delayed for several hours. Therefore, despite the proven reduction in gastroduodenal lesions with the concomitant administration of proton pump inhibitors during many weeks of NSAID therapy, there are no data indicating that this benefit occurs with concomitant dosing of shorter duration, especially with just several days dosing. 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)).

Attempts to develop NSAIDs that are inherently safer 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 addition, the COX-2 inhibitors may not be as effective as other NSAIDs at relieving 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, p C1)).

Another approach has involved the concomitant administration of a cytoprotective agent with an NSAID. 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, including, in the case of pregnant women, potential damage to the fetus.

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, a completely acceptable solution has not yet been found.

## 5 **Summary of the Invention**

The present invention is based upon the discovery of a new method for reducing the risk of side effects in people taking NSAIDs for pain relief and for other conditions. In this method, the delivery of an acid inhibitor and NSAID are coordinated in such a manner that the gastric pH of patients is raised prior to the exposure of mucosal tissue to NSAID. Thus, 10 either short or long acting acid inhibitors can be effectively used and there is no need to maintain an abnormally elevated GI pH for a prolonged period of time.

In its first aspect, the invention is directed to a pharmaceutical composition in unit dose 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 4.0 when one or more unit dosage forms are administered. The term "acid inhibitor" refers to agents that increase the pH in the GI tract of a patient. These may take the form of proton pump inhibitors or, preferably, H-2 blockers such as cimetidine, ranitidine, ebrotidine, pabutidine, 15 lafutidine, loxidine or famotidine. The most preferred acid inhibitor is famotidine present in dosage forms in an amount of between 5 mg and 100 mg.

The pharmaceutical composition also contains a non-steroidal anti-inflammatory drug in an amount effective to reduce or eliminate pain. The NSAID may be a COX-2 inhibitor such as celecoxib, rofecoxib, meloxicam, piroxicam, valdecoxib, parecoxib, etoricoxib, CS- 25 502, JTE-522, L-745,337 or NS398. Alternatively, the NSAID may be aspirin, acetaminophen, ibuprofen, flurbiprofen, ketoprofen, naproxen, oxaprozin, etodolac, indomethacin, ketorolac, nabumetane, 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, 30 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 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. One of the main distinguishing characteristics of these dosage forms is that they provide for coordinated drug release, *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 pH of the surrounding medium is 4.0 or greater. Alternatively, the inner core may dissolve at lower pHs, but be designed to dissolve at a rate such that naproxen is not released until after the pH of the gastrointestinal tract has risen to 4.0 or higher. Thus, NSAID is not released until mucosal tissue has been protected from ulcer formation.

The invention includes methods of treating a patient for pain and other conditions by administering the pharmaceutical compositions described above. Although the method may be used for any condition in which an NSAID is effective for pain relief, 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 by orally administering an acid inhibitor at a dose effective to raise a patient's gastric pH to at least 4.0. The patient is also administered an analgesic that has been coated in a polymer that only dissolves at a pH of 4.0 or greater or which dissolves at a rate that is slow enough to prevent NSAID release until after the pH has been raised. Preferably, the acid inhibitor is an H-2 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 dosage form which provides for the coordinated release of therapeutic agents. The most preferred dosage form is a bilayer tablet having an outer layer comprising an H-2 blocker and an inner core comprising an NSAID.

### 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 dosage form reaches the small intestine where the pH is above 4.0. Finally, there is an outer layer that releases an acid inhibitor such as famotadine.

Figure 2 illustrates a three layer dosage form. An acid inhibitor, *e.g.*, famotadine, is released immediately after ingestion by a patient in order to raise the pH of the gastrointestinal tract to above 4.0. The innermost layer contains naproxen.

Figure 3 is an example of a bilayer tablet that can be used in the present treatment method. Naproxen is mixed with excipients and granulated with water. The granules are dried, milled, and blended with a lubricant. They are then compacted into tablets.

Figure 4 illustrates a trilayer tablet which separates famotidine contained in the film coat from a naproxen sodium core. The dosage form has a naproxen core, a barrier film coat and an acid inhibitor 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, nabumetane 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 analgesic 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, analgesics 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, 16<sup>th</sup> 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 may be of help:

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.

Nabumetane 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.

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.

With respect to acid inhibitors, tablets or capsules may contain anywhere from 1 mg to as much as 1 g. Typical amounts for H-2 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 10 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 40 to 500 mg. Other typical amounts are: esomeprazole, 10-200 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, 16<sup>th</sup> 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.

### 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 4.0. 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 breakable 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 delay the release of naproxen sodium until the dosage form reaches the small intestine where the pH is above 4.0. The enteric coating does not dissolve in the acidic pH of the stomach. However, the coating dissolves in the upper gut at a pH above 4.5 and, as a result, naproxen sodium is released. 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. Other materials for enteric coating are ammonio methacrylate copolymer, shellac, hydroxypropylmethylcellulose phthalate, polyvinyl acetate phthalate, and cellulose acetate phthalate.

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 H-2 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 20 mg to 50 mg. A combination of a methacrylic acid copolymer dispersion (Eudragit L30 D-55) and hydroxypropylmethylcellulose is essential for the application of the fourth layer to the third layer. Other ingredients help 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. These ingredients include: plasticisers such as triethyl citrate, dibutyl phthalate, and polyethylene glycol; 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 famotidine for absorption.

<b>Core Tablet Ingredients</b>	<b>% W/W</b>	<b>mg/Tablet</b>
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

<b>Barrier Film Coating Ingredients</b>	<b>% W/W</b>
Opadry Clear® YS-1-7006	5.00
Purified water USP	95.00
	-----
Total	100.00

**Enteric Coating Dispersion**

<b>Ingredients</b>	<b>% W/W</b>
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**

<b>Ingredients</b>	<b>% W/W</b>
Famotidine, USP	5.00
Hydroxypropylmethylcellulose, USP	6.85
Methacrylic Acid Copolymer Dispersion, NF (Eudragit L30 D-55)	20.00
Polyethylene glycol 8000, NF	2.25
Titanium Dioxide, USP	7.50
Talc, USP	9.00
Magnesium Stearate, NF	3.00
Red Iron Oxide	0.40
Simethicone Emulsion, USP	0.02
Purified Water, USP	45.98
	-----
Total	100.00

**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 4.0. 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 tablet. The function of the enteric coat is to delay the release of naproxen until the dosage form reaches the small intestine where the pH is above 4.0. The coating does not dissolve in the acidic pH of the stomach. The function of methacrylic acid copolymers is to prevent the release of naproxen in the acidic pH of the stomach. Triethyl citrate is a plasticiser, simethicone emulsion is a anti-foaming agent, and sodium hydroxide is used to adjust the pH of the dispersion. Other materials for enteric

coating are ammonio methacrylate copolymer, shellac, hydroxypropylmethylcellulose phthalate, polyvinyl acetate phthalate, and cellulose acetate phthalate.

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 H-2 blocker famotidine which raises the pH of the gastrointestinal tract to above 4. The typical effective amount of famotidine in the dosage form may will from 20 mg to 50 mg. A combination of methacrylic acid copolymer dispersion (Eudragit L30 D55) and hydroxypropylmethylcellulose is essential for uniform application of the famotidine layer to the enteric coat. Other ingredients help 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. These 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. The film coating is thin and rapidly releases famotidine for absorption.

<b>Core Tablet Ingredients</b>	<b>% W/W</b>	<b>mg /Tablet</b>
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		

<b>Enteric Coating Dispersion Ingredients</b>	<b>% W/W</b>
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

<b>Famotidine Coating Dispersion Ingredients</b>	<b>% W/W</b>
Famotidine, USP	2.00
Hydroxypropylmethylcellulose, USP	5.00

	Methacrylic Acid Copolymer Dispersion, NF (Eudragit L30 D-55)	20.00
	Polyethylene glycol 8000, NF	2.25
	Titanium Dioxide, USP	7.50
5	Talc, USP	9.00
	Magnesium Stearate, NF	3.00
	Iron Oxide	0.40
	Simethicone Emulsion USP	0.02
10	Purified Water, USP	50.83
		-----
	Total	100.00

### Example 3: Naproxen Controlled Release Core and Famotidine Immediate Release

A bilayer 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 3 is an example of an appropriate bilayer 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 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 H-2 blocker famotidine which raises the pH of the gastrointestinal tract to above 4. The typical effective amount of famotidine in the dosage will vary from 20 mg to 50 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. The film coating is thin and rapidly releases famotidine for absorption.

<b>Core Tablet Ingredients</b>	<b>% W/W</b>	<b>mg/Tablet</b>
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

**Famotidine Coating Dispersion Ingredients**

	<b>% W/W</b>
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 Sodium Core and Famotidine Immediate Release**

Figure 4 illustrates a trilayered tablet which separates famotidine contained in the film coat from a naproxen sodium core. The naproxen sodium is distributed throughout a matrix of pharmaceutically acceptable fillers, excipients, binding agents, disintegrants, and lubricants and is granulated with water. The granules are dried, milled, and blended with a lubricant such as magnesium stearate. They are then compacted into tablets. 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 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 contains an "acid inhibitor" present in an effective amount and which is released from the dosage form immediately after administration to a patient. The acid inhibitor in the present example is a proton pump inhibitor or, preferably, the H-2 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 20 mg to 50 mg. A typical film coating formulation contains Opadry Clear® YS-1-7006 which is essential for film formation and for the uniform application of famotidine to the core tablet. Polymer film coating ingredients hydroxypropylmethylcellulose and Opaspray® K-1-4210A may also be used.

Other ingredients which help in the formation of the film and in 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. The film coating is thin and rapidly releases famotidine for absorption.

<b>Core Tablet Ingredients</b>	<b>% W/W</b>	<b>mg/Tablet</b>
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
Purified Water, USP qs		

<b>Barrier Film Coating Ingredients</b>	<b>% W/W</b>
Opadry Clear® (YS-1-7006)	5.0
Purified water USP	95.0
	-----
Total	100.0

<b>Famotidine Coating Dispersion Ingredients</b>	<b>% W/W</b>
Famotidine, USP	3.0
Opadry Clear® (YS-1-7006)	5.0
Talc, USP	3.0
Purified Water, USP	89.0
	-----
Total	100.0

***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 4 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 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 H-2 blocker.
3. The pharmaceutical composition of claim 2, wherein said acid inhibitor is an H-2 blocker selected from the group consisting of: cimetidine; ranitidine; ebrotidine; pabutidine; lafutidine; loxidine and famotidine.
4. The pharmaceutical composition of claim 3, wherein said H-2 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 NSAID is a cyclooxygenase-2 (COX-2) inhibitor.
6. The pharmaceutical composition of claim 5, 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.
7. The pharmaceutical composition of claim 1, wherein said NSAID is selected from the group consisting of: aspirin; acetaminophen; ibuprofen; flurbiprofen; ketoprofen; naproxen; oxaprozin; etodolac; indomethacin; ketorolac; and nabumetane.

8. The pharmaceutical composition of claim 7, wherein said NSAID is naproxen present in an amount of between 50 mg and 1500 mg.
9. The pharmaceutical composition of claim 8, wherein said naproxen is present in an amount of between 200 mg and 600 mg.
10. The pharmaceutical composition of claim 1, wherein said unit dosage form is a multilayer tablet.
11. The pharmaceutical composition of claim 10, wherein said unit dosage form is a bilayer tablet having an outer layer of said acid inhibitor and an inner core of said NSAID.
12. The pharmaceutical composition of either claim 10 or claim 11, 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 4.0 or greater.
13. A method of treating a patient for pain, comprising administering to said patient the pharmaceutical composition of claim 1.
14. The method of claim 13, wherein said patient is treated for either osteoarthritis or rheumatoid arthritis.
15. A method of treating a patient for pain, 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 4.0; and
  - (b) orally administering to said patient an analgesic that is coated in a polymer that only dissolves at a pH of 4.0 or greater.
16. The method of claim 15, wherein said acid inhibitor is an H-2 blocker.
17. The method of claim 16, wherein said H-2 blocker is selected from the group consisting of: cimetidine; ranitidine; ebrotidine; pabutidine; lafutidine; loxidine and famotidine.

18. The method of claim 17, wherein said H-2 blocker is famotidine administered at a dose of between 5 mg and 100 mg.

5 19. The method of any one of claims 15-18 wherein said analgesic is an NSAID.

20. The method of claim 19, 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.

10

21. The method of claim 19, wherein said NSAID is selected from the group consisting of: aspirin; acetaminophen; ibuprofen; flurbiprofen; ketoprofen; naproxen; oxaprozin; etodolac; indomethacin; ketorolac; and nabumetane.

15

22. The method of claim 21, wherein said NSAID is naproxen administered at a dose of between 50 mg and 1500 mg.

20

23. The method of claim 22, wherein said naproxen is administered at a dose of between 200 mg and 600 mg.

25

24. The method of claim 15, wherein said inhibitor and said analgesic are delivered as part of a single dosage form providing for the coordinated release of therapeutic agents.

25 25. The method of claim 24, wherein said single dosage form is a bilayer tablet with an outer layer comprising an H-2 blocker and in inner core comprising an NSAID.

### Abstract

The present invention is directed to drug dosage forms that sequentially release an agent that raises the pH of a patient's gastrointestinal tract, followed by a non-steroidal anti-inflammatory drug. The invention also encompasses methods of treating patients for pain by administering an NSAID under conditions in which there is a reduced risk of a patient developing gastrointestinal ulcers.

TOPTOP TOPTOP

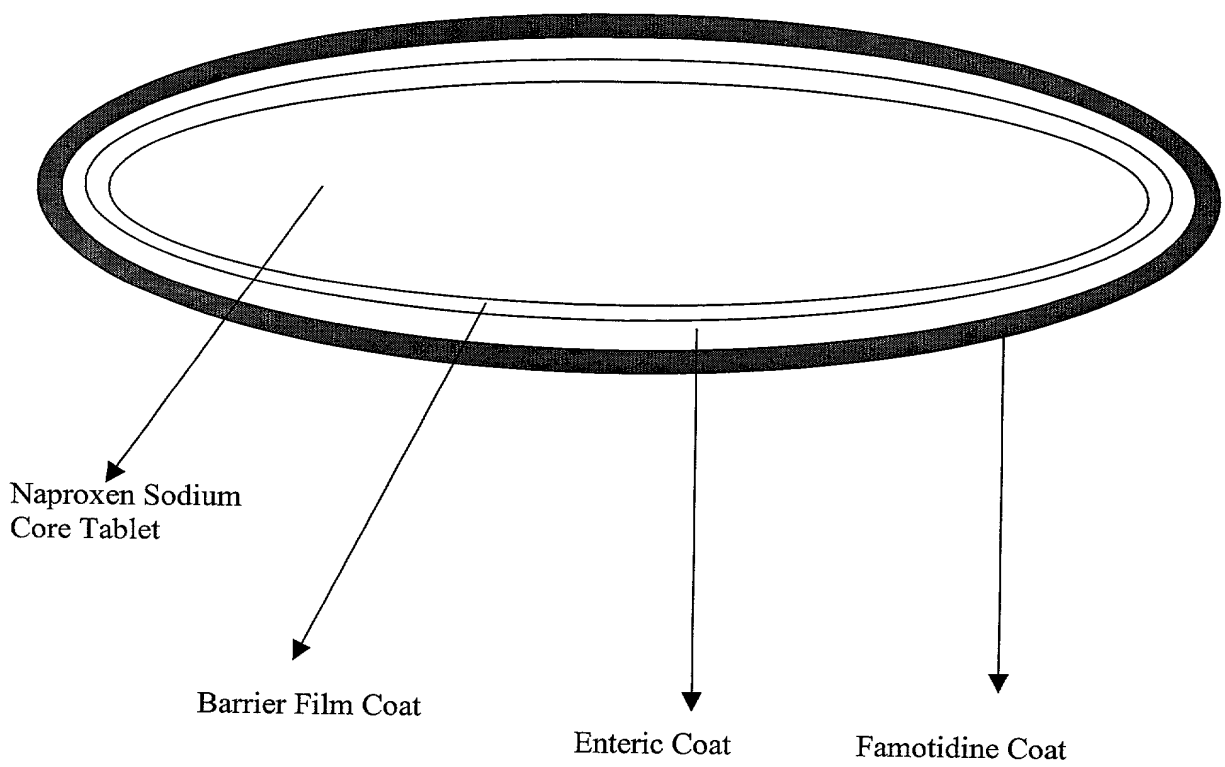


Figure 1

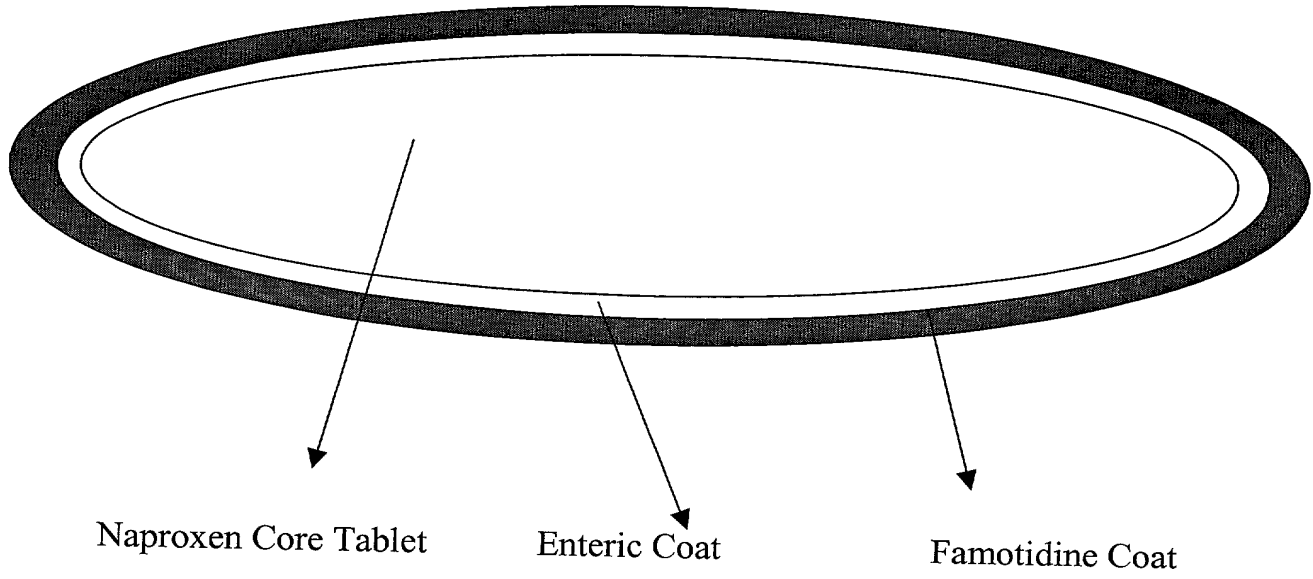


Figure 2

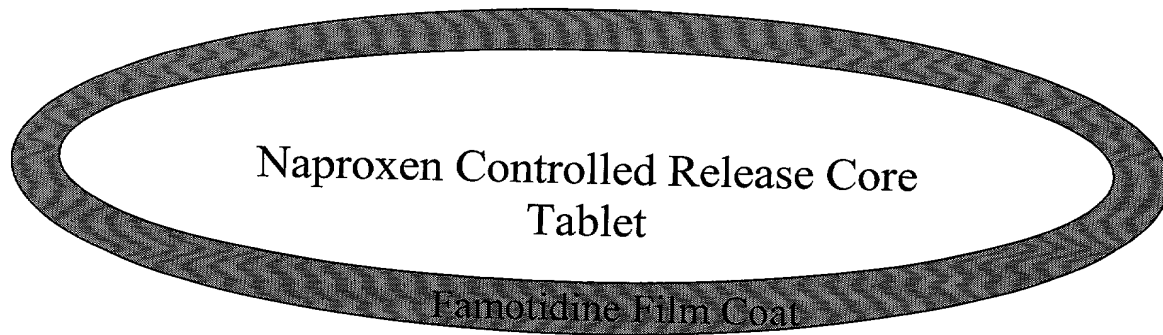


Figure 3

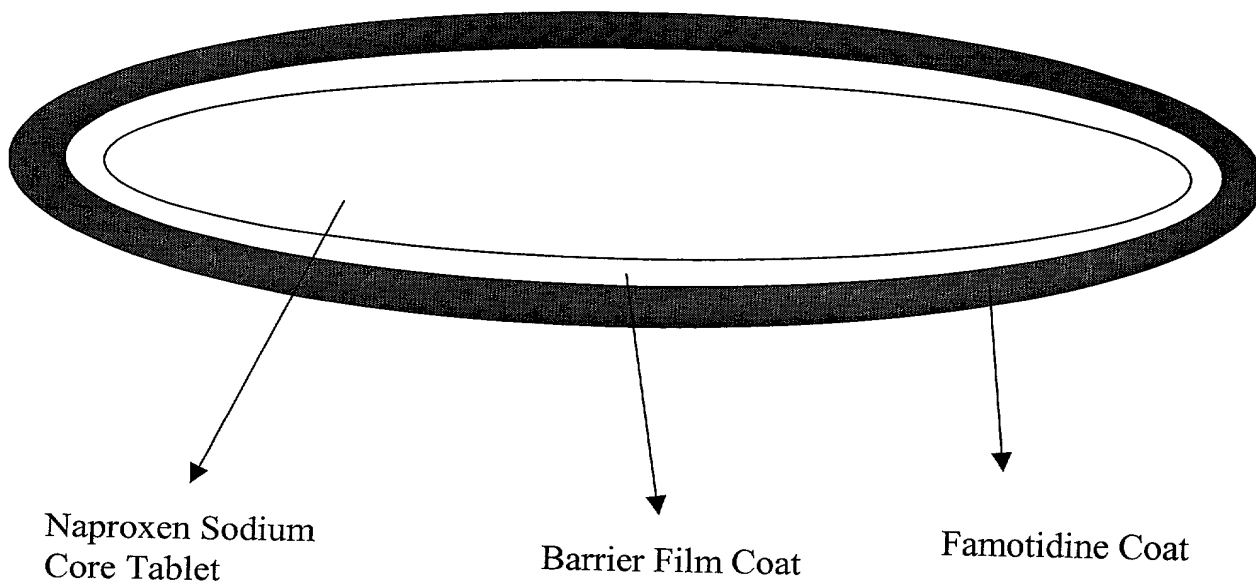


Figure 4