

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

MEDA PHARMACEUTICALS, INC. and
CIPLA LTD.

Plaintiff,

v.

APOTEX, INC. and APOTEX CORP.

Defendant.

Civil Action No. 1:14-cv-01453-LPS

EXPERT REPORT OF RAMPRAKASH GOVINDARAJAN, PH.D.

**PLAINTIFFS'
TRIAL EXHIBIT
PTX1664**

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I. INTRODUCTION

1. My name is Ramprakash Govindarajan, Ph.D. As detailed in my current *curriculum vitae*, which is attached to this declaration as Appendix A, I became Director of Preformulation at the University of Iowa Pharmaceuticals in 2015. I am also a Clinical Assistant Professor at the College of Pharmacy, University of Iowa.

2. I obtained my Ph.D in Pharmaceutics from the University of Mumbai in 2002. After that, I was a Research Associate in Pharmaceutics at the University of Minnesota until 2006. From 2006 to 2015, I worked in various product development roles at GlaxoSmithKline.

3. Throughout my career, I have had experience conducting experiments similar to the one described in this report, including making pharmaceutical formulations.

4. I have never testified as an expert witness or prepared an expert report in connection with litigation. A list of all my publications from the last 18 years is included in my *curriculum vitae*.

5. I have rendered all services in this case as an independent consultant. Apotex has compensated me for these services at in the amount of \$8,500. If additional testimony is required of me, I will be compensated at a rate of \$250/hour. My compensation does not depend on the the opinions formed in this Report or the outcome of this litigation.

6. If called to testify, I am prepared to testify regarding the results of my experiment as reported in this report and the attached documents. I am also prepared to testify about the methods I used and the research I conducted in obtaining those results.

II. SUMMARY OF WORK

7. Apotex retained me to formulate the composition in “Example III” of EP 0780127 (“Cramer”) (attached as Appendix B). To make the formulation, I was directed to follow any instructions or guidance included in the document. To the extent the Cramer reference did not

expressly provide information I needed to formulate, I was directed to proceed as an ordinarily skilled pharmaceutical formulator would have proceeded in June 2002 after reading Cramer. I was directed not to take any steps or use any equipment that was not known and readily available to an ordinarily skilled pharmaceutical formulator in 2002. Cramer was the only document given to me by Apotex's counsel.

8. I was not told what outcome(s) to try to obtain, or what outcome would be helpful to Apotex or their opponent in this litigation. I have not reviewed any patent asserted in this litigation.

9. If I was able to make a pharmaceutical formulation as described in Example III in Cramer, I was asked to make the following observations:

- a. Observe whether Example III forms a suspension, solution, or something else.
 - i. If Example 3 does form a suspension, observe whether that suspension settles.
 - 1. If it settles, observe whether it is difficult to re-suspend.
 - 2. If it settles, opine on whether the settling is unacceptable for a pharmaceutical product.
- b. Measure the osmolality in mOsm/kg.
- c. Put the resulting composition in a nasal pump with a suitable actuator. Observe if the composition comes out as a spray, a jet, or something else.

10. I was asked to record my work and the above observations/experimental results.

III. RESULTS AND OBSERVATIONS

11. The laboratory notebook entries reflecting the work I did are attached as Exhibit C.

12. I prepared three batches of the formulation in Example III during the formulation process. I conducted my final testing and made my final observations using Batch 1345-011. My laboratory notebook records the steps I took to make each batch, as well as the ingredient and equipment I used. I am prepared to discuss each of those steps if asked to do so, and I incorporate the contents of my lab notebook to this report as if set forth herein.

13. I concluded that Cramer Example III is a suspension that would be acceptable as a pharmaceutical product. There was some settling, but no settling or sedimentation in the product that would make it pharmaceutically unacceptable.

14. I further concluded that the product could be delivered as a fine spray using a nasal spray pump. I took two videos of the mist produced by Batch 1345-011 when actuated in a nasal pump with a suitable actuator. Those videos are attached as Appendix D and Appendix E.

15. I also took osmolality measurements as requested. I determined that Batch 1345-011 had an osmolality of 529 mOsm/kg.

IV. DECLARATION

I declare under penalty of perjury under the laws of the United States that the foregoing is true and correct to the best of my knowledge.

Date: 29 - June - 2016


Signed: 
Dr. Ramprakash Govindarajan

EXHIBIT A

Ramprakash (Ram) Govindarajan, PhD
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PROFESSIONAL APPOINTMENTS

UNIVERSITY OF IOWA, COLLEGE OF PHARMACY (2015 – PRESENT)

- Director, Preformulation, University of Iowa Pharmaceuticals
- Clinical Assistant Professor, College of Pharmacy, University of Iowa

GLAXOSMITHKLINE, RESEARCH TRIANGLE PARK (2006 – 2015)

- Manager (2013 - 2015); Investigator (2009 – 2013); Principal Scientist (2006 – 2009)
Served in roles of increasing responsibility in various drug product development areas including early developability assessment, clinical phase pharmaceutical product development, manufacturing process development, technical transfer and scale-up

UNIVERSITY OF NORTH CAROLINA, CHAPEL HILL

Clinical Assistant Professor (Adjunct appointment, 2007-2015)

- Taught topics included in course MOPH-862 to graduate students in Pharmaceutics
- Served on PhD dissertation committee

ACADEMIC BACKGROUND

- Research Associate, Pharmaceutics, University of Minnesota, 2002-2006
- Ph. D. (Pharmaceutics), University of Mumbai, 1998-2002
- M. Pharm. Sci. (Pharmaceutics), University of Mumbai, 1995-1997
- B. Pharm. Sci., University of Mumbai, 1991-1995

AFFILIATIONS

- Member of American Association of Pharmaceutical Scientists (AAPS)
- Scientific Reviewer for Journals – ‘Pharmaceutical Research’, ‘Journal of Pharmaceutical Sciences’ and ‘The Journal of Pharmacy and Pharmaceutical Sciences’

PUBLICATIONS /PRESENTATIONS

Journal Articles

1. Govindarajan, R.; Landis, M.; Hancock, B.; Gatlin, L.; Suryanarayanan, R.; Shalaev, E.; (2014), Surface Acidity and Solid-State Compatibility of Excipients with an Acid-Sensitive API: Case Study of Atorvastatin Calcium, AAPS PharmSciTech., 1-10.
2. Chakravarty, P.; Suryanarayanan, R.; Govindarajan, R.; (2012), Phase transformation in thiamine hydrochloride tablets: influence on tablet microstructure, physical properties, and performance, J. Pharm. Sci. 101 (4), 1410-1422.
3. Chakravarty, P.; Govindarajan, R.; Suryanarayanan, R.; (2010), Investigation of solution and vapor phase mediated phase transformation in thiamine hydrochloride, J. Pharm. Sci. 99(9), 3941-3952.
4. Chakravarty, P.; Berendt, R.; Munson, E.; Young, V.; Govindarajan, R.; Suryanarayanan, R.; (2009), Insights into the dehydration behavior of thiamine hydrochloride (vitamin B1) hydrates: Part II, J. Pharm. Sci. 99(4), 1882 - 1895.
5. Chakravarty, P.; Berendt, R.; Munson, E.; Young, V.; Govindarajan, R.; Suryanarayanan, R.; (2009), Insights into the dehydration behavior of thiamine hydrochloride (vitamin B1) hydrates: Part I, J. Pharm. Sci. 99(2), 816-827.
6. Chatterjee, K.; Shalaev, E.Y.; Suryanarayanan, R.; Govindarajan, R. (2008), Correlation between chemical reactivity and the Hammett acidity function in amorphous solids using inversion of sucrose as a model reaction, J. Pharm. Sci. 97(1), 274-286.
7. Govindarajan, R.; Zinchuk, A.V.; Hancock, B.C.; Shalaev, E.Y.; Suryanarayanan, R., (2006), Ionization states in the microenvironment of solid dosage forms: Effect of formulation variables and processing, Pharm. Res., 23(10), 2454-2468.
8. Rani, M.; Govindarajan, R.; Surana, R.; Suryanarayanan, R. (2006), Structure in dehydrated trehalose dihydrate - evaluation of the concept of partial crystallinity, Pharm. Res., 23(10), 2356-2367.
9. Govindarajan, R.; Chatterjee, K.; Gatlin, L.; Suryanarayanan, R.; Shalaev, E.Y. (2006), Impact of freeze-drying on ionization of sulfonephthalein probe molecules in trehalose-citrate systems, J. Pharm. Sci. 95(7), 1498-1510.
10. Zinchuk, A.V.; Hancock, B.C.; Shalaev, E.Y.; Reddy, R.D.; Govindarajan, R.; Novak, E. (2005), The influence of measurement conditions on the Hammett acidity function of solid pharmaceutical excipients. Eur. J. Pharm. Biopharm., 61(3), 158-170.
11. Govindarajan, R.; Nagarsenker M.S. (2005), Formulation studies and in vivo evaluation of a flurbiprofen – hydroxypropyl beta-cyclodextrin system, Pharm. Dev. Technol., 10(1), 113-122.
12. Govindarajan, R.; Nagarsenker M.S. (2004), Basic drug - enterosoluble polymer coevaporates: development of oral controlled release systems, Drug Dev. Ind. Pharm., 30(8), 847-857.
13. Govindarajan, R.; Nagarsenker M.S. (2004), Influence of preparation methodology on solid-state properties of an acidic drug-cyclodextrin system, J. Pharm. Pharmacol., 56, 725-733.

14. Nagarsenker, M.S; Meshram, R.N.; Ramprakash G. (2000). "Solid dispersion of hydroxypropyl beta-cyclodextrin and ketorolac: enhancement of in-vitro dissolution rates, improvement in anti-inflammatory activity and reduction in ulcerogenicity in rats", J. Pharm. Pharmacol., 52 (8), 949-956.
15. Nagarsenker, M.S.; Garad, S.D; Ramprakash G. (2000) "Design, optimization and evaluation of domperidone coevaporates", J. Control. Rel., 62, 31-38.
16. Nagarsenker, M.S.; Govindarajan, R., (1998) Solid dispersion for extended release of Verapamil HCl, Pharm. Pharmacol. Commun., 4 (7), 331-334.

Book Chapters

1. Govindarajan, R; Kinetic processes in Pharmaceutics, In: Pharmaceutics: Basic principles and applications to pharmacy practice, Ed. Dash, A; Singh, S; Tolman, J; (2013)
2. Govindarajan, R; Suryanarayanan, R. (2006), Processing-induced phase transformations and their implications on pharmaceutical product quality, In: Hilfiker, Rolf (Ed.) Polymorphism: In the pharmaceutical industry, Wiley-VCH Verlag GmbH & Co., KGaA, Weinheim, Germany, p 333-364.

Invited Talks

1. Govindarajan, R; "Effect of water and buffer on the Hammett acidity function in amorphous lyophiles, Amorph-2014 Symposium, Cambridge, UK, Jul 2014
2. Govindarajan, R "Partial crystallinity in dehydrated trehalose dihydrate: the one-state crystallinity", Research Triangle Institute, Research Triangle Park, North Carolina, Jun 2009.
3. Suryanarayanan, R and Govindarajan R., "Phase transformations during pharmaceutical processing-potential implications on product performance", Dr. Reddy's Laboratories Ltd., Nov 24, 2005, Hyderabad, India
4. Govindarajan, R., "Evaluation of 'acidity' of Pharmaceutical solids using indicator probes", AAPS Pharmaceutics and Drug Delivery (PDD) conference, June 2004, Philadelphia, PA.
5. Govindarajan, R., "Solid-state acidity of amorphous freeze-dried systems and surface acidity of solid dosage forms", Pfizer Global R&D, April 2003, Groton, CT.

Conference presentations

1. Campbell D, Patel R, Whigham T, Rhodes C, Palmer J, Bianco J, Everhart K, Farrier C, Clowes R, Roberts J and Govindarajan, R. Development of Fixed Dose Combinations for Extended Release of Metformin and Glimepiride. Poster presentation, at the American Association of Pharmaceutical Scientists (AAPS) Annual Meeting 2014, San Diego, CA.
2. Chakravarty, P.; Govindarajan, R.; Suryanarayanan, Effect of in situ Phase Transformation on Thiamine Hydrochloride Tablets, Poster presentation, American Association of Pharmaceutical Scientists (AAPS) Annual Meeting 2009, Los Angeles, CA.
3. Chakravarty, P.; Govindarajan, R.; Suryanarayanan, R. Stability and behavior of thiamine hydrochloride phases: role of thermodynamics, kinetics and crystal structure, Poster presentation, American Association of Pharmaceutical Scientists (AAPS) Annual Meeting 2008, Atlanta, GA.

4. Chakravarty, P.; Govindarajan, R.; Suryanarayanan, R. Hydrate Forms of Thiamine Hydrochloride: Dehydration Behavior and Phase Transformation, Poster presentation, American Association of Pharmaceutical Scientists (AAPS) Annual Meeting 2007, San Diego CA.
5. Govindarajan, R.; Rani, M.; Surana, R.; Suryanarayanan, R. Structure in dehydrated trehalose dihydrate - evaluation of the concept of partial crystallinity, Poster presentation, American Association of Pharmaceutical Scientists (AAPS) Annual Meeting 2006, San Antonio, TX.
6. Chakravarty, P.; Govindarajan, R.; Suryanarayanan, R. Phase transformations in Thiamine HCl during simulated pharmaceutical processing, Poster presentation, American Association of Pharmaceutical Scientists (AAPS) Annual Meeting 2006, San Antonio, TX.
7. Liao, X.; Govindarajan, R.; Suryanarayanan, R., Use of Atomic Force Microscopy to Detect Surface Crystallization, Poster presentation, American Association of Pharmaceutical Scientists (AAPS) Annual Meeting 2005, Nashville, TN.
8. Govindarajan, R.; Chatterjee, K.; Gatlin, L. A.; Shalaev, E. Y.; Suryanarayanan, R., Evaluation of buffered amorphous lyophiles using indicator probes: use of the Hammett acidity function, Poster presentation, American Association of Pharmaceutical Scientists (AAPS) Annual Meeting 2005, Nashville, TN.
9. Govindarajan, R.; Gatlin, L.; Shalaev, E.Y.; Suryanarayanan, R., Effect of water content on the acidity and ionization states in buffered amorphous sugar lyophiles., Poster presentation, American Association of Pharmaceutical Scientists (AAPS) Annual Meeting 2004, Baltimore, MD.
10. Govindarajan, R.; Zinchuk, A.V.; Hancock, B.C.; Shalaev, E.Y.; Suryanarayanan, R., Surface acidity of pharmaceutical excipients: Effect of formulation variables, Poster presentation, American Association of Pharmaceutical Scientists (AAPS) Annual Meeting 2004, Baltimore, MD.
11. Rani, M; Surana, R.; Govindarajan, R.; Pyne, A.; Suryanarayanan, R., Study of enthalpic relaxation in ternary frozen aqueous solutions using differential scanning calorimetry, Poster presentation, American Association of Pharmaceutical Scientists (AAPS) Annual Meeting 2004, Baltimore, MD.
12. Govindarajan, R.; Shalaev, E.Y.; Gatlin, L.; Suryanarayanan, R., Effect of citrate buffer concentration on the degree of ionization of an indicator probe in an amorphous sugar lyophile, Poster presentation, July 28-31, 2004: NSF Conference on Freeze-Drying of Pharmaceuticals and Biologicals, Breckenridge, CO.
13. Govindarajan, R.; Chatterjee, K.; Gatlin, L.; Shalaev, E.Y.; Suryanarayanan, R., Study of the solid-state acid/base relationships in amorphous freeze-dried sugar-citrate systems using colyophilized pH indicators and diffuse reflectance spectroscopy, Poster presentation, American Association of Pharmaceutical Scientists (AAPS) Annual Meeting 2003, Salt Lake City, UT.
14. Chatterjee, K.; Govindarajan, R.; Gatlin, L.; Suryanarayanan, R.; Shalaev, E.Y., Effect of buffers on the acid/base properties of amorphous freeze-dried systems, Poster presentation, American Association of Pharmaceutical Scientists (AAPS) Annual Meeting 2003, Salt Lake City, UT.
15. Govindarajan, R.; Chatterjee, K.; Hancock, B.C.; Shalaev, E.Y.; Suryanarayanan, R., Evaluation of the surface acidity of pharmaceutical excipients and formulations using pH indicators as probe molecules and diffuse reflectance spectroscopy, Poster presentation, American Association of Pharmaceutical Scientists (AAPS) Annual Meeting 2003, Salt Lake City, UT.
16. Rani, M; Govindarajan, R.; Surana, R.; Suryanarayanan, R., Preparation, characterization and physical stability evaluation of the alpha-polymorph of anhydrous trehalose, Poster presentation, American Association of Pharmaceutical Scientists (AAPS) Annual Meeting 2003, Salt Lake City, UT.
17. Rani, M; Govindarajan, R.; Surana, R.; Suryanarayanan, R., Effect Of Glass Fragility On The Enthalpic Relaxation Measured By Differential Scanning Calorimetry, Poster presentation, American Association of Pharmaceutical Scientists (AAPS) Annual Meeting 2003, Salt Lake City, UT.
18. Govindarajan, R.; Chatterjee, K.; Hancock, B.C.; Shalaev, E.Y. Suryanarayanan, R., Surface acidity of pharmaceutical excipients and formulations, Poster presentation, AAPS Northeast Regional Discussion group (NERDG) meeting 2003, Rocky Hill, CT.
19. Govindarajan, R; Nagarsenker, MS., Effect of succinic acid on release of verapamil HCl from hydrophilic matrix, Poster presentation, 53rd Indian Pharmaceutical Congress, December 2001, New Delhi, India.

20. Govindarajan, R; Nagarsenker, MS., Cyclodextrin based oral delivery of flurbiprofen: effect of method of preparation on drug release and studies on in-vivo performance, Poster presentation, 28th Controlled Release Society Annual Symposium, June 2001, San Diego, California, USA.
21. Govindarajan, R; Nagarsenker, MS., pH independent oral controlled release of verapamil HCl: solubilisation in the microenvironment using enterosoluble polymer or organic acid, Poster presentation, 28th Controlled Release Society Annual Symposium, June 2001, San Diego, California, USA.
22. Govindarajan, R; Nagarsenker, MS, Development of oral controlled release systems for pH independent release of a weak base, Poster presentation, 3rd International Symposium on Advances in Technology and business potential of new drug delivery systems, October 2000, Ootacamund, India.
23. Nagarsenker, MS.; Meshram, R.; Govindarajan, R, Solid dispersion of hydroxypropyl beta-cyclodextrin and ketorolac: enhancement of dissolution rates, improvement in anti-inflammatory activity and reduction in ulcerogenicity, Poster presentation, 10th International Cyclodextrin Symposium, May 2000, Ann Arbor, Michigan.
24. Govindarajan, R; Nagarsenker, MS, Role of hydroxypropyl beta-cyclodextrin in improving dissolution and reducing ulcerogenicity of flurbiprofen: effect of l-tyrosine on bioavailability from coevaporate, Poster presentation, 10th International Cyclodextrin Symposium, May 2000, Ann Arbor, Michigan.
25. Govindarajan, R; Nagarsenker, MS, Solid dispersion of Flurbiprofen with Hydroxypropyl beta-cyclodextrin, Poster presentation, 4th International symposium on innovations in pharmaceutical sciences and technology, February 2000, Ahmedabad, India.
26. Govindarajan, R; Nagarsenker, MS, Verapamil HCl coevaporates using enterosoluble polymer: Development of oral controlled release systems, Podium presentation, 50th Indian Pharmaceutical Congress and the 17th Asian Congress of Pharmaceutical Sciences, December 1998, Mumbai, India.

EXHIBIT B



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1 item in my patents list

Displaying selected publications

Publication	Title	Page
EP0780127 (A1)	A nasal spray containing a steroid an...	2



(12) **EUROPEAN PATENT APPLICATION**

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(54) **A nasal spray containing a steroid and a antihistamine**

(57) The present invention relates to novel nasal
spray compositions comprising a safe and effective

amount of a glucocorticosteroid and an antihistamine
possessing leukotriene inhibiting properties.

EP 0 780 127 A1

Description**TECHNICAL FIELD**

- 5 The present invention relates to novel nasal spray compositions comprising a safe and effective amount of a glucocorticosteroid and an antihistamine.

BACKGROUND OF THE INVENTION

10 Allergic disorders remain a leading cause of both acute and chronic illnesses the world over. These illnesses are often times present in the form of acute or chronic rhinoconjunctivitis. The symptoms of allergic rhinoconjunctivitis are reddening of the eyes, ocular secretions, nasal congestion, ocular and palatal irritation, sneezing and hypersecretion. These symptoms occur following exposure to allergens. The most common allergens are grass and/or tree pollens; hence, allergic rhinoconjunctivitis is most common during the spring and summer months.

15 The symptoms of allergic rhinoconjunctivitis are believed to be due primarily to the stimulation of H-1 receptors by histamine, followed by reflexive activation of parasympathetic nerves causing increases in nasal secretion and obstruction. Histamine is initially released from the tissue mast cells upon sensitization of the mast cells. This sensitization results when airborne allergens combine with specific IgE antibodies attached to mast cell membranes.

20 Antihistamines and/or decongestants have traditionally been the drugs of choice in treating allergic rhinoconjunctivitis. Other forms of therapy include the use of cromolyn sodium, hypertonic salt solutions or immunotherapy.

In addition, Hagen et al., U.S. Patent 4,767,612, discloses nasal corticosteroid therapy as an effective means of treating allergic rhinoconjunctivitis; and is herein incorporated by reference in its entirety. Notwithstanding the many disclosures in the area of allergic rhinoconjunctivitis, there is still a need for additional formulations which provide improved symptomatic relief with increased user acceptance and compliance.

25 The present inventor has found that by combining a nasal corticosteroid with a leukotriene inhibiting antihistamine, improved intranasal compositions result, providing improved relief of symptoms generally associated with either seasonal or perennial allergic rhinoconjunctivitis.

It is, therefore, an object of the present invention to provide pharmaceutical compositions having improved effectiveness in the treatment of symptoms generally associated with either seasonal or perennial allergic rhinoconjunctivitis.

30 A further object of the present invention is to provide a safe and effective method for treating the symptoms of seasonal or perennial allergic rhinoconjunctivitis.

These objects and other objects will become more apparent from the detailed description that follows.

SUMMARY OF THE INVENTION

35 The present invention relates to pharmaceutical compositions for nasal administration comprising:

- a) a safe and effective amount of a glucocorticoid selected from the group consisting of beclomethasone, flunisolide, triamcinolone, fluticasone, mometasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof;
- 40 b) a safe and effective amount of a leukotriene inhibiting antihistamine selected from the group consisting of cetirizine, loratadine, azelastine, pharmaceutically acceptable salts thereof, optically active racemates thereof and mixtures thereof; and
- c.) an intranasal carrier.

45 The intranasal carrier of the present invention is preferably aqueous.

The present invention also relates to a method for the treatment of symptoms associated with seasonal or perennial allergic rhinoconjunctivitis comprising the administration of a safe and effective amount of the intranasal pharmaceutical compositions of the present invention. By "symptoms of seasonal or perennial allergic rhinoconjunctivitis" or "symptoms associated with seasonal or perennial allergic rhinoconjunctivitis," is meant ocular and palatal irritation, ocular secretions, reddening of the eyes, sneezing, mucoid hypersecretion, nasal congestion and itching.

50 By "safe and effective amount," as used herein, is an amount that is effective to mitigate and/or treat the symptoms for which the active ingredient is indicated in a human without undue adverse side effects commensurate with a reasonable risk/benefit ratio.

55 By "leukotriene inhibiting antihistamine," as used herein, is meant an antihistamine effective in inhibiting or reducing *in vivo* the biosynthesis of and/or cellular release of leukotrienes or otherwise modulating mammalian leukotriene levels. The pH of the compositions is preferably from about 4.5 to about 9, more preferably from about 6 to about 7.

All percentages and ratios herein are by weight unless otherwise specified. Additionally, all measurements are

made at 25°C unless otherwise specified.

DETAILED DESCRIPTION OF THE INVENTION

5 The compositions of the present invention contain the essential components as well as various optional components as indicated below.

More specifically, the compositions of the instant invention are for nasal administration and contain a therapeutically effective amount of the herein described pharmaceutical agents. They are preferably provided as isotonic aqueous solutions, suspensions or viscous compositions which may be buffered to a selected pH.

10

Essential Ingredients

Glucocorticoid Agents

15 Agents within this class have potent glucocorticoid activity and weak mineralocorticoid activity. Glucocorticoid agents most useful to the present invention include those selected from the group consisting of beclomethasone, flunisolide, triamcinolone, fluticasone, mometasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof.

20 When used in the compositions of the present invention, the glucocorticoid component is preferably present at a concentration of from about 0.001% to about 0.2%, more preferably from about 0.01% to about 0.1%.

Leukotriene Inhibiting, Antihistaminic Agents

25 Antihistamines useful to the present invention are histamine H-1 receptor antagonists which also reduce mammalian leukotriene levels. Such H-1 receptor antihistamines may be selected from among the following groups of antihistamines: piperazines, phenothiazines, piperidines.

30 Examples of useful leukotriene inhibiting antihistamines include cetirizine, loratadine, azelastine and the like, optically active racemates thereof, pharmaceutically acceptable salts thereof and mixtures thereof. When used in the compositions of the present invention, the antihistamine component is preferably present at a concentration of from about 0.01% to about 4.0%, more preferably from about 0.01% to about 1%.

Pharmaceutically-Acceptable Aqueous Nasal Carrier

35 One other essential component of the present invention is a pharmaceutically-acceptable intranasal carrier. Preferred for use herein are aqueous saline solution carriers. These solutions which generally contain sodium chloride as the salt are fully described in Remington's Pharmaceutical Sciences, 17th edition (1985) p. 835, which is herein incorporated by reference. The salt is present in the solution at a level of about 0.01% to about 2%, preferably from about 0.5% to about 1.0%.

40 The combination of any of the above described antihistamines and glucocorticoids can be conveniently administered nasally to warm-blooded animals to elicit the desired therapeutic response by formulating it into a nasal dosage form, together with a nontoxic pharmaceutically-acceptable nasal carrier. Suitable nontoxic pharmaceutically-acceptable nasal carriers are known to those skilled in the art and are also fully disclosed in Remington's Pharmaceutical Sciences, 17th edition, 1985. Obviously, the choice of suitable carrier forms will depend on the exact nature of the particular nasal dosage form required, e.g., whether the drug(s) is to be formulated into a nasal solution (for use as drops or as a spray), a nasal suspension, a nasal ointment, a nasal gel or another nasal form. Preferred nasal dosage forms are solutions, suspensions and gels, which normally contain sodium chloride in a major amount of water (preferably purified water) in addition to the antihistamine and glucocorticoid. Minor amounts of other ingredients such as pH adjusters (e.g., an acid such as HCl), emulsifiers or dispersing agents, buffering agents, preservatives, wetting agents and jelling agents (e.g., methylcellulose) may also be present. Most preferably, the nasal composition is isotonic, i.e., it has the same osmotic pressure as blood and lacrimal fluid.

55 Preferably the composition is applied to the nasal mucosa via topical application of a safe and effective amount of the composition to treat nasal symptoms. The amount of the antihistamine and glucocorticoid combination and frequency of topical application to the nasal mucosa may vary, depending upon personal or medical needs, but it is suggested, as an example, that topical application range from about once per day to about four times daily, preferably twice daily, most preferably once daily. As a practical matter the selected therapeutic compositions will normally be prepared in unit dosage forms or actuations to contain therapeutically effective amounts of the selected antihistamine and glucocorticoid combination. In specific instances fractions of these dosage units or multiple dosage units will be employed. Typically, dosage units may be prepared to deliver from about 0.5 mcg to about 100 mcg of the glucocorticoid

agent and from about 5 mcg to about 1000 mcg of the antihistaminic agent per spray actuation (e.g., 50 mg to about 200 mg of the spray composition). A typical dose contains one to four sprays per nostril.

Optional Ingredients

Optional ingredients useful in the present invention include decongestants. Decongestants useful to the present invention may be selected from among the class of sympathomimetic agents, examples of which include pseudoephedrine, desoxyephedrine, propylhexedrine, phenylpropanolamine, xylometazoline, phenylephrine, tetrahydrozoline, naphazoline, oxymetazoline, tramazoline and pharmaceutically acceptable salts thereof. Also useful as decongestants are the 5-(2-imidazolylamino)benzimidazole compounds. Mixtures of these decongestants can also be used.

When used in the compositions of the present invention, the sympathomimetic agents may be incorporated at concentrations, preferably, of from about 0.01% to about 0.5%, more preferably from about 0.05% to about 0.1%.

The compositions of the present invention may also contain antiallergics. Suitable antiallergics include, but are not limited to, cromolyn, ketotifen, N-allyl-(dichloro-3, 4-benzyl)-2-methylamino-2-propanol-1, AP-582 (Pharmaprojects No. 3055-under investigation by Ariad Pharmaceuticals), Andolast, oxatamide and pharmaceutically-acceptable salts thereof. Mixtures of these antiallergics may also be used.

Similarly, mucolytics such as acetylcysteine and anticholinergics such as ipratropium bromide may also be used in the compositions of the present invention.

Also of optional use in the compositions of the present invention are nonopiate analgesics such as oxaprozin. The intranasal use of oxaprozin is described in Namiki et al., Studies on improvement of pharmaceutical preparations prescribed in hospitals. VI. oxaprozin nasal spray, Drug Design and Delivery 1988;2:pp. 311-321, herein incorporated by reference. Further examples of preferred nonopiate analgesics include, but are not limited to, acetaminophen, acetylsalicylic acid, ibuprofen, etodolac, fenbuprofen, fenoprofen, flurbiprofen, indomethacin, ketoprofen, naproxen, pharmaceutically-acceptable salts thereof, optically active racemates thereof and mixtures thereof. Still further examples of such drugs are disclosed in U.S. Patent No. 4,522,828, to Sunshine et al., issued June 11, 1985; this patent being incorporated herein by reference in its entirety.

Synthetic opiate analgesics such as butorphanol may also be incorporated into the compositions of the present invention. The intranasal use of butorphanol is described in Baumel, Migraine: A pharmacologic review with newer options and delivery modalities, Neurology 1994;44(supp):pp. s13-s17, herein incorporated by reference. Further examples of preferred synthetic opioid analgesics include alfentanil, buprenorphine, fentanyl, meperidine, methadone, nalbuphine, naltrexone, propoxyphene, pentazocine, sufentanil, pharmaceutically-acceptable salts thereof and mixtures thereof.

Compounds commonly known as lipoxygenase inhibitors and receptor antagonists are also optionally useful in the compositions of the present invention. Suitable lipoxygenase inhibitors are described in U.S. Patent 4,873,259, to Summers et al., issued October 10, 1989 and European Patent Application 318093, both of which are herein incorporated by reference. Lipoxygenase antagonists suitable for use in the present invention include Zafirlukast (Accolate, Zeneca).

Leukotriene receptor antagonists may also be incorporated into the compositions of the present invention. Suitable examples include, but are not limited to, experimental agents such as LY171883, Wy-45,911, LY163443, ONO-RS-411 and ONO-RS-347 and ICI 196,615. A more detailed discussion of leukotriene receptor antagonists is found in Fleisch, J. H., Development of Cysteinyl Leukotriene Receptor Antagonists, Vol. 12 Advances in Inflammation Research 173-189 (A. Lewis et al. ed, 1988), herein incorporated by reference in its entirety.

Various aromatic components (e.g., aldehydes and esters) may also be used. These aromatics include, for example, menthol, camphor, eucalyptol, benzaldehyde (cherry, almond); citral (lemon, lime); nerol; decanal (orange, lemon); aldehyde C-8, aldehyde C-9 and aldehyde C-12 (citrus fruits); tolyl aldehyde (cherry, almond); 2,6-dimethyl-octanal (green fruit); and 2-dodecenal (citrus, mandarin). Additional aromatic components suitable for use in the present invention include those described in U.S. Patent 4,136,163 to Watson et al., U.S. Patent 4,459,425 to Amano et al., and U.S. Patent 4,230,688 to Rowsell et al.; all of which are herein incorporated by reference. Mixtures of these aromatics can also be used.

The desired isotonicity of the compositions of this invention may be accomplished using, for example, the sodium chloride already present, or other pharmaceutically-acceptable agents such as dextrose, boric acid, citric acid, sodium tartrate, sodium phosphate, potassium phosphate, propylene glycol or other inorganic or organic solutes or mixtures thereof. Sodium chloride is preferred particularly for buffers containing sodium ions. Further examples of sodium chloride equivalents are disclosed in Remington's Pharmaceutical Sciences pp. 1491-1497 (Alfonso Gennaro 18th ed. 1990).

Viscosity of the compositions may be maintained at the selected level using a pharmaceutically-acceptable thickening agent. Methyl cellulose is preferred because it is readily and economically available and is easy to work with. Other suitable thickening agents include, for example, xanthan gum, microcrystalline cellulose, carboxymethyl cellu-

lose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, carboxyvinyl polymer, carbomer, and the like or pharmaceutical salts thereof. Mixtures of such thickening agents may also be used. The preferred concentration of the thickener will depend upon the agent selected. The important point is to use an amount which will achieve the selected viscosity. Viscous compositions are normally prepared from solutions by the addition of such thickening agents.

Preferred compositions within the scope of this invention will contain from about 0.01% to about 5% of a humectant to inhibit drying of the mucous membrane and to prevent irritation. Any of a variety of pharmaceutically-acceptable humectants can be employed including, for example sorbitol, propylene glycol, polyethylene glycol, glycerol or mixtures thereof. As with the thickeners, the concentration will vary with the selected agent, although the presence or absence of these agents, or their concentration is not an essential feature of the invention.

Enhanced absorption across the nasal membrane can be accomplished employing a therapeutically acceptable surfactant. Typical useful surfactants for these therapeutic compositions include polyoxyethylene derivatives of fatty acid partial esters of sorbitol anhydrides such as Polysorbate 80, Polyoxyl 40 Stearate, Polyoxyethylene 50 Stearate and Octoxynol, as well as Oxyethylated tertiary octyl phenol formaldehyde polymer (available from Sterling Organics as tyloxapol) or mixtures thereof. The usual concentration is from 0.5% to 10% based on the total weight.

A pharmaceutically-acceptable preservative is generally employed to increase the shelf life of the compositions of the present invention. Benzyl alcohol is suitable, although a variety of preservatives including, for example, parabens, phenylethyl alcohol, thimerosal, chlorobutanol, phenylmercuric acetate or benzalkonium chloride may also be employed. The most preferred preservative system for use herein comprises a combination of benzalkonium chloride, chlorhexidine gluconate and disodium EDTA. A suitable concentration of the preservative will be from 0.001% to 2% based on the total weight, although there may be appreciable variation depending upon the agent selected. Mixtures of these preservatives may also be used.

Other Optional Components. A variety of additional ingredients may be added to the emulsion compositions of the present invention. These additional ingredients include various polymers for aiding the film-forming properties and substantivity of the formulation, antioxidants, and agents suitable for aesthetic purposes such as fragrances, pigments, and colorings.

The compositions can also contain low levels of insoluble ingredients added, for example for visual effect purposes, e.g. thermochromic liquid crystalline materials such as the microencapsulated cholesteryl esters and chiral nematic (nonsterol) based chemicals such as the (2-methylbutyl) phenyl 4-alkyl(oxy)benzoates available from Hallcrest, Glenview, Illinois 60025, U.S.A. Mixtures of these ingredients may also be used.

EXAMPLES

The following examples further describe and demonstrate embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention, as many variations thereof are possible without departing from the spirit and scope of the invention.

Example I

The intranasally administered pharmaceutical composition of the present invention is prepared by combining the following components utilizing conventional mixing techniques similar to that described below.

Component	Wgt %
beclomethasone dipropionate, monohydrate	0.042
loratadine	0.200
avicel RC - 591 ¹	1.200
dextrose	5.100
polysorbate 80	0.025
benzalkonium chloride	0.040
phenylethyl alcohol	0.250
distilled water	q.s. to vol.

¹microcrystalline cellulose and sodium carboxymethyl cellulose, supplied by FMC corporation.

In an appropriately sized vessel, the dextrose, polysorbate 80 and benzalkonium chloride are added one at a time to water with mixing, allowing each to dissolve or completely disperse before adding the next. To this is added, with mixing, a premixed slurry of the avicel and water. Upon forming a uniform solution, the beclomethasone, loratadine

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and phenylethyl alcohol are added. After all the ingredients are added, purified water is used to bring the batch to the appropriate weight.

Administration of approximately 0.4 grams of the composition is used for topical nasal application to provide relief from allergy or allergy-like symptoms.

Example II

The intranasally administered pharmaceutical composition of the present invention is prepared by combining the following components utilizing conventional mixing techniques similar to that described in Example I.

Component	Wgt %
flunisolide	0.025
cetirizine	0.200
propylene glycol	2.000
polyethylene glycol	1.000
sodium chloride	0.900
ethylenediamine tetraacetic acid	0.050
benzalkonium chloride	0.010
distilled water	q.s. to vol.

Administration of approximately 0.4 grams of the composition is used for topical nasal application to provide relief from allergy or allergy-like symptoms.

Example III

The intranasally administered pharmaceutical composition of the present invention is prepared by combining the following components utilizing conventional mixing techniques similar to that described in Example I.

Component	Wgt %
triamcinolone acetonide	0.050
azelastine HCl	0.070
polysorbate 80	0.050
glycerin	2.000
hydroxypropyl methyl cellulose	1.000
sodium chloride	0.900
ethylenediamine tetraacetic acid	0.050
benzalkonium chloride	0.020
distilled water	q.s. to vol.

Administration of approximately 0.4 grams of the composition is used for topical nasal application to provide relief from allergy or allergy-like symptoms. Additionally, substantially similar results are also obtained using, in whole or in part, equivalent amounts of other glucocorticoid agents such as fluticasone, mometasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof. Furthermore, the above described compositions may also contain a decongestant such as pseudoephedrine, phenylpropanolamine, phenylephrine, tetrahydrozoline, naphazoline, oxymetazoline, tramazoline, 5-(2-imidazolylamino)benzimidazoles, optically active racemates thereof, pharmaceutically acceptable salts thereof and mixtures thereof. Those skilled in the art will quickly realize other suitable ingredients, diluents and dosage forms (or readily ascertain such using routine experimentation) which may further be incorporated into the above compositions without departing from the scope and spirit of the present invention.

Claims

1. A pharmaceutical composition comprising:

a) a safe and effective amount of a glucocorticoid selected from the group consisting of beclomethasone,

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flunisolide, triamcinolone, fluticasone, mometasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof;

b) a safe and effective amount of a leukotriene inhibiting antihistamine selected from the group consisting of cetirizine, loratadine, azelastine, pharmaceutically acceptable salts thereof, optically active racemates thereof and mixtures thereof; and

c.) an intranasal carrier.

2. A composition according to Claim 1 in the form of an isotonic aqueous solution

3. A composition according to Claim 1 or 2 wherein the glucocorticoid is selected from the group consisting of beclomethasone, budesonide, fluticasone and mixtures thereof.

4. A pharmaceutical composition according to any of Claims 1-3, which further comprises a sympathomimetic amine selected from the group consisting of pseudoephedrine, desoxyephedrine, propylhexedrine, phenylpropanolamine, xylometazoline, phenylephrine, tetrahydrozoline, naphazoline, oxymetazoline, tramazoline, 5-(2-imidazolinyllamino)benzimidazoles, pharmaceutically acceptable salts thereof, optically active racemates thereof and mixtures thereof.

5. A pharmaceutical composition according to any of Claims 1-4, which further comprises a non-steroidal anti-inflammatory agent, or optically active racemates thereof and mixtures thereof.

6. A pharmaceutical composition according to any of Claims 1-5, which further comprises a lipoxigenase inhibitor or antagonist, a leukotriene receptor antagonist, a nonopioid analgesic, a mucolytic, an antiallergic, and pharmaceutically acceptable salts thereof and mixtures thereof.

European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 96 30 8852

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.6)
X,Y	ADVANCES IN THERAPY, vol. 12, no. 6, November 1995 - December 1995, USA, pages 340-349, XP000651473 DROUIN ET AL: "ADDING LORATADINE TO TOPICAL NASAL STEROID THERAPY IMPROVES MODERATELY SEVERE SEASONAL ALLERGIC RHINOCONJUNCTIVITIS" * the whole document *	1-6	A61K31/57 A61K31/58 A61K31/56 A61K31/495 A61K31/445 A61K31/55 // (A61K31/56, A61K31/495), (A61K31/56, A61K31/445), (A61K31/56, A61K31/55), (A61K31/57, A61K31/495), (A61K31/57, A61K31/445), (A61K31/57, A61K31/55),
X,Y	CLINICAL AND EXPERIMENTAL ALLERGY, vol. 22, no. 10, October 1992, UK, pages 916-922, XP000651660 ARMITAGE ET AL: "INVESTIGATION OF THE TENDENCY TO WHEEZE IN POLLEN SENSITIVE PATIENTS" * the whole document *	1-6	
X,Y	DRUG INVESTIGATION, vol. 8, no. 4, 1994, UK, pages 225-233, XP000651434 BENINCASA ET AL: "EVALUATION OF FLUTICASONE PROPIONATE AQUEOUS NASAL SPRAY TAKEN ALONE AND IN COMBINATION WITH CETIRIZINE IN THE PROPHYLACTIC TREATMENT OF SEASONAL ALLERGIC RHINITIS" * the whole document *	1-6	TECHNICAL FIELDS SEARCHED (Int.Cl.6) A61K
D,Y	US 4 767 612 A (HAGEN NICHOLAS S ET AL) 30 August 1988 * abstract *	1,2,4-6	
Y	JAMES E.F. REYNOLDS: "MARTINDALE THE EXTRA PHARMACOPOEIA, 13TH EDITION" 1993, THE PHARMACEUTICAL PRESS, LONDON XP002028542 PAGE 931: AZELASTINE --- -/-	1-6	
The present search report has been drawn up for all claims			
Place of search MUNICH		Date of completion of the search 1 April 1997	Examiner Herrera, S
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 U : non-written disclosure P : intermediate document I : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application I : document cited for other reasons A : member of the same patent family, corresponding document			

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Office

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Application Number
EP 96 30 8852

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.6)
Y	EP 0 605 203 A (SENJU PHARMA CO) 6 July 1994 * the whole document * -----	1-6	(A61K31/58, A61K31:495), (A61K31/58, A61K31:445)
			TECHNICAL FIELDS SEARCHED (Int.Cl.6)
The present search report has been drawn up for all claims			
Place of search MUNICH		Date of completion of the search 1 April 1997	Examiner Herrera, S
<p>CATEGORY OF CITED DOCUMENTS</p> <p>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</p> <p>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</p>			

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EXHIBIT C

Triamcinolone Acetonide & Azelastine HCl nasal
1345-001

Winston - ^{Spray} Strawn

1345 1

Trial preparation and background

S Rp 10 Jun 2016

Background 10 - June - 2016

The purpose is to determine an appropriate preparation procedure for the composition described below, prepare a batch with the said composition, and evaluate physical properties of the final batch.

Ingredient and Concentration

Triamcinolone Acetonide	-	0.05 % w/v
Azelastine HCl	-	0.07 % w/v
Polysorbate 80	-	0.05 % w/v
Glycerin	-	2.0 % w/v
Hypromellose	-	1.0 % w/v
Sodium chloride	-	0.9 % w/v
Ethylenediamine tetraacetic acid	-	0.05 % w/v
Benzalkonium chloride	-	0.02 % w/v
Distilled water	-	q.s. to final volume

US Patent 6017909 reports a solubility for the HCl salt of azelastine as 1%. Based on this it is expected that in the composition reported above, azelastine could be completely in solution.

Block and Patel (1973) report solubility of Triamcinolone Acetonide in water to be $< 20 \text{ mg/ml}$ with reduced solubility @ higher ionic strength. Ignoring the possible solubilizing effects of the surfactant (Tween 80) and glycerin, it is likely that the concentration of triamcinolone acetonide would exceed the solubility of the drug.

The surfactant (Polysorbate 80) would help with wetting of the suspended particles and hypromellose would increase the viscosity of the medium to decrease sedimentation rates.

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Polysonbat 80 and glycerin can help with initial dispersion and surface wetting of the drug particles before their addition to the bulk of the aqueous vehicle.

Sodium chloride provides the desired tonicity (osmolality) to the preparation.

Ethylene diamine tetraacetic acid, a chelating agent may serve as a stabilizer against oxidative degradation.

Benzalkonium chloride could function as an anti-microbial preservative. EDTA may contribute anti-microbial activity as well.

Azidarine HCl, polysonbat 80, hypromellose, sodium chloride, glycerin, and benzalkonium chloride, being S. P. 10 Jun 2016, have sufficient aqueous solubility to be in solution in this composition.

Triamcinolone acetonide is expected to remain partially undissolved and suspended in the vehicle.

The reported solubility of EDTA is 1 in 500 parts (from the Handbook of Pharmaceutical Excipients) and hence should also be in solution. But there are other reports of much lower solubility. From Yoshino et al (1958) the solubility at 20°C is 1.153 mM (~33.6 mg/100 mL). In the process of preparation therefore rapid dissolution of EDTA was not expected.

Yoshino et al (1958), Bull. Chem. Soc. Jap 31(7), 892
Black and Patel, J. Pharm Sci 62(4), 617, 1972

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Chemicals used

- Hypromellose USP, Type 2910, Pharmedat 606, Shin Etsu Lot # 1088348
- Benzalkonium chloride Sigma, Material B6295 Lot # 60K2609
- Sodium chloride USP, Sigma Lot # CDBC0348V
- Glycerin USP, Sigma Aldrich Lot - SHBG1128V
- PolySorbate 80 Ph. Eur Sigma Lot - BCBQ4721V
- Ethylenediamine tetraacetic acid (EDTA) Aldrich (99.995 %) Lot # MKBW2470V
- Triamcinolone Acetonide USP, Sigma Aldrich Lot # LRAA6967
- Azelastine HCl, Sigma Aldrich Lot # LRAA5303
- Purified water USP, from UIP part #

10 Jun 2016 Equipment List

- IKA Eurostar 20 overhead stirrer, Model Euro-ST 20D S001
- Fisher Thermix magnetic stirrer and hot plate Model 11-495, Serial # 118
- IKA RO 10 magnetic stirrer
- Branson Ultrasonic bath, Model CPX5800H Serial # BG0021670670B
- Mettler Toledo XSE 105 dual range balance Serial # B617383248
- Ohaus analytical balance AX124 (Sno B530216186)
- IKA T25 digital Ultra Turrax homogenizer Model T25 D51 # 03445841
- IKA homogenization tool S2SN-18G
- VWR vortex mixer SN-160315017

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Analyst

S. Rappholz

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Tramcinolone Acetonide and Azelastine HCl nasal spray 1345-004

Total Suspension Preparation

S. Ly 10 Jun 2016

Purpose - Preparation of a trial batch of tramcinolone acetonide (0.05%) and azelastine HCl (0.07%) nasal spray. Expt. Ref 1345-004

Composition for a 100mL batch. (ingredient details - page 3)

Ingredient	Target qty	Actual quantity
① Tramcinolone Acetonide	0.05g	0.05011g
② Azelastine HCl	0.07g	0.07023g
③ Polysonbat 80	0.05g	0.05040g
④ Glywin	2.00g	1.994g
⑤ Hypromellose	1.00g	0.9989g
⑥ Sodium chloride	0.90g	0.9012g
⑦ Edetic Acid	0.05g	0.05072g
⑧ Benzalkonium chloride	0.02g	0.01981g
⑨ Purified water	qs 100mL	qs 100mL

Procedure: In this attempt to prepare a nasal spray with the composition listed above ingredients ②, ⑥ and ⑧ will be weighed out and transferred to approximately ~~50~~ 50mL of deionized water under stirring till all of them dissolve. ⑤ will be added under vigorous stirring to generate a vortex. ⑤ will be slowly sprinkled into the solution. After addition is complete stirring will continue till a clear dispersion is obtained. ③, ④, ① and ⑦ will be added sequentially into a vial and the contents will be mixed well on a vortex mixer followed by sonication. A small portion of the purified water will be added under stirring to obtain a pourable dispersion. This dispersion will be added to the aqueous phase containing ②, ⑤, ⑥ ⑧ and a portion of the water, while being mixed with a homogenizer.

S. Ly

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when homogenization is complete, Sufficient water will be used to rinse the container originally used to prepare a mixture of ① ③ ④ & ⑦ and transferred to the bulk container. Homogenization will be continued till a uniform dispersion is visually confirmed. Additional water may be added to adjust the final volume to 100 ml and appropriate additional mixing will be carried out. The final preparation will be filled into a suitable container for observation.

11-Jan-2016 - This procedure will incorporate edetic acid as a chelating agent in glycerol and poly-sorbitol 80 and upon addition to the aqueous phase with homogenization is expected to dissolve to the extent of its solubility in the vehicle.

13-Jun-2016

Benzalkonium chloride was transferred (weighed out) in a 20ml-vial and approximately 10ml of water was added. The contents were mixed manually to obtain a solution.

In a 100ml beaker, approximately 30ml of water was transferred and the weighed quantity of Sodium chloride was added to it under stirring using a magnetic stir-bar. When the Sodium chloride had dissolved, the benzalkonium chloride solution was transferred to the beaker and additional 10ml of water was used to rinse out the vial and transferred to the beaker. Azilantime HCl was then weighed out and transferred to the aqueous solution. Under stirring. After about a minute of stirring

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the beaker was placed in an ultra sonic bath for 1min to break up the few remaining undissolved aggregates of azelastine HCl to facilitate dissolution. An additional 1 minute of stirring yielded a clear solution.

While stirring to create a vortex the hypromellose was weighed out and ~~sprinkled~~ sprinkled into the solution. The solution was continued to stir to hydrate and disperse the hypromellose to yield a clear solution. This aqueous solution was stirred using a magnetic stir bar while the second pre-mix of ingredients was prepared.

Glycerin, Polysorbate 80, triamcinolone acetonide and edetic acid were weighed out and transferred into a 20mL vial. The contents were mixed on a vortex mixer for 30 seconds to yield a uniform slurry. Approximately 8mL of water was added to this slurry while being mixed with a magnetic stir-bar. This yielded a hazy dispersion of the solids in the water + glycerin + polysorbate 80 vehicle. The magnetic stir-bars were removed from both containers. The beaker containing the aqueous solution was placed on the homogenizer stand and the contents were mixed at 2800 rpm. The dispersion containing the undissolved solids was added to the beaker while being mixed. Additional water was added to the vial, and the rinse water was added to the beaker in two portions of 10mL each. Homogenization was continued for 5 min at 6000 rpm. The homogenization tool was raised on the beaker stand. The contents were allowed to stand for

Analyzed by:

S. Lepech

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DML

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the foam to subside. ① The final volume was made up to 100 mL and homogenized at 6000 rpm/5 min. The preparation was stored overnight to be observed the next day in a stoppered vial.

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The preparation was a cloudy dispersion. It exhibited presence of fine settled solid upon shaking. The solid was easily redispersed upon gentle agitation by overturning the vial 3-4 times.

The contents were transferred to a 250 mL beaker and homogenized at 1000 rpm for 10 min. The final preparation was transferred back to a stoppered 100 mL capacity serum vial and stored at room temperature.

① On 13-Jun-2016, the final volume was made up by transferring the contents to a 250 mL beaker marked for 100 mL volume and making up volume by adding water used to rinse out the original container and S. P. 14-Jun-2016.

Conclusion - A uniform suspension product was prepared. Although settling of the suspended solid was observed, the sediment was readily and uniformly resuspended with gentle agitation.

S. P. 14 Jun 2016

APPROVED BY
S. P. 14 Jun 2016

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REFERENCE

END

Triamcinolone Acetonide and Azelastine HCl nasal spray 1345-008

Trial Suspension preparation. S/L 14 Jun 2016

Purpose - Preparation of a trial batch of a nasal spray composition containing 0.05% w/v of triamcinolone acetonide and 0.07% w/v of azelastine HCl. (14 Jun 2016)

Composition for a 100 mL batch (ingredient details - pg 3)

Ingredient	Target qty	Actual qty
① Triamcinolone acetonide	0.05 g	0.04981 g
- ② Azelastine HCl	0.07 g	0.07036 g
③ Polysorbate 80	0.05 g	0.05039 g
④ Glycerin	2.00 g	2.0162 g
- ⑤ Hypromellose	1.00 g	0.9992 g
- ⑥ Sodium chloride	0.90 g	0.9002 g
- ⑦ Edetic Acid	0.05 g	0.04991 g
- ⑧ Benzalkonium chloride	0.02 g	0.02027 g
⑨ Purified water	qs 100 mL	qs 100 mL

In this preparation procedure EDTA will be dissolved in the aqueous phase with the aid of heat and a slurry of glycerin, polysorbate 80 and triamcinolone will be added to the aqueous phase containing the remaining ingredients, followed by homogenization and making up of the volume.

Preparation.

- Benzalkonium chloride weighed out in a 20 mL vial. 10 mL of water added and mixed to dissolve completely.
- In a 100 mL beaker, approximately 60 mL of water heated to 70°C and EDTA added to the heated water with stirring. Stirring continued till the EDTA is dissolved. Took about 10 min of stirring.
- Sodium chloride added and stirring continued

S. Rapp
14 Jun 2016

Reviewed by

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- til clear solution was obtained.
- Benzalkonium chloride solution added to the beaker and an additional 5ml of water used to rinse the container and transferred to the beaker under stirring.
 - The solution was allowed to cool down to below 35°C.
 - Azelastine HCl was weighed out and transferred to the solution under stirring, which was continued till all the added drug dissolved.
 - While stirring with a magnetic stir-bar to create a vortex, the hypromellose was slowly added in portions and allowed to wet and get suspended. The mixing was continued till a clear solution was obtained.
 - This solution was kept aside while the triamcinolone slurry was prepared.
 - Triamcinolone acetonide, glycerin and polysorbate 80 were weighed and transferred into a 20ml vial. The contents were mixed well on a vortex mixer to obtain a uniform slurry. Approximately 8ml of water was added to the vial and the contents mixed well to obtain a suspension.
 - The aqueous mixture of ② ⑤ ⑥ ⑦ ⑧ and a portion of the water was transferred to a 250ml beaker. The slurry of ① in a mixture of ③ and ④ with some water was added to the aqueous mixture with homogenization at 3000 rpm. The two containers were rinsed with approximately 15ml of water and the rinse was transferred to the main container.
 - Homogenization was continued at 1000 rpm for 15 minutes.

Analysed by

S. Rajapakse

Date

14 Jun 2016

Reviewed by

Date

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- The homogenization tool was raised, foam was allowed to subside to enable making up the volume.
- Sufficient water was added after de-foaming to make up the volume to 100 mL.
- The final mixture was homogenized at 6000rpm for 5 additional minutes.
- The final product was transferred to a 100 mL capacity serum bottle with stopper and allowed to stand at room temperature.
- After about 1 hr of standing the product was observed and compared with the batch prepared in 1345-004.
- Both preparations looked similar to the naked eye. Both exhibited presence of a fine sediment and visually no difference was observed between the two. In both cases, gently rotating the vials redispersed the fine sediment uniformly and no larger suspended particles were observed. The suspension had a hazy appearance with uniformly dispersed solid phase.

Conclusion - The modified preparation method which utilized heat to first dissolve EDTA yielded a uniform suspension which was similar to the batch obtained in 1345-004. Settling of the suspended solid occurred over time, but the sediment was easily and uniformly resuspendable.

S. Ly 14 Jun - 2016

S. Rappell
14 Jun - 2016

END

Triamcinolone Acetonide and Azelastine HCl nasal spray 1345-011

Batch preparation and
analysis.

S. Ry 16 Jun 2016

Purpose - Preparation of a 500 mL batch of nasal
spray containing 0.05% Triamcinolone Acetonide and
0.07% Azelastine HCl. 16-June-2016

Composition (Ingredient details on Page 3)

<u>Ingredients</u>	<u>Target qty</u>	<u>Actual qty</u>
- Triamcinolone Acetonide	0.250 g	0.24968 g
- Azelastine HCl	0.350 g	0.3499 g
- Ethylene diamine tetraacetic acid	0.250 g	0.2503 g
- Polysorbate 80	0.250 g	0.2510 g
- Glycerin	10.000 g	10.0087 g
- Benzalkonium chloride	0.100 g	0.1005 g
- Sodium chloride	4.500 g	4.5022 g
- Purified water S. Ry 16 Jun 2016	q.s 500 mL	q.s 500 mL
- Hypromellose	5.000 g	5.0040 g
- Purified water	q.s 500 mL	q.s 500 mL

Preparation

- 1) The 500 mL graduation on a 750 mL beaker was confirmed using 500 mL of water.
- 2) Benzalkonium chloride was weighed out into a 20 mL vial. Approximately 10 mL of water was added and the contents mixed well on a vortex mixer.
- 3) Approximately 250 mL of Purified water heated to 70°C
- 4) EDTA added to water with stirring. After most of the added solid had dissolved, the beaker was placed in an ultrasonic bath for 30 seconds and an additional 100 mL of water was added. Stirring resulted in a clear solution with ~~not~~ S. Ry 16 Jun 2016 no undissolved particles observed visually. Solution temperature was 65°C
- 5) Sodium chloride was transferred to the

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Solution under stirring using a magnetic stir-bar. Heating was stopped and the solution was allowed to cool on a cold surface with continued stirring.

- 6) When solution temperature was $\sim 35^{\circ}\text{C}$, azelastine HCl was transferred to the solution under stirring. The container was then placed in an ultrasonic bath for 1 minute and stirring was continued till a clear solution resulted.
- 7) Benzalkonium chloride solution was transferred to the beaker with stirring. An additional 10 mL of water was used to rinse out the vial and transferred to the beaker with stirring.
- 8) While stirring to create a vortex, the hypromellose was added in small portions till all the added hypromellose was wetted and suspended.
- 9) Stirring was continued.
- 10) In a 20 mL vial, polysorbate 80, glycerin and triamcinolone acetonide were weighed out or transferred. S. Ep 16 Jun 2016
- 11) The contents were mixed in a vortex mixer to obtain a smooth uniform slurry. An additional 5 mL of water was added to this slurry and the contents were mixed on a vortex mixer to obtain a uniform dispersion.
- 12) The aqueous solution phase from step 9 was a clear solution. It was transferred to the 750 mL beaker from step 1. While the contents were mixed using a homogenizer, the dispersion from step 11 was added.
- 13) The vial from step 11 and the beaker from step 9 were rinsed with 10 mL portions of purified

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water 4 times and the rinses were transferred to the main container with continued homogenization at 3000 rpm.

14) The mixture obtained was then homogenized at 7400 rpm for 30 min.

15) The homogenizing tool was raised and the preparation ~~was~~ (S. Rp 16 Jun 2016) was allowed to stand to allow the batch to 'de-foam'.

16) After 45 min, de-foaming was complete. Additional pumped water was carefully added to make-up the final volume to 500 mL.

17) Settled Solid was observed while making up the volume. The final ~~so~~ (S. Rp 16 Jun 2016) Suspension was homogenized @ 8000 rpm for 5 min and then at 10,000 rpm for 30 min. The suspension was allowed to deaerate and mixed well with a stirrer & filled into a 1000 mL capacity LDPE Bottle.

18) After 1 hr a fine sediment was observed which was readily and uniformly resuspendable.

Sedimentation behavior

The bulk container containing the final suspension product was then mixed well manually to uniformly suspend the solid particles. A 100 mL portion of the suspension was transferred to a 100 mL graduated cylinder and allowed to stand undisturbed on the lab bench.

The initial suspension appeared hazy but uniform ~~with~~ (S. Rp 16 Jun 2016).

Discrete suspended particulate matter could not be visually discerned.

After 10 min, there was no change in the visual

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appearance of the suspension.
 After 20 minutes the suspension continued to appear uniform.
 After 30 minutes of standing, there was some visual evidence of settled solid particles at the bottom of the cylinder.
 After 45 minutes the presence of settled solid was clearly evident.
 The suspension was allowed to stand overnight along with the bulk container for observation the next day.

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After overnight storage all the containers that had the suspension still appeared hazy with ~~no~~ (S. Ry 17-Jun-2016) settled solid at the bottom of the container.

In each case, gently inverting the container five to six times resulted in the solid being readily resuspended.

The 100ml Serum vials containing batches 1345-004 and 1345-008 had been left undisturbed for 3 days (S. Ry 17-Jun-2016) 14th to 17th June 2016.

The sediment in the ~~both~~ S. Ry 17 Jun 2016 vials also seemed to be easily resuspendable by gently inverting the vials 5-6 times, yielding a uniform suspension.

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Analysis Parameters

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Measurement of Osmolality 17-Jun-2016

- Fiske One-Ten Osmometer Asset ID 498658
- Sample: Triamcinolone Acetonide (0.05%) and Azelastine HCl (0.07%) nasal spray suspension Lot # NB 1345-011

Standards used: ~~200 mOsm~~ 290 mOsm/kg and 500 mOsm/kg

Sample measurement 1 - 529 mOsm/kg
 Sample measurement 2 - 529 mOsm/kg

Spray delivery

On 16-Jun 2016 after the bulk suspension was mixed and transferred to the graduated cylinder for observation of the sedimentation behavior, a portion of the suspension was filled into a 60cc clear glass bottle and a screw cap with a nasal spray pump (Aptar VP-7 pump Part # 5766, Lot # M6242) was used to close the bottle.

The delivery of the suspension by the spray pump was visually observed, and the resultant delivery pattern of the suspension was recorded using a video camera. It was observed that the prepared suspension (lot 1345-011) was delivered as a fine spray using the nasal spray pump.

Conclusion - A 500mL batch of Triamcinolone Acetonide (0.05%) and Azelastine HCl (0.07%) nasal spray suspension was prepared. A uniform product was obtained. Settling occurred but was readily & uniformly resuspendable. The product could be delivered as a fine spray using a nasal spray pump. Osmolality was measured.

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EXHIBIT D

Video Provided via FTP

EXHIBIT E

Video Provided via FTP