positively charged drug molecules away from the electrode and into the tissues. In one embodiment, iontophoresis is used to deliver proton pump inhibitors to infants for treating and/or preventing GI disorders. In one embodiment, the gastrointestinal disorder is GERD.

The invention provides for the proton pump inhibitors and, optionally, other active ingredients, to be administered nasally to a patient to treat the diseases and disorders described herein and those described, for example, in PCT Application No. PCT/US02/36857, the disclosure of which is incorporated by reference herein in its entirety. "Administered nasally" or "nasal administration" is intended to mean that at least one proton pump inhibitor is combined with a suitable delivery system for absorption across the nasal mucosa of a patient, preferably a human.

The proton pump inhibitors of the invention can be administered, for example, as nasal sprays, nasal drops, nasal suspensions, nasal gels, nasal ointments, nasal creams or nasal powders. The proton pump inhibitors can also be administered using nasal tampons or nasal sponges. The proton pump inhibitors of the invention can be brought into a viscous basis via systems conventionally used, for example, natural gums, methylcellulose and derivatives, acrylic polymers (carbopol) and vinyl polymers (polyvinylpyrrolidone). In the compositions, many other excipients known in the art can be added such as water, preservatives, surfactants, solvents, adhesives, antioxidants, buffers, bio-adhesives, viscosity enhancing agents and agents to adjust the pH and the osmolarity.

The nasal delivery systems can take various forms including aqueous solutions, non-aqueous solutions and combinations thereof. Aqueous solutions include, for example, aqueous gels, aqueous suspensions, aqueous liposomal dispersions, aqueous emulsions, aqueous microemulsions and combinations thereof. Non-aqueous solutions include, for example, non-aqueous gels, non-aqueous suspensions, non-aqueous liposomal dispersions, non-aqueous emulsions, non-aqueous microemulsions and combinations thereof.

In other embodiments, the nasal delivery system can be a powder formulation. Powder formulations include, for example, powder mixtures, powder microspheres, coated powder microspheres, liposomal dispersions and combinations thereof. Preferably, the powder formulation is powder microspheres. The powder microspheres

are preferably formed from various polysaccharides and celluloses selected from starch, methylcellulose, xanthan gum, carboxymethylcellulose, hydroxypropyl cellulose, carbomer, alginate polyvinyl alcohol, acacia, chitosans, and mixtures of two or more thereof.

In certain embodiments, the particle size of the droplets of the aqueous and/or non-aqueous solution or of the powders delivered to the nasal mucosa can be, for example, about 0.1 micron to about 100 microns; from about 1 micron to about 70 microns; from about 5 microns to about 50 microns; or from about 10 microns to about 20 microns. The particle sizes can be obtained using suitable containers or metering devices known in the art. Exemplary devices include mechanical pumps in which delivery is made by movement of a piston; compressed air mechanisms in which delivery is made by hand pumping air into the container; compressed gas (e.g., nitrogen) techniques in which delivery is made by the controlled release of a compressed gas in the sealed container; liquefied propellant techniques in which a low boiling liquid hydrocarbon (e.g., butane) is vaporized to exert a pressure and force the composition through the metered valve; and the like. Powders may be administered, for example, in such a manner that they are placed in a capsule that is then set in an inhalation or insufflation device. A needle is penetrated through the capsule to make pores at the top and the bottom of the capsule and air is sent to blow out the powder particles. Powder formulation can also be administered in a jet-spray of an inert gas or suspended in liquid organic fluids.

In one embodiment, the invention provides a nasally administrable pharmaceutical composition comprising at least one proton pump inhibitor dispersed in a nasal delivery system that improves the solubility of the proton pump inhibitor. The nasal delivery system that improves solubility can include one of the following or combinations thereof: (i) a glycol derivative (e.g., propylene glycol, polyethylene glycol, mixtures thereof); (ii) a sugar alcohol (e.g., mannitol, xylitol, mixtures thereof); (iii) glycerin; (iv) a glycol derivative (e.g., propylene glycol, polyethylene glycol or mixtures thereof) and glycerin; (v) ascorbic acid and water; (vi) sodium ascorbate and water; or (vii) sodium metabisulfite and water.

In another embodiment, the invention provides a nasally administrable pharmaceutical composition comprising at least one proton pump inhibitor and a nasal

delivery system, where the nasal delivery system comprises at least one buffer to maintain the pH of the proton pump inhibitor, at least one pharmaceutically acceptable thickening agent and at least one humectant. The nasal delivery system can optionally further comprise surfactants, preservatives, antioxidants, bio-adhesives, pH adjusting agents, isotonicity agents, solubilizing agents, and/or other pharmaceutically acceptable excipients. The proton pump inhibitor can optionally be dispersed in a nasal delivery system that improves its solubility.

In another embodiment, the invention provides a nasally administrable pharmaceutical composition comprising at least one proton pump inhibitor and a nasal delivery system, where the nasal delivery system comprises at least one solubilizing agent, at least one pharmaceutically acceptable thickening agent and at least one humectant. The nasal delivery system can optionally further comprise buffers, pH adjusting agents, isotonicity agents, surfactants, preservatives, antioxidants, bio-adhesives, and/or other pharmaceutically acceptable excipients. The proton pump inhibitor can optionally be dispersed in a nasal delivery system that improves its solubility.

In another embodiment, the invention provides a nasally administrable pharmaceutical composition comprising at least one proton pump inhibitor and a nasal delivery system, where the nasal delivery system comprises at least one buffer to maintain the pH of the proton pump inhibitor, at least one pharmaceutically acceptable thickening agent, at least one humectant, and at least one surfactant. The nasal delivery system can optionally further comprise pH adjusting agents, isotonicity agents, solubilizing agents, preservatives, antioxidants, bio-adhesives, and/or other pharmaceutically acceptable excipients. The proton pump inhibitor can optionally be dispersed in a nasal delivery system that improves its solubility.

In yet another embodiment, the invention provides a nasally administrable pharmaceutical composition comprising at least one proton pump inhibitor and a nasal delivery system, where the nasal delivery system comprises at least one pharmaceutically acceptable thickening agent, at least one humectant, at least one surfactant, and at least one solubilizing agent. The nasal delivery system can optionally further comprise buffers, pH adjusting agents, isotonicity agents, preservatives, antioxidants, bio-adhesives, and/or other pharmaceutically acceptable excipients. The

proton pump inhibitor can optionally be dispersed in a nasal delivery system that improves its solubility.

In yet another embodiment, the invention provides a nasally administrable pharmaceutical composition comprising at least one proton pump inhibitor and a nasal delivery system, where the nasal delivery system comprises at least one buffer to maintain the pH of the proton pump inhibitor, at least one pharmaceutically acceptable thickening agent, at least one humectant, at least one surfactant, and at least one solubilizing agent. The nasal delivery system can optionally further comprise buffers, pH adjusting agents, isotonicity agents, preservatives, antioxidants, bio-adhesives, and/or other pharmaceutically acceptable excipients. The proton pump inhibitor can optionally be dispersed in a nasal delivery system that improves its solubility.

The nasally administrable pharmaceutical compositions of the invention preferably provide a peak plasma concentration of the proton pump inhibitor in less than one hour, preferably within about 5 minutes to about 30 minutes, more preferably within about 5 minutes to about 20 minutes, after administration to the patient.

The buffer has a pH that is selected to optimize the absorption of the proton pump inhibitor across the nasal mucosa. The particular pH of the buffer can vary depending upon the particular nasal delivery formulation as well as the specific proton pump inhibitor selected. Buffers that are suitable for use in the invention include acetate (e.g., sodium acetate), citrate (e.g., sodium citrate dihydrate), phthalate, borate, prolamine, trolamine, carbonate, phosphate (e.g., monopotassium phosphate, disodium phosphate), and mixtures of two or more thereof.

The pH of the compositions should be maintained from about 3.0 to about 10.0. Compositions having a pH of less than about 3.0 or greater than about 10.0 can increase the risk of irritating the nasal mucosa of the patient. Further, it is preferable that the pH of the compositions be maintained from about 3.0 to about 9.0. With respect to the non-aqueous nasal formulations, suitable forms of buffering agents can be selected such that when the formulation is delivered into the nasal cavity of a mammal, selected pH ranges are achieved therein upon contact with, e.g., a nasal mucosa.

The solubilizing agent for use in the compositions of the invention can be any known in the art, such as carboxylic acids and salts thereof. Exemplary carboxylic acid salts include acetate, gluconate, ascorbate, citrate, fumurate, lactate, tartrate, malate,

maleate, succinate, or mixtures of two or more thereof.

The viscosity of the compositions of the present invention can be maintained at a desired level using a pharmaceutically acceptable thickening agent. For example, the viscosity may be at least 1000 cps; from about 1000 to about 10,000 cps; from about 2000 cps to about 6500 cps; or from about 2500 cps to about 5000 cps. Thickening agents that can be used in accordance with the present invention include, for example, methyl cellulose, xanthan gum, carboxymethyl cellulose, hydroxypropyl cellulose, carbomer, polyvinyl alcohol, alginates, acacia, chitosans, and mixtures of two or more thereof. The concentration of the thickening agent will depend upon the agent selected and the viscosity desired. Such agents can also be used in a powder formulation.

The nasally administrable compositions can also include a humectant to reduce or prevent drying of the mucus membrane and to prevent irritation thereof. Suitable humectants that can be used include, for example, sorbitol, mineral oil, vegetable oil and glycerol; soothing agents; membrane conditioners; sweeteners; and mixtures of two or more thereof. The concentration of the humectant will vary depending upon the agent selected. In one embodiment, the humectant can be present in the nasal delivery system in a concentration ranging from about 0.01% to about 20% by weight of the composition.

In other embodiments, the nasal delivery system can further comprise surfactants which enhance the absorption of the proton pump inhibitor. Suitable surfactants include non-ionic, anionic and cationic surfactants. Exemplary surfactants include oleic acid, polyoxyethylene derivatives of fatty acids, partial esters of sorbitol anhydride, such as for example, Tweens (e.g., Tween 80, Tween 40, Tween 20), Spans (e.g., Span 40, Span 80, Span 20), polyoxyl 40 stearate, polyoxy ethylene 50 stearate, fusieates, bile salts, octoxynol, and mixtures of two or more thereof. Exemplary anionic surfactants include salts of long chain hydrocarbons (e.g., C_{6-30} or C_{10-20}) having one or more of the following functional groups: carboxylates; sulfonates; and sulfates. Salts of long chain hydrocarbons having sulfate functional groups are preferred, such as sodium cetostearyl sulfate, sodium dodecyl sulfate and sodium tetradecyl sulfate. One particularly preferred anionic surfactant is sodium lauryl sulfate (i.e., sodium dodecyl sulfate). The surfactants can be present in an amount from about 0.001% to about 50% by weight, or from about 0.001% to about 20% by weight.

The pharmaceutical compositions of the invention may further comprise an isotonicity agent, such as sodium chloride, dextrose, boric acid, sodium tartrate or other inorganic or organic solutes.

The nasal pharmaceutical compositions of the invention can optionally be used in combination with a pH adjusting agent. Exemplary pH adjusting agents include sulfuric acid, sodium hydroxide, hydrochloric acid, and the like.

To extend shelf life, preservatives can be added to the nasally administrable compositions. Suitable preservatives that can be used include benzyl alcohol, parabens, thimerosal, chlorobutanol, benzalkonium chloride, or mixtures of two or more thereof. Preferably benzalkonium chloride is used. Typically, the preservative will be present in a concentration of up to about 2% by weight. The exact concentration of the preservative, however, will vary depending upon the intended use and can be easily ascertained by one skilled in the art.

Other ingredients which extend shelf life can be added such as for example, antioxidants. Some examples of antioxidants include sodium metabisulfite, potassium metabisulfite, ascorbyl palmitate and the like. Typically, the antioxidant will be present in the compositions in a concentration of from about 0.001% up to about 5% by weight of the total composition.

Other optional ingredients can also be incorporated into the nasal delivery system provided that they do not interfere with the action of the proton pump inhibitor or significantly decrease the absorption of the proton pump inhibitor across the nasal mucosa.

The nasal delivery systems can be made following the processes described in, for example, U.S. Patent Nos. 6,451,848, 6,436,950, and 5,874,450, and WO 00/00199, the disclosures of which are incorporated by reference herein in their entirety.

Each of the patents and publications cited herein are incorporated by reference herein in their entirety.

It will be apparent to one skilled in the art that various modifications can be made to the invention without departing from the spirit or scope of the appended claims.

Claims

What is claimed is:

1. A method for treating or preventing a gastrointestinal disorder induced or caused by a nonsteroidal anti-inflammatory drug comprising administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor and at least one nonsteroidal anti-inflammatory drug selected from the group consisting of diclofenac, celecoxib, rofecoxib, and valdecoxib.

2. The method of claim 1, wherein the proton pump inhibitor is rabeprazole.

3. A method for treating cystic fibrosis in a patient in need thereof comprising administering a therapeutically effective amount of at least one proton pump inhibitor and at least one cystic fibrosis drug selected from the group consisting of albuterol, theophylline, ipratropium, guaifenesin, dnase, n-acetylcysteine, triamcinolone, flunisolide, fluticasone, beclomethasone, prednisone, methylprednisone, ibuprofen, montelukast, cromolyn, ciprofloxacin, co-trimoxazole, tobramycin, cephalexin, colistin, dicloxacillin, azithromycin, vitamins, pancrelipase, docusate, casanthranol/docusate, omeprazole, ranitidine, loratadine, cetirizine, and fexofenadine.

4. A method for treating or preventing radiation therapy induced emesis in a patient in need thereof comprising administering a therapeutically effective amount of at least one proton pump inhibitor.

5. A method for treating or preventing chronic ear infection in a patient in need thereof comprising administering a therapeutically effective amount of at least one proton pump inhibitor and, optionally, at least one antibiotic.

6. The method of claim 5, wherein the antibiotic is selected from the group comprising of amoxicillin, amoxicillin and clavulanate potassium, cefpodoxime proxetil, ceftriaxone, cefuroxime, and trimethoprim/sulfamethoxazole.

7. A method for treating or preventing bruxism in a patient in need thereof comprising administering a therapeutically effective amount of at least one proton pump inhibitor.

8. A method for treating or preventing gastroesophageal reflux in a patient comprising administering a therapeutically effective amount of at least one proton pump inhibitor prior to anesthesia.

9. The method of claim 8, wherein the proton pump inhibitor is administered before surgery when the patient is anesthetized.

10. The method of claim 8, wherein the proton pump inhibitor is administered during surgery when the patient is anesthetized.

11. The method of claim 8, wherein the proton pump inhibitor is administered after surgery when the patient is anesthetized.

12. A method for treating or preventing motion sickness in a patient in need thereof comprising administering a therapeutically effective amount of at least one proton pump inhibitor and, optionally, at least one motion sickness drug.

13. The method of claim 12, wherein the motion sickness drug is selected from the group comprising of scopolamine, promethazine hydrochloride, dimenhydrinate, diphenhydramine, cyclizine, buclizine, and meclizine.

14. A method for treating or preventing migraines in a patient in need thereof comprising administering a therapeutically effective amount of at least one proton pump inhibitor and at least one migraine drug selected from the group consisting of diclofenac, celecoxib, rofecoxib, and valdecoxib.

15. A method for treating or preventing tooth decay caused by emesis in a patient in need thereof comprising administering a therapeutically effective amount of at least one proton pump inhibitor.

16. A method for treating gastroesophageal reflux disease in an infant in need thereof comprising administering a therapeutically effective amount of at least one proton pump inhibitor to the infant by iontophoresis.

17. A method for treating or preventing exercise-induced gastroesophageal reflux disease in a patient in need thereof comprising administering a therapeutically effective amount of at least one proton pump inhibitor.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 August 2005 (18.08.2005)

PCT

(10) International Publication Number
WO 2005/074536 A3

(51) International Patent Classification[7]: A61K 31/415, 31/435

(21) International Application Number: PCT/US2005/002674

(22) International Filing Date: 31 January 2005 (31.01.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/539,981 30 January 2004 (30.01.2004) US

(71) Applicant *(for all designated States except US)*: **EISAI CO., LTD.** [JP/JP]; Koishikawa 4-6-10, Bunkyo-ku, Tokyo 112-8088 (JP).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **IENI, John** [US/US]; 253 Ridgewood Avenue, Glen Ridge, NJ 07028 (US).

(74) Agents: **GRIEFF, Edward, D.** et al.; Wilmer Cutler Pickering Hale and Dorr LLP, 1455 Pennsylvania Avenue, N.W., Washington, DC 20004 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
29 December 2005

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COMPOSITIONS AND METHODS USING PROTON PUMP INHIBITORS

(57) Abstract: The invention provides methods for treating and preventing cystic fibrosis, radiation therapy-induced emesis, chronic ear infections, bruxism, motion, sickness, tooth decay due to emesis and other disorders by administering to a patient a therapeutically effective amount of at least one proton pump inhibitor. In other embodiments, the proton pump inhibitor can be administered with one or more cystic fibrosis drugs, motion sickness drugs, antibiotics, NSAIDs, and migraine drugs.

WO 2005/074536 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/02674

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/415, 435

US CL : 514/277, 396

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/277, 396

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6,649,629 B2 (BANDARAGE et al.) 18 November 2003 (18.11.2003), abstract, column 3, lines 43-65, column 57, lines 16-25, lines 53-65, column 58, lines 28-43).	1-17
X	US 6,544,556 B1 (CHEN et al.) 08 April 2003 (08.04.2003), abstract, column 5, lines 58-65, column 7, lines 9-11, column 3)	1-17

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

22 September 2005 (22.09.2005)

Date of mailing of the international search report

03 NOV 2005

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Facsimile No. (703) 305-3230

Authorized officer

Sreenivasan Padmanabhan

Telephone No. 703-308-1235

Form PCT/ISA/210 (second sheet) (April 2005)

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 August 2005 (18.08.2005)

PCT

(10) International Publication Number
WO 2005/074930 A1

(51) International Patent Classification[7]: A61K 31/4439, 31/00, A61P 1/04

(21) International Application Number:
PCT/EP2005/050335

(22) International Filing Date: 27 January 2005 (27.01.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
04001755.0 28 January 2004 (28.01.2004) EP

(71) Applicant *(for all designated States except US)*: **ALTANA PHARMA AG** [DE/DE]; Byk-Gulden-Str. 2, 78467 Konstanz (DE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **HUBER, Reinhard** [DE/DE]; Oehmdwiesenweg 10, 78476 Allensbach (DE). **KOHL, Bernhard** [DE/DE]; Zum Bruehl 9, 78465 Konstanz (DE). **KROMER, Wolfgang** [DE/DE]; Hinterhauserstr. 5, 78464 Konstanz (DE). **SIMON, Wolfgang-Alexander** [DE/DE]; Schubertstrasse 17, 78464 Konstanz (DE).

(74) Agents: **WOLF, Ulrich** et al.; c/o ALTANA Pharma AG, Byk-Gulden-Str. 2, 78467 Konstanz (DE).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PHARMACEUTICAL COMBINATIONS OF (S) -PANTOPRAZOLE WITH NSAID OR CORTICOSTEROIDS

(57) Abstract: The present invention relates to new combinations and new use of (S)-pantoprazole and/or its salts in the prevention or treatment of medicament caused gastrointestinal diseases.

WO 2005/074930 A1

PHARMACEUTICAL COMBINATIONS OF (S)-PANTOPRAZOLE WITH NSAID OR CORTICOSTEROIDS

Field of application of the invention

The invention relates to the new use of (S)-pantoprazole and its salts in the prevention or treatment of medicament caused gastrointestinal diseases and/or medicament associated gastrointestinal disorders and to new use of (S)-pantoprazole and its salts in combination therapy, and to new combinations comprising (S)-pantoprazole and its salts.

Known technical background

In U. S. Patent 6,544,556 pharmaceutical formulations containing a non-steroidal anti-inflammatory drug (NSAID) and a proton pump inhibitor are disclosed. - In European Patent Application 1 352 660 oral pharmaceutical dosage forms comprising a proton pump inhibitor and an NSAID are described and claimed. - U. S. Patent Application 2003/069255 is directed to drug dosage forms that release an agent that raises the pH of a patient's gastrointestinal tract, for example a proton pump inhibitor, followed by an NSAID. - International Patent Application WO 03/075884 provides effervescent composition comprising a bisphosphonate, an acidic compound, an alkaline effervescing component, and optionally an anti-ulcer agent, such as a proton pump inhibitor, and methods of treating osteoporosis in a mammal using the effervescent compositions. - In U. S. Patent 5,888,535, according to the abstract of said patent "methods and compositions are disclosed utilizing optically pure (-)-pantoprazole for the treatment of ulcers in humans while substantially reducing the concomitant liability of adverse effects associated with the racemic mixture of pantoprazole." - In U. S. Patent 6,410,569 the dihydrate of the magnesium salt of pantoprazole is disclosed.

Description of the invention

It has now been found that (S)-pantoprazole and its salts, which are described in greater detail below, have, as a first aspect (aspect 1) of the present invention, advantageous gastro-protective action against certain medicaments (such as, for example, those medicaments mentioned below in the description of this invention, especially antiinflammatoriies and antirheumatics, and/or, in particular, those medicaments which cause erosive changes and/or lesions in the gastrointestinal system) and/or are well useful and effective in prevention or treatment of gastrointestinal disorders associated with certain medicaments indicated below and/or are particularly useful and effective in prevention or treatment of gastrointestinal diseases caused by certain medicaments selected from the group consisting of NSAIDs (non-steroidal antiinflammatory drugs), COX-2 (cyclooxygenase 2) inhibitors, NO-NSAIDs (nitric oxide releasing NSAID), bisphosphonates and corticosteroids, and/or can be used, as a second aspect (aspect 2) of the present invention, in combination therapy of diseases and/or disorders

which can be treated, ameliorated or prevented with said certain medicaments mentioned above in aspect 1, particularly with those medicaments selected from the group consisting of NSAIDs (non-steroidal antiinflammatory drugs), COX-2 (cyclooxygenase 2) inhibitors, NO-NSAIDs (nitric oxide releasing NSAID), bisphosphonates and corticosteroids, whereby said combination therapy is characterised by improved gastrointestinal safety and tolerance compared to mono therapy.

Unexpectedly it has been found, that the gastrointestinal safety and tolerability of a combination comprising (a) (S)-pantoprazole and/or its salts as defined herein, and (b) an agent selected from the group consisting from NSAIDs, COX-2 inhibitors, NO-NSAIDs, bisphosphonates and corticosteroids is greater than that, which can be achieved with said agent (b) alone, i.e. greater than the gastrointestinal safety and tolerability of a mono therapy using only said agent (b) unpartnered with (S)-pantoprazole and/or its salts.

Within the scope of this invention, "(S)-pantoprazole and/or its salts" is understood to include:
- (S)-pantoprazole and/or its salts [which is the same as (-)-pantoprazole and its salts]
- (S)-pantoprazole [(-)-pantoprazole]
- salts of (S)-pantoprazole [(-)-pantoprazole]
- (S)-pantoprazole [(-)-pantoprazole] and/or its salts being substantially free of (R)-pantoprazole [(+)-pantoprazole] and /or its salts
- (S)-pantoprazole [(-)-pantoprazole] being substantially free of (R)-pantoprazole [(+)-pantoprazole]
- salts of (S)-pantoprazole [(-)-pantoprazole] being substantially free of salts of (R)-pantoprazole [(+)-pantoprazole].

"Salts" in the context of the invention means all pharmaceutically acceptable salts prepared by reacting (S)-pantoprazole [(-)-pantoprazole] with a suitable inorganic or organic base. Examples of salts with bases which may be mentioned are aluminium, sodium, potassium, lithium, magnesium, zinc or calcium salts. Particularly preferred is the magnesium salt. If (S)-pantoprazole and/or its salts are isolated in crystalline form, the crystals may contain variable amounts of solvent. Accordingly, according to the invention, the term "(S)-pantoprazole and/or its salts" also includes all solvates, in particular all hydrates, of (S)-pantoprazole and/or its salts. An exemplary hydrate of (S)-pantoprazole and/or its salts, which may be mentioned, is (S)-pantoprazole-sodium sesquihydrate [= (S)-pantoprazole-sodium x 1.5 H_2O]. A particularly preferred hydrate of (S)-pantoprazole and/or its salts is the (S)-pantoprazole-magnesium dihydrate.

"Substantially free" in the context of the invention means that (S)-pantoprazole and/or its salts contains less than 10 % by weight of (R)-pantoprazole. Preferably, "substantially free" means that (S)-pantoprazole and/or its salts contains less than 5 % by weight of (R)-pantoprazole. In the most preferred embodiment, "substantially free" means that (S)-pantoprazole and/or its salts contains less than 1 % by weight of (R)-pantoprazole.

Within the scope of this invention the terms "medicament caused gastrointestinal diseases" and "gastrointestinal diseases caused by certain medicaments" refer to gastrointestinal diseases which are induced and/or caused by certain medicaments selected from the group consisting of NSAIDs (non-steroidal antiinflammatory drugs), COX-2 (cyclooxygenase 2) inhibitors, NO-NSAIDs (nitric oxide releasing NSAID), bisphosphonates and corticosteroids, whereby NSAIDs, COX-2 inhibitors, NO-NSAIDs and bisphosphonates are particularly worthy to be mentioned; NSAIDs, COX-2 inhibitors and NO-NSAIDs are to be emphasized, NSAIDs and COX-2 inhibitors are more to be emphasized, and NSAIDs are particularly to be emphasized.

Exemplary NSAIDs within the meaning of the present invention are, in an embodiment (embodiment 1) according to the present invention, glycolic acid [o-(2,6-dichloroanilino)phenyl]acetate(ester) [INN: ACECLOFENAC]; 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid carboxymethyl ester [INN: ACEMETACIN]; 2-(acetyloxy)benzoic acid [ACETYLSALICYLIC ACID], 2-methoxyphenyl-alpha-methyl-4-(isobutyl)phenylacetate [Research Code: AF-2259], (4-allyloxy-3-chlorophenyl)acetic acid [INN: ALCLOFENAC], p-[(2-methylallyl)amino]hydratropic acid [INN: ALMINOPROFEN], 2-amino-3-benzoylphenylacetic acid [INN: AMFENAC], (plus/minus)-4-(1-hydroxyethoxy)-2-methyl-N-2-pyridyl-2H-1,2-benzothiazine-3-carboxamide ethylcarbonate (ester), 1,1-dioxide [INN: AMPIROXICAM], 2-methoxyphenyl-1-methyl-5-(p-methylbenzoyl)pyrrol-2-acetamido-acetate [INN: AMTOLMETINGUACIL], (plus/minus)-2,3-dihydro-5-(4-methoxybenzoyl)-1H pyrrolizine-1-carboxylic acid [INN: ANIROLAC], 2-[4-(alpha,alpha,alpha-trifluoro-m-tolyl)-1-piperazinyl]ethyl-N-(7-trifluoromethyl-4-quinolyl)anthranilate [INN: ANTRAFENINE], 5-(dimethylamino)-9-methyl-2-propyl-1H-pyrazolo[1,2-a][1,2,4]benzo-triazine-1,3(2H)-dione [INN: AZAPROPAZONE], 4-acetamidophenyl salicylate acetate [INN: BENORILATE], 2-(8-methyl-10,11-dihydro-11-oxodibenz[b,f]oxepin-2-yl)propionic acid [INN: BERMOPROFEN], 2-[(1-benzyl-1H-indazol-3-yl)methoxy]-2-methylpropionic acid [INN: BINDARIT], [2-amino-3-(p-bromobenzoyl)phenyl]acetic acid [INN: BROMFENAC], 3-(3-chloro-4-cyclohexylbenzoyl)propionic acid [INN: BUCLOXIC ACID], 5-butyl-1-cyclohexylbarbituric acid [INN: BUCOLOM], 4-butoxy-N-hydroxybenzeneacetamide [INN: BUFEXAMAC], butylmalonic acid mono(1,2-diphenylhydrazide) [INN: BUMADIZONE], alpha-ethyl-4-(2-methylpropyl)benzeneacetic acid [INN: BUTIBUFEN], 2-(4-biphenylyl)butyric acid, trans-4-phenylcyclohexylamine salt (1:1) [INN: BUTIXIRATE], 2-(acetyloxy)-benzoic acid, calcium salt, compound with urea (1:1) [INN: CARBASALATE CALCIUM], (plus/minus)-6-chloro-alpha-methylcarbazole-2-acetic acid [INN: CARPROFEN], 1-cinnamoyl-5-methoxy-2-methylindole-3-acetic acid [INN: CINMETACIN], N-(2-pyridyl)-2-methyl-4-cinnamoyloxy-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide [INN: CINNOXICAM], 6-chloro-5-cyclohexyl-1-indancarboxylic acid [INN: CLIDANAC], 2-[4-(p-chlorophenyl)benzyloxy]-2-methylpropionic acid [INN: CLOBUZARIT], 5-methoxy-2-methyl-3-indolylacetohydroxamic acid [INN: DEBOXAMET], (S)-(+)-p-isobutylhydratropic acid [INN: DEXIBUPROFEN], (+)-(S)-m-benzoylhydratropic acid [INN: DEXKETOPROFEN], 2-[(2,6-dichlorophenyl)amino]benzeneacetic acid [INN: DICLOFENAC], 2',4'-Difluoro-4-hydroxy-3-biphenylcarboxylic acid [INN: DIFLUNISAL], 4-(2,6-dichloroanilino)-3-thiopheneacetic acid [INN: ELTENAC], N-beta-phenethyl-anthranilic acid [INN: ENFENAMIC ACID] salicylic acid acetate, ester with

beta-hydroxy p-acetophenetidide [INN: ETERSALATE], 1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid [INN: ETODOLAC], 2-[[3-(trifluoromethyl)phenyl]amino]benzoic acid 2-(2-hydroxyethoxy)-ethyl ester [INN: ETOFENAMATE], p-chlorobenzoic acid, ester with 4-butyl-4-(hydroxymethyl)-1,2-diphenyl-3,5-pyrazolidinedione [INN: FECLOBUZONE], 4-biphenylacetic acid [INN: FELBINAC], 3-(4-biphenylylcarbonyl)propionic acid [INN: FENBUFEN], [o-(2,4-dichlorophenoxy)phenyl]acetic acid [INN: FENCLOFENAC], (plus/minus)-m-phenoxyhydratropic acid [INN: FENOPROFEN], 4-(p-chlorophenyl)-2-phenyl-5-thiazoleacetic acid [INN: FENTIAZAC], (plus/minus)-alpha-[[(2-hydroxy-1,1-dimethylethyl)amino]methyl]-benzyl alcohol [INN: FEPRADINOL], 4-(2',4'-difluorobiphenylyl)-4-oxo-2-methylbutanoic acid [INN: FLOBUFEN], 2,3-dihydroxypropyl N-[8-(trifluoromethyl)-4-quinoly]anthranilate [INN: FLOCTAFENINE], N-(alpha,alpha,alpha-trifluoro-m-tolyl)anthranilic acid [INN: FLUFENAMIC ACID], (plus)-2-(p-fluorophenyl)-alpha-methyl-5-benz-oxazoleacetic acid [INN: FLUNOXAPROFEN], 2-fluoro-alpha-methyl-4-biphenylacetic acid [INN: FLURBIPROFEN], (plus/minus)-2-(2-fluoro-4-biphenylyl)propionic acid 1 (acetoxy)ethyl ester [INN: FLURBIPROFEN AXETIL], 2-ethyl-2,3-dihydro-5-benzofuranacetic acid [INN: FUROFENAC], 2-[4-(2'-furoyl)phenyl]propionic acid [INN: FURPROFEN], 2-[2-[1-(p-chlorobenzoyl)-5-methoxy-2-methylindol-3-yl]acetamido]-2-deoxy-D-glucose [INN: GLUCAMETACIN], 2-(2-fluorobiphenyl-4-yl)propionic acid 4-nitrooxybutylester [Research Code: HCT-1026], (p-isobutylphenyl)acetic acid [INN: IBUFENAC], alpha-p-isobutylphenylpropionic acid [INN: IBUPROFEN], methyl 4-(3-thienyl)phenyl-alpha-methylacetate [Research Code: IDPH-8261], (plus/minus)-2-[p-(1-oxo-2-isoindolinyl)phenyl]butyric acid [INN: INDOBUFEN], 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid [INN: INDOMETACIN], 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid, 3,7,11-trimethyl-2,6,10-dodecatrienyl ester [INN: INDOMETACIN FARNESIL], p-(1-oxo-2-isoindolinyl)hydratropic acid [INN: INDOPROFEN], 2-(10-methoxy-4H-benzo[4,5]cyclohepta[1,2-b]thiophen-4-ylidene)-acetic acid [Research Code: IX-207-887], m-benzoylhydratropic acid [INN: KETOPROFEN], (DL)-5-benzoyl-3H-1,2-dihydropyrrolo[1,2-a]pyrrole-1-carboxylic acid [INN: KETOROLAC], 2,3-dihydro-5-hydroxy-6-[2-(hydroxymethyl)cinnamyl]benzofuran [Research Code: L-651896], N-(2-carboxyphenyl)-4-chloroanthranilic acid [INN: LOBENZARIT], 3-(p-chlorophenyl)-1-phenylpyrazole-4-acetic acid [INN: LONAZOLAC], 6-chloro-4-hydroxy-2-methyl-N-2-pyridyl-2H-thieno[2,3-e]-1,2-thiazine-3-carboxamide 1,1-dioxide [INN: LORNOXICAM], 2-[4-(2-oxocyclopentan-1-ylmethyl)phenyl]-propionate [INN: LOXOPROFEN], 2(R)-[4-(3-methyl-2-thienyl)phenyl]propionic acid [Research Code: M-5010], N-(2,3-xylyl)anthranilic acid [INN: MEFENAMIC ACID], 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide [INN: MELOXICAM], 5-aminosalicylic acid [INN: MESALAZINE], (2,2-dimethyl-6-(4-chlorophenyl)-7-phenyl-2,3-dihydro-1H-pyrrolizin-5-yl)-acetic acid [Research Code: ML-3000], 3,4-bis(4-methoxyphenyl)-5-isoxazoleacetic acid [INN: MOFEZOLAC], 4-(6-methoxy-2-naphthyl)-2-butanone [INN: NABUMETONE], (plus)-6-methoxy-alpha-methyl-2-naphthalineacetic acid [INN: NAPROXEN], 2-[3-(trifluoromethyl)anilino]nicotinic acid [INN: NIFLUMIC ACID], 5,5'-azodisalicylic acid [INN: OLSALAZINE], 4,5-diphenyl-2-oxazolepropionic acid [INN: OXAPROZIN], alpha-methyl-4-[(2-oxocyclohexylidene)methyl]benzene acetic acid [INN: PELUBIPROFEN], 4-butyl-1,2-diphenyl-3,5-pyrazolidinedione [INN: PHENYLBUTAZONE], 2-(p-isobutylphenyl)propionic acid 2-pyridyl-methyl ester [INN: PIMEPROFEN], 4-(p-chlorophenyl)-1-(p-

fluorophenyl)pyrazole-3-acetic acid [INN: PIRAZOLAC], 4-hydroxy-2-methyl-N-2-pyridyl-2H-1,2-benzothiadiazin-3-carboxamide 1,1-dioxide [INN: PIROXICAM], 3-chloro-4-(3-pyrrolin-1-yl)hydratropic acid [INN: PIRPROFEN], 2-[5H-(1)benzopyrano]2,3-b]pyridin-7-yl]propionic acid [INN: PRANOPROFEN], 2,6-di-tert-butyl-4-(2'-thenoyl)phenol [INN: PRIFELONE], alpha-cyano-1-methyl-beta-oxopyrrole-2-propionanilide [INN: PRINOMIDE], 3-[4-(2-hydroxyethyl)-1-piperazinyl]-propyl-D,L-4-benzamido-N,N-dipropylglutaramat 1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetate (ester) [INN: PROGLUMETACIN], 7-methyl-1-(1-methylethyl)-4-phenyl-2(1H)quinazolinone [INN: PRO-QUAZONE], 7-methoxy-alpha,10-dimethylphenothiazine-2-acetic acid [INN: PROTIZINIC] ACID], 2-[[2-(p-chlorophenyl)-4-methyl-5-oxazolyl]methoxy]-2-methylpropionic acid [INN: ROMAZARIT], o-hydroxybenzamide [SALICYLAMIDE], 2-hydroxybenzoic acid [SALICYLIC ACID], N-acetyl-L-cysteine salicylate (ester), acetate (ester) [INN: SALMISTEINE], N-acetyl-L-cysteine salicylate (ester) [INN: SALNACEDIN], 2-hydroxybenzoic acid 2-carboxyphenyl ester [INN: SALSALATE], 4-[1-(2-fluorobiphenyl-4-yl)ethyl]-N-methylthiazole-2-amine [Research Code: SM-8849], (Z)-5-fluoro-2-methyl-1-[p-(methylsulfinyl)benzylidene]indene-3-acetic acid [INN: SULINDAC], p-2-thenoylhydratropic acid [INN: SUPROFEN] 2-(4-(3-methyl-2-butenyl)phenyl)propionic acid [Research Code: TA-60], phthalidyl 2-(alpha,alpha,alpha-trifluoro-m-toluidino)nicotinate [INN: TALNIFLUMATE], (Z)-5-chloro-3-(2-thenoyl)-2-oxoindole-1-carboxamide [INN: TENIDAP], 2-thiophenecarboxylic acid, ester with salicylic acid [INN: TENOSAL], 4-hydroxy-2-methyl-N-2-pyridyl-2H-thieno[2,3-e]-1,2-thiazine-3-carboxamide [INN: TENOXICAM], 5-(4-chlorophenyl)-N-hydroxy-1-(4-methoxyphenyl)-N-methyl-1H-pyrazole-3-propionamide [INN: TEPOXALIN], alpha-(5-benzoyl-2-thienyl)propionic acid [INN: TIAPROFENIC ACID], 5-chloro-3-[4-(2-hydroxyethyl)-1-piperazinyl]carbonylmethyl-2-benzo-thiazolin one [INN: TIARAMIDE], 2-(2-methyl-5H-[1]benzopyrano[2,3-b]pyridin-7-yl)-propionic acid N,N-dimethylcarbamoylmethyl ester [INN: TIMNOPROFEN ARBAMEL], 1-Cyclohexyl-2-(2-methyl-4-quinolyl)-3-(2-thiazolyl)guanidine [INN: TIMEGADINE], 2-amino-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine [INN: TINORIDINE], N-(3-chloro-o-tolyl)anthranilic acid [INN: TOLFENAMIC ACID], 1-methyl-5-(4-methylbenzoyl)-1H-pyrrole-2-acetic acid [INN: TOLMETIN], hydroxybis[alpha-methyl-4-(2-methylpropyl)benzene acetato-O]-aluminium [Research Code: U-18573-G], N-(3-trifluoromethylphenyl)-anthranilic acid n-butyl ester [INN: UFENAMATE], 2-[4-[3-(hydroxyimino)cyclohexyl]phenyl]propionic acid [INN: XIMOPROFEN], 2-(10,11-dihydro-10-oxo-dibenz[b,f]thiepin-2-yl-propionic acid [INN: ZALTOPROFEN] and 2-[4-(2-thiazolyloxy)phenyl]-propionic acid [INN: ZOLIPROFEN], as well as the pharmaceutically acceptable derivatives of these compounds.

Exemplary NSAIDs according to embodiment 1 which are to be emphasized are: ACETYLSALICYLIC ACID, DICLOFENAC, DIFLUNISAL, ETODOLAC, FENOPROFEN, FLOCTAFENINE, FLURBIPROFEN, IBUPROFEN, INDOMETHACIN, KETOPROFEN, MECLOFENAMATE, MEFENAMIC ACID, MELOXICAM, NABUMETONE, NAPROXEN, OXAPROZIN, PHENYLBUTAZONE, PIROXICAM, SULINDAC, TENOXICAM, TIAPROFENIC ACID and TOLMETIN, as well as the pharmaceutically acceptable derivatives of these compounds.

In an alternative embodiment, exemplary NSAIDs according to embodiment 1 which are to be emphasized are: DICLOFENAC, DIFLUNISAL, ETODOLAC, FENOPROFEN, FLOCTAFENINE, FLURBIPROFEN, IBUPROFEN, INDOMETHACIN, KETOPROFEN, MECLOFENAMATE, MEFENAMIC ACID, MELOXICAM, NABUMETONE, NAPROXEN, OXAPROZIN, PHENYLBUTAZONE, PIROXICAM, SULINDAC, TENOXICAM, TIAPROFENIC ACID and TOLMETIN, as well as the pharmaceutically acceptable derivatives of these compounds.

Preferred exemplary NSAIDs according to embodiment 1, which are selected from the above-defined group of exemplary NSAIDs, are 2-(acetyloxy)benzoic acid [ACETYLSALICYLIC ACID], 2-[(2,6-dichlorophenyl)amino]benzeneacetic acid [INN: DICLOFENAC], alpha-p-isobutylphenylpropionic acid [INN: IBUPROFEN], 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid [INN: INDOMETACIN], (plus)-6-methoxy-alpha-methyl-2-naphthalineacetic acid [INN: NAPROXEN] and 4-hydroxy-2-methyl-N-2-pyridyl-2H-1,2-benzothiadiazin-3-carboxamide 1,1-dioxide [INN: PIROXICAM], as well as the pharmaceutically acceptable derivatives of these compounds.

In an alternative embodiment, preferred exemplary NSAIDs according to embodiment 1, which are selected from the above-defined group of exemplary NSAIDs, are 2-[(2,6-dichlorophenyl)amino]-benzeneacetic acid [INN: DICLOFENAC], alpha-p-isobutylphenylpropionic acid [INN: IBUPROFEN], 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid [INN: INDOMETACIN], (plus)-6-methoxy-alpha-methyl-2-naphthalineacetic acid [INN: NAPROXEN] and 4-hydroxy-2-methyl-N-2-pyridyl-2H-1,2-benzothiadiazin-3-carboxamide 1,1-dioxide [INN: PIROXICAM], as well as the pharmaceutically acceptable derivatives of these compounds.

Particularly preferred exemplary NSAIDs according to embodiment 1 are 2-[(2,6-dichlorophenyl)amino]benzeneacetic acid [INN: DICLOFENAC] and 2-(acetyloxy)benzoic acid [ACETYLSALICYLIC ACID], as well as the pharmaceutically acceptable derivatives of these compounds.

A selected, particular preferred exemplary NSAID according to embodiment 1 is 2-[(2,6-dichlorophenyl)amino]benzeneacetic acid [INN: DICLOFENAC] or a pharmaceutically acceptable derivative thereof.

Examples of NO-NSAIDs to be used in the present invention include, but are not limited to, those disclosed, particularly those individualized or disclosed as examples, in WO 96/32946, WO 96/35416, WO 96/38136, WO 96/39409, WO 00/50037, US 6,057,347, WO 94/04484, WO 94/12463, WO 95/09831, WO 95/30641, WO 97/31654, WO 99/44595, WO 99/45004 and WO 01/45703, as well as the pharmaceutically acceptable derivatives of these compounds.

As exemplary COX-2 inhibitors within the scope of this invention can be mentioned in one embodiment (embodiment 2) according to the present invention, without being restricted to: 5-chloro-6'-

methyl-3-[4-(methylsulfonyl)phenyl]-2,3'-bipyridine [INN: ETORICOXIB], 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzene-sulfonamide [INN: CELECOXIB], 4-[p-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone [INN: ROFECOXIB], N-[[p-(5-methyl-3-phenyl-4-isoxazolyl)phenyl]sulfonyl]propion-amide [INN: PARECOXIB], p-(5-methyl-3-phenyl-4-isoxazolyl)benzenesulfonamide [INN: VALDECOXIB], 2-[2-(2-chloro-6-fluorophenylamino)-5-methylphenyl]acetic acid [INN: LUMIRACOXIB], 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzene-sulfonamide [INN: TILMACOXIB], 4-[4-chloro-5-(3-fluoro-4-methoxyphenyl)-1H-imidazol-1-yl]benzene-sulfonamide [INN: CIMICOXIB], 4'-nitro-2'-phenoxymethanesulfonanilide [INN: NIMESULIDE], 6-(2,4-difluorophenoxy)-5-methylsulfonylamino-1-indanone [INN: FLOSULIDE], 5-bromo-2-(4-fluoro-phenyl)-3-(4-methanesulfonyl-phenyl)-thiophene [DUP-697], 4-acetyl-2-(2,4-difluorophenoxy)methanesulfonanilide [FK-3311], N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide [NS-398], 5-methanesulfonamido-6-(2,4-difluorophenylthio)-1-indanone [L-745337], 8-acetyl-3-(4-fluorophenyl)-2-[4-(methanesulfonyl)phenyl]imidazo[1,2-a]-pyridine [GR-253035], 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)pyrazol-1-yl]benzenesulfon-amide [SC-58236], 4-(2,3-dihydro-2-oxo-3-phenyl-4-oxazolyl)-benzenesulfonamide [LAS-33815], CS-502, 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methyl-sulfonyl)phenyl]-3(2H)-pyridazinone [ABT-963], or GW-406381, or those COX-2 inhibitors disclosed in the applications WO 02096427, WO 02096886 or WO 02096885, which are all incorporated by reference into the specification of the present invention in their entirety for all purposes, as well as the pharmaceutically acceptable derivatives of these compounds.

COX-2 inhibitors according to embodiment 2 of this invention which are to be emphasized include, but are not limited to, 5-chloro-6'-methyl-3-[4-(methylsulfonyl)phenyl]-2,3'-bipyridine [INN: ETORICOXIB], 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzene-sulfonamide [INN: CELECOXIB], 4-[p-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone [INN: ROFECOXIB], N-[[p-(5-methyl-3-phenyl-4-isoxazolyl)phenyl]sulfonyl]propion-amide [INN: PARECOXIB], p-(5-methyl-3-phenyl-4-isoxazolyl)benzenesulfonamide [INN: VALDECOXIB], 2-[2-(2-chloro-6-fluorophenylamino)-5-methylphenyl]acetic acid [INN: LUMIRACOXIB], 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzene-sulfonamide [INN: TILMACOXIB], and 4-[4-chloro-5-(3-fluoro-4-methoxyphenyl)-1H-imidazol-1-yl]benzene-sulfonamide [INN: CIMICOXIB], as well as the pharmaceutically acceptable derivatives of these compounds.

As exemplary COX-2 inhibitors within the scope of this invention can be also mentioned in another embodiment (embodiment 2') according to the present invention, without being restricted to: CELECOXIB ROFECOXIB, as well as the pharmaceutically acceptable derivatives of these compounds.

As examples of bisphosphonates within the meaning of this invention can be mentioned in one embodiment (embodiment 3) according to the present invention, without being restricted to, ALENDRONIC ACID, RISEDRONIC ACID, TILUDRONIC ACID, IBANDRONIC ACID, ZOLEDRONIC

ACID, CLODRONIC ACID, INCADRONIC ACID, OLPADRONIC ACID, MINODRONIC ACID, PAMIDRONIC ACID and ETIDRONIC ACID, as well as the pharmaceutically acceptable derivatives of these compounds.

Examples of bisphosphonates to be used in the present invention include also in another embodiment (embodiment 3') according to the present invention, but are not limited to, ALENDRONIC ACID, RISEDRONIC ACID, TILUDRONIC ACID, IBANDRONIC ACID, ZOLEDRONIC ACID and ETIDRONIC ACID, as well as the pharmaceutically acceptable derivatives of these compounds.

As examples of corticosteroids within the meaning of this invention can be mentioned in one embodiment (embodiment 4) according to the present invention, without being restricted to, HYDROCORTISONE, PREDNISONE, PREDNISOLONE, METHYLPREDNISOLONE, TRIAMCINOLONE ACETONIDE, AMCINONIDE, CLOBETASONE, CLOBETASOL, DEFLAZACORT, DESONIDE, CLOPREDNOL, DEXAMETHASONE, DIFLORASONE, DIFLUCORTOLONE, DIFLUPREDNATE, FLUDROXYCORTIDE, FLUDROCORTISONE, FLUMETASONE, TIXOCORTOL PIVALATE, FLUOCORTIN BUTYL, CLOCORTOLONE, FLUOCINOLONE ACETONIDE, FLUOCORTOLONE, FLUOROMETHOLONE, FLUPREDNIDENE, FLUPREDNISOLONE, BETAMETHASONE, HALCINONIDE, BUDESONIDE, HALOMETASONE, RIMEXOLONE, PARAMETHASONE, PREDNYLIDENE, LOTEPREDNOL ETABONATE, PREDNICARBATE, as well as the pharmaceutically acceptable derivatives of these compounds.

Examples of preferred corticosteroids to be used in the present invention include also in another embodiment (embodiment 4') according to the present invention, but are not limited to, BETAMETHASONE, HYDROCORTISONE, METHYLPREDNISOLONE, PREDNISOLONE, PREDNISONE, TRIAMCINOLONE ACETONIDE, DEXAMETHASONE, DESONIDE, FLUMETASONE, TIXOCORTOL PIVALATE, FLUDROCORTISONE, DEFLAZACORT, BUDESONIDE, LOTEPREDNOL ETABONATE, FLUOCORTOLONE, as well as the pharmaceutically acceptable derivatives of these compounds.

A particularly preferred corticosteroid to be used in the present invention is BETAMETHASONE, DEXAMETHASONE, FLUOCORTOLONE, METHYLPREDNISOLONE, PREDNISOLONE, PREDNISONE, HYDROCORTISONE, BUDESONIDE, TRIAMCINOLONE ACETONIDE, as well as the pharmaceutically acceptable derivatives of these compounds.

In the context of the present invention, the term "pharmaceutically acceptable derivative" means a pharmaceutically acceptable salt, ester or solvate (e.g. hydrate) or a pharmaceutically acceptable solvate of such salt or ester.

Within the scope of this invention the term "gastrointestinal diseases" in the context of "medicament caused gastrointestinal diseases" or "gastrointestinal diseases caused by certain medicaments" refers

to those gastrointestinal diseases, which are known to the art-skilled person on the base of his/her expert knowledge, to be caused by certain medicaments such as, for example, art-known gastrointestinal inflammatory diseases and lesions, particularly gastric ulcer (e.g. stomach ulcer or duodenal ulcer), heartburn, bleeding or medicament related functional gastropathy, whereby gastric ulcer is particularly to be emphasized.

In the meaning of this invention, the terms "medicament associated gastrointestinal disorders" and "gastrointestinal disorders associated with certain medicaments" refer to gastrointestinal disorders known to the person skilled in the art (such as e.g. indigestion, mild forms of heartburn, stomach irritation or pain) which are associated with certain medicaments such as, for example, those mentioned above, particularly NSAIDs, as well as e.g. chloroquine, theophylline, dihydralazine, salazosulfapyridine, thiazides, iodine-containing contrast media, gold preparations or antibiotics (e.g. tetracyclines, sulfonamides or cotrimoxazol).

In this connection, it is to be understood for the skilled person that the abovementioned gastrointestinal diseases or disorders are caused or associated mainly with the active agents or ingredients of the abovementioned medicaments.

Any or all of the listed combination partners as defined herein can be suitable to be used in the combination therapy or in the combinations according to the present invention.

In a further aspect, this invention relates to the use of (S)-pantoprazole and/or its salts in the prevention or treatment of medicament caused gastrointestinal diseases and/or medicament associated disorders.

A further aspect of the present invention is the use of (S)-pantoprazole and/or its salts in the prevention and/or treatment of medicament induced gastric ulcer.

A further aspect of the present invention is the use of (S)-pantoprazole and/or its salts in the manufacture of pharmaceutical compositions for the prevention and/or treatment of medicament caused gastrointestinal diseases, particularly medicament induced gastric ulcer.

A further aspect of the present invention is the use of (S)-pantoprazole and/or its salts in the manufacture of pharmaceutical compositions for the prevention of medicament associated gastrointestinal disorders.

A further aspect of the present invention is the use of (S)-pantoprazole and/or its salts in the manufacture of pharmaceutical compositions for the well-tolerated treatment and/or prevention of inflammatory diseases and/or inflammation associated disorders.

A further aspect of the present invention is the use of (S)-pantoprazole and/or its salts in the manufacture of pharmaceutical compositions for treating and/or preventing of gastrointestinal or, particularly, non-gastrointestinal inflammatory diseases and/or inflammation associated disorders, and for reducing the risk of medicament associated gastrointestinal disorders or, particularly, for reducing medicament caused gastrointestinal diseases, particularly medicament induced gastric ulcer.

A further aspect of the present invention is the use of (S)-pantoprazole and/or its salts in the manufacture of pharmaceutical compositions comprising an antiinflammatory or antirheumatic ingredient which is selected from a group consisting of NSAIDs, COX-2 inhibitors, NO-NSAIDs, bisphosphonates and corticosteroids for use in combination therapy, e.g. for use in the treatment and/or prevention of diseases or disorders conventionally treated, ameliorated or prevented monotherapeutically with said antiinflammatory or antirheumatic ingredient, particularly those diseases or disorders mentioned in the specification of this invention.

A further aspect of the present invention is the use of said selected tricyclic imidazo[1,2-a]pyridine compounds in the manufacture of pharmaceutical compositions comprising an active ingredient which is selected from a group consisting of NSAIDs, COX-2 inhibitors, NO-NSAIDs, bisphosphonates and corticosteroids for treating and/or preventing of diseases or disorders which can be treated, ameliorated or prevented by said active ingredient, particularly those diseases or disorders mentioned in the specification of this invention, and for reducing the risk of medicament associated gastrointestinal disorders or, particularly, for reducing medicament caused gastrointestinal diseases, particularly those mentioned in this invention.

A further aspect of the present invention is the simultaneous, separate or sequential co-administration of a NSAID, a COX-2 inhibitor, a NO-NSAID, a bisphosphonate or a corticosteroid, preferably a NSAID, with (S)-pantoprazole and/or its salts to prevent medicament caused gastrointestinal diseases, particularly medicament induced gastric ulcer.

A further aspect of the present invention is the simultaneous, separate or sequential co-administration of a NSAID, a COX-2 inhibitor, a NO-NSAID, a bisphosphonate or a corticosteroid with (S)-pantoprazole and/or its salts to treat, ameliorate or prevent diseases or disorders which can be treated, ameliorated or prevented by this NSAID, COX-2 inhibitor, NO-NSAID or bisphosphonate.

A further aspect of the present invention is a method for prevention and/or treatment of medicament caused gastrointestinal diseases, particularly medicament induced gastric ulcer, comprising administering a therapeutically effective amount of one or more of (S)-pantoprazole and/or its salts simultaneously, separately or sequentially with at least one NSAID, COX-2 inhibitor, NO-NSAID, bisphosphonate or corticosteroid to a mammal.

A further aspect of the present invention is a method for prevention and/or treatment of medicament associated gastrointestinal disorders comprising administering a therapeutically effective amount of (S)-pantoprazole and/or its salts simultaneously, separately or sequentially with said medicament to a human in need thereof.

A further aspect of the present invention is a method for treatment or prevention of inflammatory diseases and/or inflammation associated disorders comprising administering a therapeutically effective amount of (S)-pantoprazole and/or its salts simultaneously, separately or sequentially with at least one NSAID, COX-2 inhibitor, NO-NSAID, bisphosphonate or corticosteroid to a mammal.

A further aspect of the present invention is a method for amelioration the gastrointestinal tolerance of the therapy of inflammatory diseases and/or inflammation associated disorders comprising administering a therapeutically effective amount of (S)-pantoprazole and/or its salts simultaneously, separately or sequentially with at least one NSAID, COX-2 inhibitor, NO-NSAID, bisphosphonate or corticosteroid to a mammal.

A further aspect of the present invention is a method for treating, ameliorating or preventing of diseases or disorders, which can be treated, ameliorated or prevented by an agent selected from a group consisting of NSAIDs, COX-2 inhibitors, NO-NSAIDs, bisphosphonates and corticosteroids, and reducing the risk of gastrointestinal diseases caused by said agent or reducing the risk of gastrointestinal disorders associated with said agent, in a human patient in need of such treatment, amelioration or prevention and at risk of gastrointestinal diseases caused by said agent or gastrointestinal disorders associated with said agent comprising administering to said patient an agent selected from the group consisting of NSAIDs, COX-2 inhibitors, NO-NSAIDs, bisphosphonates and corticosteroids in an amount effective to treat, to ameliorate or to prevent diseases or disorders, which can be treated, ameliorated or prevented by said agent selected from a group consisting of NSAIDs, COX-2 inhibitors, NO-NSAIDs, bisphosphonates and corticosteroids, simultaneously, separately or sequentially with (S)-pantoprazole and/or its salts an amount effective to reduce the risk of gastrointestinal diseases caused by said agent or gastrointestinal disorders associated with said agent.

A further aspect of the present invention is a method for treating, ameliorating or preventing of diseases or disorders, which can be treated, ameliorated or prevented by an agent selected from a group consisting of NSAIDs, COX-2 inhibitors, NO-NSAIDs, bisphosphonates and corticosteroids, and reducing the risk of gastrointestinal diseases or disorders caused by or associated with said agent in a patient in need thereof comprising administering to said patient a combination or a composition according to this invention.

A further aspect of the present invention is a preferably orally applicable pharmaceutical composition for simultaneous administration comprising, in admixture, a first active ingredient, which is selected from a group consisting of NSAIDs, COX-2 inhibitors, NO-NSAIDs, bisphosphonates and corticoster-

oids, and a second active ingredient, which is (S)-pantoprazole and/or its salts, to prevent medicament caused gastrointestinal diseases, particularly medicament induced gastric ulcer, in a mammal.

A further aspect of the present invention is a pharmaceutical composition comprising a first active ingredient, which is selected from a group consisting of NSAIDs, COX-2 inhibitors, NO-NSAIDs, bisphosphonates or corticosteroids, and a second active ingredient, which is (S)-pantoprazole and/or its salts, to prevent and/or treat medicament caused gastrointestinal diseases, particularly medicament induced gastric ulcer, in a mammal.

A further aspect of the present invention is a pharmaceutical composition comprising a first active ingredient, which is selected from a group consisting of chloroquine, theophylline, dihydralazine, salazosulfapyridine, thiazides, iodine-containing contrast media, gold preparations and antibiotics (e.g. tetracyclines, sulfonamides or cotrimoxazol), and a second active ingredient, which is (S)-pantoprazole and/or its salts, to prevent medicament associated gastrointestinal disorders in a human.

A further aspect of the present invention is a pharmaceutical composition for simultaneous administration comprising a NSAID, a COX-2 inhibitor, a NO-NSAID, a bisphosphonate or a corticosteroid together with (S)-pantoprazole and/or its salts.

A further aspect of the present invention is a composition comprising a first active ingredient, which is a NSAID or a COX-2 inhibitor or a NO-NSAID or a bisphosphonate or a corticosteroid, and a second active ingredient, which is (S)-pantoprazole and/or its salts, for simultaneous, sequential or separate use in therapy in any order.

A further aspect of the present invention is a preferably orally applicable pharmaceutical composition in unit dosage comprising a NSAID or a COX-2 inhibitor or a NO-NSAID or a bisphosphonate or a corticosteroid together with (S)-pantoprazole and/or its salts for use in therapy, e.g. to prevent medicament induced gastric ulcer in a mammal.

A further aspect of the present invention is a pharmaceutical composition comprising a NSAID or a COX-2 inhibitor or a NO-NSAID or a bisphosphonate or a corticosteroid together with (S)-pantoprazole and/or its salts, wherein the NSAID, the COX-2 inhibitor, the NO-NSAID, the bisphosphonate or the corticosteroid and (S)-pantoprazole and/or its salts are administered in a single dosage form, such that the NSAID, the COX-2 inhibitor, the NO-NSAID, the bisphosphonate or the corticosteroid and (S)-pantoprazole and/or its salts are physically separated from each other.

A further aspect of the present invention is a composition comprising a first active ingredient selected from the group consisting of NSAIDs, COX-2 inhibitors, NO-NSAIDs, bisphosphonates and corticosteroids, and a second active ingredient which is (S)-pantoprazole and/or its salts, together with a pharmaceutically acceptable carrier.

A further aspect of this invention is a pharmaceutical composition comprising:

(a) a pharmaceutically effective amount of (S)-pantoprazole and/or its salts; and

(b) a pharmaceutically effective amount of at least one NSAID, COX-2 inhibitor, NO-NSAID, bisphosphonate or corticosteroid.

A further aspect of this invention is a pharmaceutical composition comprising:

(a) a pharmaceutically effective amount of (S)-pantoprazole and/or its salts; and

(b) a pharmaceutically effective amount of at least one NSAID, COX-2 inhibitor, NO-NSAID, bisphosphonate or corticosteroid;

wherein component (a) and component (b) are maintained in the same delivery vehicle.

A further aspect of this invention is a pharmaceutical composition comprising:

(a) a pharmaceutically effective amount of (S)-pantoprazole and/or its salts; and

(b) a pharmaceutically effective amount of at least one NSAID, COX-2 inhibitor, NO-NSAID, bisphosphonate or corticosteroid;

wherein component (a) and component (b) are maintained in different delivery vehicles.

A further aspect of the present invention is a preferably orally applicable pharmaceutical formulation comprising a first active ingredient, which is selected from a group consisting of NSAIDs, COX-2 inhibitors, NO-NSAIDs, bisphosphonates and corticosteroids, a second active ingredient, which is (S)-pantoprazole and/or its salts, and a pharmaceutically acceptable carrier, diluent, adjuvant, auxiliary or excipient for use in therapy, e.g. to prevent medicament induced gastric ulcer in a mammal.

A further aspect of the present invention is a first pharmaceutical formulation comprising (S)-pantoprazole and/or its salts and a pharmaceutically acceptable carrier or diluent; and a second pharmaceutical formulation comprising a NSAID or a COX-2 inhibitor or a NO-NSAID or a bisphosphonate or a corticosteroid and a pharmaceutically acceptable carrier or diluent.

A further aspect of the present invention is a combination comprising a NSAID, a COX-2 inhibitor, a NO-NSAID, a bisphosphonate or a corticosteroid and (S)-pantoprazole and/or its salts for simultaneous, sequential or separate use in therapy, e.g. to prevent medicament induced gastric ulcer in a mammal.

A further aspect of the present invention is a combination comprising a medicament selected from a group consisting of chloroquine, theophylline, dihydralazine, salazosulfapyridine, thiazides, iodine-containing contrast media, gold preparations and antibiotics (e.g. tetracyclines, sulfonamides or cotrimoxazol), and (S)-pantoprazole and/or its salts, for simultaneous, sequential or separate use in therapy, e.g. to prevent medicament associated gastrointestinal disorders in a human.

A further aspect of the present invention is a combination, particularly a pharmaceutical combination, such as, for example, a combined preparation, e.g. a kit of parts, or a composition, particularly a pharmaceutical composition, comprising a first active ingredient which is an agent selected from a group consisting of NSAIDs, COX-2 inhibitors, NO-NSAIDs, bisphosphonates and corticosteroids, and a second active ingredient which is (S)-pantoprazole and/or its salts as mentioned in the present invention and, optionally, at least one pharmaceutically acceptable carrier for simultaneous, sequential, separate or chronologically staggered use in therapy, and/or for use as combined unit dosage form or as separate unit dosage forms in therapy, and/or for use as fixed combination in therapy, and/or for use as admixture in therapy, e.g. to treat, to ameliorate or to prevent in a mammal, including human, diseases or disorders, which can be treated, ameliorated or prevented by said first active ingredient, and, in combination therewith, to reduce, to treat, to ameliorate or to prevent in a mammal, including human, gastrointestinal diseases caused by said first active ingredient or to reduce, to treat, to ameliorate or to prevent gastrointestinal disorders associated with said first active ingredient.

A further aspect of the present invention relates to combining separate pharmaceutical compositions in kit form.

A further aspect of the present invention is a pharmaceutical product comprising, in combination, a preparation of a first active ingredient, which is (S)-pantoprazole and/or its salts, and a preparation of a second active ingredient, which is selected from a group consisting of NSAIDs, COX-2 inhibitors, NO-NSAIDs, bisphosphonates and corticosteroids, for simultaneous, sequential or separate use in therapy, e.g. to prevent medicament induced gastric ulcer in a mammal.

A further aspect of the present invention is a commercial package comprising as active ingredients a NSAID or a COX-2 inhibitor or a NO-NSAID or a bisphosphonate or a corticosteroid as well as (S)-pantoprazole and/or its salts together with instructions for simultaneous, sequential or separate use in therapy.

A further aspect of the present invention is a commercial package comprising (S)-pantoprazole and/or its salts as active ingredient together with instructions for simultaneous, sequential or separate use with a NSAID or a COX-2 inhibitor or a NO-NSAID or a bisphosphonate or a corticosteroid.

A further aspect of the present invention is a commercial package comprising a NSAID, a COX-2 inhibitor, a NO-NSAID, a bisphosphonate or a corticosteroid as active ingredient together with instructions for simultaneous, sequential or separate use with (S)-pantoprazole and/or its salts.

A further aspect of the present invention is a commercial package comprising a medicament selected from the group consisting of chloroquine, theophylline, dihydralazine, salazosulfapyridine, thiazides, iodine-containing contrast media, gold preparations and antibiotics (e.g. tetracyclines, sulfonamides or

cotrimoxazol) together with instructions for simultaneous, sequential or separate use with (S)-pantoprazole and/or its salts.

A further aspect of the present invention is a pharmaceutical product, such as, for example, a commercial package, comprising a combination, such as, for example, a combined preparation, e.g. a kit of parts, or a pharmaceutical composition, comprising a first active ingredient which is an agent selected from a group consisting of NSAIDs, COX-2 inhibitors, NO-NSAIDs, bisphosphonates and corticosteroids, and a second active ingredient which is (S)-pantoprazole and/or its salts as mentioned in the present invention and, optionally, at least one pharmaceutically acceptable carrier for simultaneous, sequential, separate or chronologically staggered use in therapy, and/or for use as combined unit dosage form or for use as separate unit dosage forms in therapy, and/or for use as fixed combination in therapy, and/or for use as admixture in therapy; together with standard packaging material, and together with instructions for simultaneous, sequential, separate or chronologically staggered use in therapy, e.g. to treat, to ameliorate or to prevent in a mammal, including human, diseases or disorders, which can be treated, ameliorated or prevented by said first active ingredient, and, in combination therewith, to treat, to ameliorate or to prevent in a mammal, including human, gastrointestinal diseases caused by said first active ingredient or to treat, to ameliorate or to prevent gastrointestinal disorders associated with said first active ingredient.

A further aspect of the present invention is a kit comprising at least one dosage unit of a NSAID or a COX-2 inhibitor or a NO-NSAID or a bisphosphonate or a corticosteroid as well as at least one dosage unit of (S)-pantoprazole and/or its salts for simultaneous, sequential or separate use in therapy. Optionally, abovementioned kit can be provided with instructions for use.

A further aspect of the present invention is a kit comprising a preparation of a first active ingredient, which is (S)-pantoprazole and/or its salts, a preparation of a second active ingredient, which is selected from a group consisting of NSAIDs, COX-2 inhibitors, NO-NSAIDs, bisphosphonates and corticosteroids, and instructions for simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

A further aspect of the present invention is the use of a pharmaceutical composition, pharmaceutical product, formulation, preparation, combination, commercial package or kit according to the invention in the manufacture of a medicament for the treatment of an inflammatory disease and/or inflammation associated disorder.

A further aspect of the present invention is the use of the pharmaceutical compositions, formulations, preparations, combined preparations, combinations or kits according to this invention in the manufacture of a pharmaceutical product, such as e.g. a commercial package, for the treatment or prevention of diseases or disorders which can be conventionally treated by NSAIDs, COX-2 inhibitors, NO-NSAIDs, bisphosphonates or corticosteroids.

A further aspect of the present invention is the use of the pharmaceutical compositions, formulations, preparations, combined preparations, combinations or kits according to this invention in the manufacture of a pharmaceutical product, such as e.g. a commercial package, for the treatment or prevention of gastrointestinal diseases or disorders caused by or associated with NSAIDs, COX-2 inhibitors, NO-NSAIDs, bisphosphonates or corticosteroids.

A further aspect of the present invention is the use of the pharmaceutical compositions, formulations, preparations, combined preparations, combinations or kits, particularly pharmaceutical compositions and kits, according to this invention in the manufacture of a medicament for treating or preventing of diseases or disorders which can be treated by agents selected from NSAIDs, COX-2 inhibitors, NO-NSAIDs, bisphosphonates and corticosteroids, and for treating or preventing of gastrointestinal diseases or disorders caused by or associated with the therapeutic use of said agents.

A further aspect of the present invention is a pharmaceutical composition comprising, in admixture, a first active ingredient, which is (S)-pantoprazole and/or its salts, and a second active ingredient, which is selected from a group consisting of NSAIDs, COX-2 inhibitors, NO-NSAIDs, bisphosphonates and corticosteroids.

A further aspect of the present invention is a pharmaceutical product comprising, in combination, a preparation of a first active ingredient, which is (S)-pantoprazole and/or its salts, and a preparation of a second active ingredient, which is a NSAID or a COX-2 inhibitor or a NO-NSAID or a bisphosphonate or a corticosteroid, for simultaneous, sequential or separate use in therapy, e.g. to prevent medicament induced gastric ulcer in a mammal.

A further aspect of the present invention is a kit comprising a preparation of a first active ingredient, which is (S)-pantoprazole and/or its salts, a preparation of a second active ingredient, which is selected from a group consisting of NSAIDs, COX-2 inhibitors, NO-NSAIDs, bisphosphonates and corticosteroids, and instructions for simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

A preferred aspect of the present invention is a pharmaceutical composition comprising a first active ingredient which is (S)-pantoprazole magnesium; and a second active ingredient selected from the group consisting of NSAIDs, COX-2 inhibitors, NO-NSAIDs, bisphosphonates and corticosteroids.

A further preferred aspect of the present invention is a pharmaceutical product (such as, for example, a commercial package) comprising a first active ingredient which is (S)-pantoprazole magnesium, and a second active ingredient selected from the group consisting of NSAIDs, COX-2 inhibitors, NO-NSAIDs, bisphosphonates and corticosteroids; together with instructions for simultaneous, sequential or separate use, e.g. to treat or prevent gastrointestinal diseases caused by said second active ingre-

dient and/or to treat or prevent diseases which can be treated or prevented by said second active ingredient.

A further preferred aspect of the present invention is a kit comprising a first active ingredient which is (S)-pantoprazole magnesium; and a second active ingredient selected from the group consisting of NSAIDs, COX-2 inhibitors, NO-NSAIDs, bisphosphonates and corticosteroids; together with instructions for simultaneous, sequential or separate use in therapy, e.g. to treat or prevent gastrointestinal diseases caused by said second active ingredient and/or to treat or prevent diseases which can be treated or prevented by said second active ingredient.

A more preferred aspect of the present invention is a pharmaceutical composition comprising, in admixture, a first active ingredient, which is (S)-pantoprazole magnesium dihydrate, and a second active ingredient, which is selected from a group consisting of NSAIDs, COX-2 inhibitors, NO-NSAIDs, bisphosphonates and corticosteroids.

A further more preferred aspect of the present invention is a pharmaceutical product comprising, in combination, a preparation of (S)-pantoprazole magnesium dihydrate, and a preparation of a second active ingredient, which is a NSAID or a COX-2 inhibitor or a NO-NSAID or a bisphosphonate or a corticosteroid, for simultaneous, sequential or separate use in therapy, e.g. to prevent medicament induced gastric ulcer in a mammal.

A further more preferred aspect of the present invention is a kit comprising a preparation of a first active ingredient, which is (S)-pantoprazole magnesium dihydrate, a preparation of a second active ingredient, which is selected from a group consisting of NSAIDs, COX-2 inhibitors, NO-NSAIDs, bisphosphonates and corticosteroids, and instructions for simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

Another preferred aspect of the present invention is a pharmaceutical composition comprising a first active ingredient which is (S)-pantoprazole and/or its salts; and
a second active ingredient which is
a NSAID, a COX-2 inhibitor, a NO-NSAID, a bisphosphonate or a corticosteroid, or, in particular,
a NSAID, a COX-2 inhibitor, a bisphosphonate or a corticosteroid, or, in a first sub-aspect,
a NSAID, such as e.g. one of those NSAIDs mentioned exemplarily above, or, in a second sub-aspect,
a COX-2 inhibitor, such as e.g. one of those COX-2 inhibitors mentioned exemplarily above, or, in a third sub-aspect,
a bisphosphonate, such as e.g. one of those bisphosphonates mentioned exemplarily above, or, in a fourth sub-aspect
a corticosteroid, such as e.g. one of those corticosteroids mentioned exemplarily above, or, in a more detailed sub-aspect,
an agent selected from the group consisting of

ACETYLSALICYLIC ACID, DICLOFENAC, DIFLUNISAL, ETODOLAC, FENOPROFEN, FLOCTAFENINE, FLURBIPROFEN, IBUPROFEN, INDOMETHACIN, KETOPROFEN, MECLOFENAMATE, MEFENAMIC ACID, MELOXICAM, NABUMETONE, NAPROXEN, OXAPROZIN, PHENYLBUTAZONE, PIROXICAM, SULINDAC, TENOXICAM, TIAPROFENIC ACID, TOLMETIN, ETORICOXIB, CELECOXIB, ROFECOXIB, PARECOXIB, VALDECOXIB, LUMIRACOXIB, TILMACOXIB, CIMICOXIB, ALENDRONIC ACID, RISEDRONIC ACID, TILUDRONIC ACID, IBANDRONIC ACID, ZOLANDRONIC ACID, INCADRONIC ACID, OLPADRONIC ACID, MINODRONIC ACID, CLODRONIC ACID, PAMIDRONIC ACID, ETIDRONIC ACID, BETAMETHASONE, HYDROCORTISONE, METHYLPREDNISOLONE, PREDNISOLONE, PREDNISONE, TRIAMCINOLONE ACETONIDE, DEXAMETHASONE, DESONIDE, FLUMETASONE, TIXOCORTOL PIVALATE, FLUDROCORTISONE, DEFLAZACORT, BUDESONIDE, LOTEPREDNOL ETABONATE, FLUOCORTOLONE
or a pharmaceutically acceptable derivative thereof.

A more preferred aspect of the present invention is a pharmaceutical composition comprising a first active ingredient which is (S)-pantoprazole and/or its salts; and
a second active ingredient which is
a NSAID, such as e.g. one of those NSAIDs mentioned exemplarily above, or, in a more detailed sub-aspect,
a NSAID selected from the group consisting of
ACETYLSALICYLIC ACID, DICLOFENAC, DIFLUNISAL, ETODOLAC, FENOPROFEN, FLOCTAFENINE, FLURBIPROFEN, IBUPROFEN, INDOMETHACIN, KETOPROFEN, MECLOFENAMATE, MEFENAMIC ACID, MELOXICAM, NABUMETONE, NAPROXEN, OXAPROZIN, PHENYLBUTAZONE, PIROXICAM, SULINDAC, TENOXICAM, TIAPROFENIC ACID AND TOLMETIN,
or a pharmaceutically acceptable derivative thereof.

A further more preferred aspect of embodiment a of the present invention is a pharmaceutical composition comprising a first active ingredient which is (S)-pantoprazole and/or its salts; and
a second active ingredient which is
a COX-2 inhibitor, such as e.g. one of those COX-2 inhibitors mentioned exemplarily above, or, in a more detailed sub-aspect,
a COX-2 inhibitor selected from the group consisting of
ETORICOXIB, CELECOXIB, ROFECOXIB, PARECOXIB, VALDECOXIB, LUMIRACOXIB, TILMACOXIB and CIMICOXIB,
or a pharmaceutically acceptable derivative thereof.

A further more preferred aspect of the present invention is a pharmaceutical composition comprising a first active ingredient which is (S)-pantoprazole and/or its salts; and
a second active ingredient which is

a bisphosphonate, such as e.g. one of those bisphosphonates mentioned exemplarily above, or, in a more detailed sub-aspect,
a bisphosphonate selected from the group consisting of
ALENDRONIC ACID, RISEDRONIC ACID, TILUDRONIC ACID, IBANDRONIC ACID, ZOLANDRONIC ACID, INCADRONIC ACID, OLPADRONIC ACID, MINODRONIC ACID, CLODRONIC ACID, PAMIDRONIC ACID and ETIDRONIC ACID,
or a pharmaceutically acceptable derivative thereof.

A further more preferred aspect of the present invention is a pharmaceutical composition comprising a first active ingredient which is (S)-pantoprazole and/or its salts; and
a second active ingredient which is
a corticosteroid, such as e.g. one of those corticosteroids mentioned exemplarily above, or, in a more detailed sub-aspect,
a corticosteroid selected from the group consisting of
BETAMETHASONE, HYDROCORTISONE, METHYLPREDNISOLONE, PREDNISOLONE, PREDNISONE, TRIAMCINOLONE ACETONIDE, DEXAMETHASONE, DESONIDE, FLUMETASONE, TIXOCORTOL PIVALATE, FLUDROCORTISONE, DEFLAZACORT, BUDESONIDE, LOTEPREDNOL ETABONATE, FLUOCORTOLONE,
or a pharmaceutically acceptable derivative thereof.

A particularly preferred aspect of embodiment a of the present invention is a pharmaceutical composition comprising a first active ingredient which is
(S)-pantoprazole magnesium; and
a second active ingredient which is
a NSAID, a COX-2 inhibitor, a NO-NSAID, a bisphosphonate or a corticosteroid, or, in particular,
a NSAID, a COX-2 inhibitor, a bisphosphonate or a corticosteroid, or, in a first sub-aspect,
a NSAID, such as e.g. one of those NSAIDs mentioned above, or, in a second sub-aspect,
a COX-2 inhibitor, such as e.g. one of those COX-2 inhibitors mentioned above, or, in a third sub-aspect,
a bisphosphonate, such as e.g. one of those bisphosphonates mentioned above, or, in a fourth sub-aspect,
a corticosteroid, such as e.g. one of those corticosteroids mentioned above, or, in a more detailed sub-aspect,
an agent selected from the group consisting of
ACETYLSALICYLIC ACID, DICLOFENAC, DIFLUNISAL, ETODOLAC, FENOPROFEN, FLOCTAFENINE, FLURBIPROFEN, IBUPROFEN, INDOMETHACIN, KETOPROFEN, MECLOFENAMATE, MEFENAMIC ACID, MELOXICAM, NABUMETONE, NAPROXEN, OXAPROZIN, PHENYLBUTAZONE, PIROXICAM, SULINDAC, TENOXICAM, TIAPROFENIC ACID, TOLMETIN, ETORICOXIB, CELECOXIB, ROFECOXIB, PARECOXIB, VALDECOXIB, LUMIRACOXIB, TILMACOXIB, CIMICOXIB, ALENDRONIC ACID, RISEDRONIC ACID, TILUDRONIC ACID,

IBANDRONIC ACID, ZOLANDRONIC ACID, INCADRONIC ACID, OLPADRONIC ACID, MINODRONIC ACID, CLODRONIC ACID, PAMIDRONIC ACID, ETIDRONIC ACID, BETAMETHASONE, HYDROCORTISONE, METHYLPREDNISOLONE, PREDNISOLONE, PREDNISONE, TRIAMCINOLONE ACETONIDE, DEXAMETHASONE, DESONIDE, FLUMETASONE, TIXOCORTOL PIVALATE, FLUDROCORTISONE, DEFLAZACORT, BUDESONIDE, LOTEPREDNOL ETABONATE, FLUOCORTOLONE
or a pharmaceutically acceptable derivative thereof.

A yet further particularly preferred aspect of embodiment a of the present invention is a pharmaceutical product (such as, for example, a commercial package) comprising a first active ingredient which is (S)-pantoprazole magnesium; and
a second active ingredient which is
a NSAID, a COX-2 inhibitor, a NO-NSAID, a bisphosphonate or a corticosteroid, or, in particular,
a NSAID, a COX-2 inhibitor, a bisphosphonate or a corticosteroid, or, in a first sub-aspect,
a NSAID, such as e.g. one of those NSAIDs mentioned above, or, in a second sub-aspect,
a COX-2 inhibitor, such as e.g. one of those COX-2 inhibitors mentioned above, or, in a third sub-aspect,
a bisphosphonate, such as e.g. one of those bisphosphonates mentioned above, or, in a fourth sub-aspect,
a corticosteroid, such as e.g. one of those corticosteroids mentioned above, or, in a more detailed sub-aspect,
an agent selected from the group consisting of
ACETYLSALICYLIC ACID, DICLOFENAC, DIFLUNISAL, ETODOLAC, FENOPROFEN, FLOCTAFENINE, FLURBIPROFEN, IBUPROFEN, INDOMETHACIN, KETOPROFEN, MECLOFENAMATE, MEFENAMIC ACID, MELOXICAM, NABUMETONE, NAPROXEN, OXAPROZIN, PHENYLBUTAZONE, PIROXICAM, SULINDAC, TENOXICAM, TIAPROFENIC ACID, TOLMETIN, ETORICOXIB, CELECOXIB, ROFECOXIB, PARECOXIB, VALDECOXIB, LUMIRACOXIB, TILMACOXIB, CIMICOXIB, ALENDRONIC ACID, RISEDRONIC ACID, TILUDRONIC ACID, IBANDRONIC ACID, ZOLANDRONIC ACID, INCADRONIC ACID, OLPADRONIC ACID, MINODRONIC ACID, CLODRONIC ACID, PAMIDRONIC ACID and ETIDRONIC ACID, BETAMETHASONE, HYDROCORTISONE, METHYLPREDNISOLONE, PREDNISOLONE, PREDNISONE, TRIAMCINOLONE ACETONIDE, DEXAMETHASONE, DESONIDE, FLUMETASONE, TIXOCORTOL PIVALATE, FLUDROCORTISONE, DEFLAZACORT, BUDESONIDE, LOTEPREDNOL ETABONATE, FLUOCORTOLONE,
or a pharmaceutically acceptable derivative thereof,
together with instructions for simultaneous, sequential or separate use, e.g. to treat or prevent gastrointestinal diseases caused by said second active ingredient and/or to treat or prevent diseases which can be treated or prevented by said second active ingredient.

A still further particularly preferred aspect of embodiment a of the present invention is a kit comprising a first active ingredient which is
(S)-pantoprazole magnesium; and
a second active ingredient which is
a NSAID, a COX-2 inhibitor, a NO-NSAID, a bisphosphonate or a corticosteroid, or, in particular,
a NSAID, a COX-2 inhibitor, a bisphosphonate or a corticosteroid, or, in a first sub-aspect,
a NSAID, such as e.g. one of those NSAIDs mentioned above, or, in a second sub-aspect,
a COX-2 inhibitor, such as e.g. one of those COX-2 inhibitors mentioned above, or, in a third sub-aspect,
a bisphosphonate, such as e.g. one of those bisphosphonates mentioned above, or, in a fourth sub-aspect,
a corticosteroid, such as e.g. one of those corticosteroids mentioned above, or, in a more detailed sub-aspect,
an agent selected from the group consisting of
ACETYLSALICYLIC ACID, DICLOFENAC, DIFLUNISAL, ETODOLAC, FENOPROFEN, FLOCTAFENINE, FLURBIPROFEN, IBUPROFEN, INDOMETHACIN, KETOPROFEN, MECLOFENAMATE, MEFENAMIC ACID, MELOXICAM, NABUMETONE, NAPROXEN, OXAPROZIN, PHENYLBUTAZONE, PIROXICAM, SULINDAC, TENOXICAM, TIAPROFENIC ACID, TOLMETIN, ETORICOXIB, CELECOXIB, ROFECOXIB, PARECOXIB, VALDECOXIB, LUMIRACOXIB, TILMACOXIB, CIMICOXIB, ALENDRONIC ACID, RISEDRONIC ACID, TILUDRONIC ACID, IBANDRONIC ACID, ZOLANDRONIC ACID, INCADRONIC ACID, OLPADRONIC ACID, MINODRONIC ACID, CLODRONIC ACID, PAMIDRONIC ACID and ETIDRONIC ACID, BETAMETHASONE, HYDROCORTISONE, METHYLPREDNISOLONE, PREDNISOLONE, PREDNISONE, TRIAMCINOLONE ACETONIDE, DEXAMETHASONE, DESONIDE, FLUMETASONE, TIXOCORTOL PIVALATE, FLUDROCORTISONE, DEFLAZACORT, BUDESONIDE, LOTEPREDNOL ETABONATE, FLUOCORTOLONE,
or a pharmaceutically acceptable derivative thereof,
together with instructions for simultaneous, sequential or separate use, e.g. to treat or prevent gastrointestinal diseases caused by said second active ingredient and/or to treat or prevent diseases which can be treated or prevented by said second active ingredient.

A particularly preferred aspect of the present invention is a pharmaceutical composition comprising, in admixture, a first active ingredient, which is (S)-pantoprazole magnesium, and a second active ingredient, which is a NSAID or a COX-2 inhibitor or a NO-NSAID or a bisphosphonate or a corticosteroid selected from the group consisting of ACETYLSALICYLIC ACID, DICLOFENAC, DIFLUNISAL, ETODOLAC, FENOPROFEN, FLOCTAFENINE, FLURBIPROFEN, IBUPROFEN, INDOMETHACIN, KETOPROFEN, MECLOFENAMATE, MEFENAMIC ACID, MELOXICAM, NABUMETONE, NAPROXEN, OXAPROZIN, PHENYLBUTAZONE, PIROXICAM, SULINDAC, TENOXICAM, TIAPROFENIC ACID, TOLMETIN, CELECOXIB, ROFECOXIB, ALENDRONIC ACID, RISEDRONIC ACID, TILUDRONIC ACID, INCADRONIC ACID, OLPADRONIC ACID, MINODRONIC ACID,

IBANDRONIC ACID, ZOLANDRONIC ACID, ETIDRONIC ACID, BETAMETHASONE, HYDROCORTISONE, METHYLPREDNISOLONE, PREDNISOLONE, PREDNISONE, TRIAMCINOLONE ACETONIDE, DEXAMETHASONE, DESONIDE, FLUMETASONE, TIXOCORTOL PIVALATE, FLUDROCORTISONE, DEFLAZACORT, BUDESONIDE, LOTEPREDNOL ETABONATE, FLUOCORTOLONE and the pharmaceutically acceptable derivatives of these compounds.

A further particularly preferred aspect of the present invention is a pharmaceutical product comprising, in combination, a preparation of a first active ingredient, which is (S)-pantoprazole magnesium, and a preparation of a second active ingredient, which is a NSAID or a COX-2 inhibitor or a NO-NSAID or a bisphosphonate or a corticosteroid selected from the group consisting of ACETYLSALICYLIC ACID, DICLOFENAC, DIFLUNISAL, ETODOLAC, FENOPROFEN, FLOCTAFENINE, FLURBIPROFEN, IBUPROFEN, INDOMETHACIN, KETOPROFEN, MECLOFENAMATE, MEFENAMIC ACID, MELOXICAM, NABUMETONE, NAPROXEN, OXAPROZIN, PHENYLBUTAZONE, PIROXICAM, SULINDAC, TENOXICAM, TIAPROFENIC ACID, TOLMETIN, CELECOXIB, ROFECOXIB, ALENDRONIC ACID, RISEDRONIC ACID, TILUDRONIC ACID, IBANDRONIC ACID, ZOLANDRONIC ACID, INCADRONIC ACID, OLPADRONIC ACID, MINODRONIC ACID, ETIDRONIC ACID, BETAMETHASONE, HYDROCORTISONE, METHYLPREDNISOLONE, PREDNISOLONE, PREDNISONE, TRIAMCINOLONE ACETONIDE, DEXAMETHASONE, DESONIDE, FLUMETASONE, TIXOCORTOL PIVALATE, FLUDROCORTISONE, DEFLAZACORT, BUDESONIDE, LOTEPREDNOL ETABONATE, FLUOCORTOLONE and the pharmaceutically acceptable derivatives of these compounds, for simultaneous, sequential or separate use in therapy, e.g. to prevent medicament induced gastric ulcer in a mammal.

A further particularly preferred aspect of the present invention is a kit comprising a preparation of a first active ingredient, which is (S)-pantoprazole magnesium, a preparation of a second active ingredient, which is a NSAID or a COX-2 inhibitor or a NO-NSAID or a bisphosphonate or a corticosteroid selected from the group consisting of ACETYLSALICYLIC ACID, DICLOFENAC, DIFLUNISAL, ETODOLAC, FENOPROFEN, FLOCTAFENINE, FLURBIPROFEN, IBUPROFEN, INDOMETHACIN, KETOPROFEN, MECLOFENAMATE, MEFENAMIC ACID, MELOXICAM, NABUMETONE, NAPROXEN, OXAPROZIN, PHENYLBUTAZONE, PIROXICAM, SULINDAC, TENOXICAM, TIAPROFENIC ACID, TOLMETIN, CELECOXIB, ROFECOXIB, ALENDRONIC ACID, RISEDRONIC ACID, TILUDRONIC ACID, IBANDRONIC ACID, INCADRONIC ACID, OLPADRONIC ACID, MINODRONIC ACID, ZOLANDRONIC ACID, ETIDRONIC ACID, BETAMETHASONE, HYDROCORTISONE, METHYLPREDNISOLONE, PREDNISOLONE, PREDNISONE, TRIAMCINOLONE ACETONIDE, DEXAMETHASONE, DESONIDE, FLUMETASONE, TIXOCORTOL PIVALATE, FLUDROCORTISONE, DEFLAZACORT, BUDESONIDE, LOTEPREDNOL ETABONATE, FLUOCORTOLONE and the pharmaceutically acceptable derivatives of these compounds, and instructions for simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

A particularly preferred aspect of the present invention to be especially emphasized is a pharmaceutical composition comprising, in admixture, a first active ingredient, which is (S)-pantoprazole magnesium, and a second active ingredient, which is a NSAID or a COX-2 inhibitor or a NO-NSAID selected from the group consisting of ACETYLSALICYLIC ACID, DICLOFENAC, DIFLUNISAL, ETODOLAC, FENOPROFEN, FLOCTAFENINE, FLURBIPROFEN, IBUPROFEN, INDOMETHACIN, KETOPROFEN, MECLOFENAMATE, MEFENAMIC ACID, MELOXICAM, NABUMETONE, NAPROXEN, OXAPROZIN, PHENYLBUTAZONE, PIROXICAM, SULINDAC, TENOXICAM, TIAPROFENIC ACID, TOLMETIN, CELECOXIB, ROFECOXIB and the pharmaceutically acceptable derivatives of these compounds.

A further particularly preferred aspect of the present invention to be especially emphasized is a pharmaceutical product comprising, in combination, a preparation of a first active ingredient, which is (S)-pantoprazole magnesium, and a preparation of a second active ingredient, which is a NSAID or a COX-2 inhibitor or a NO-NSAID selected from the group consisting of ACETYLSALICYLIC ACID, DICLOFENAC, DIFLUNISAL, ETODOLAC, FENOPROFEN, FLOCTAFENINE, FLURBIPROFEN, IBUPROFEN, INDOMETHACIN, KETOPROFEN, MECLOFENAMATE, MEFENAMIC ACID, MELOXICAM, NABUMETONE, NAPROXEN, OXAPROZIN, PHENYLBUTAZONE, PIROXICAM, SULINDAC, TENOXICAM, TIAPROFENIC ACID, TOLMETIN, CELECOXIB, ROFECOXIB and the pharmaceutically acceptable derivatives of these compounds, for simultaneous, sequential or separate use in therapy, e.g. to prevent medicament induced gastric ulcer in a mammal.

A further particularly preferred aspect of the present invention to be especially emphasized is a kit comprising a preparation of a first active ingredient, which is (S)-pantoprazole magnesium, a preparation of a second active ingredient, which is a NSAID or a COX-2 inhibitor or a NO-NSAID selected from the group consisting of ACETYLSALICYLIC ACID, DICLOFENAC, DIFLUNISAL, ETODOLAC, FENOPROFEN, FLOCTAFENINE, FLURBIPROFEN, IBUPROFEN, INDOMETHACIN, KETOPROFEN, MECLOFENAMATE, MEFENAMIC ACID, MELOXICAM, NABUMETONE, NAPROXEN, OXAPROZIN, PHENYLBUTAZONE, PIROXICAM, SULINDAC, TENOXICAM, TIAPROFENIC ACID, TOLMETIN, CELECOXIB, ROFECOXIB and the pharmaceutically acceptable derivatives of these compounds, and instructions for simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

A selected particularly preferred aspect of the present invention is a pharmaceutical composition comprising, in admixture, a first active ingredient, which is (S)-pantoprazole magnesium dihydrate, and a second active ingredient, which is a NSAID or a COX-2 inhibitor or a NO-NSAID or a bisphosphonate or a corticosteroid selected from the group consisting of ACETYLSALICYLIC ACID, DICLOFENAC, DIFLUNISAL, ETODOLAC, FENOPROFEN, FLOCTAFENINE, FLURBIPROFEN, IBUPROFEN, INDOMETHACIN, KETOPROFEN, MECLOFENAMATE, MEFENAMIC ACID, MELOXICAM, NABUMETONE, NAPROXEN, OXAPROZIN, PHENYLBUTAZONE, PIROXICAM, SULINDAC, TENOXICAM, TIAPROFENIC ACID, TOLMETIN, CELECOXIB, ROFECOXIB, ALENDRONIC ACID,

RISEDRONIC ACID, TILUDRONIC ACID, INCADRONIC ACID, OLPADRONIC ACID, MINODRONIC ACID, IBANDRONIC ACID, ZOLANDRONIC ACID, ETIDRONIC ACID BETAMETHASONE, DEXAMETHASONE, FLUOCORTOLONE, METHYLPREDNISOLONE, PREDNISOLONE, PREDNISONE, HYDROCORTISONE, BUDESONIDE, TRIAMCINOLONE ACETONIDE and the pharmaceutically acceptable derivatives of these compounds.

A further selected particularly preferred aspect of the present invention is a pharmaceutical product comprising, in combination, a preparation of a first active ingredient, which is (S)-pantoprazole magnesium dihydrate, and a preparation of a second active ingredient, which is a NSAID or a COX-2 inhibitor or a NO-NSAID or a bisphosphonate or a corticosteroid selected from the group consisting of ACETYLSALICYLIC ACID, DICLOFENAC, DIFLUNISAL, ETODOLAC, FENOPROFEN, FLOCTAFENINE, FLURBIPROFEN, IBUPROFEN, INDOMETHACIN, KETOPROFEN, MECLOFENAMATE, MEFENAMIC ACID, MELOXICAM, NABUMETONE, NAPROXEN, OXAPROZIN, PHENYLBUTAZONE, PIROXICAM, SULINDAC, TENOXICAM, TIAPROFENIC ACID, TOLMETIN, CELECOXIB, ROFECOXIB, ALENDRONIC ACID, RISEDRONIC ACID, TILUDRONIC ACID, IBANDRONIC ACID, INCADRONIC ACID, OLPADRONIC ACID, MINODRONIC ACID, ZOLANDRONIC ACID, ETIDRONIC ACID, BETAMETHASONE, DEXAMETHASONE, FLUOCORTOLONE, METHYLPREDNISOLONE, PREDNISOLONE, PREDNISONE, HYDROCORTISONE, BUDESONIDE, TRIAMCINOLONE ACETONIDE and the pharmaceutically acceptable derivatives of these compounds, for simultaneous, sequential or separate use in therapy, e.g. to prevent medicament induced gastric ulcer in a mammal.

A further selected particularly preferred aspect of the present invention is a kit comprising a preparation of a first active ingredient, which is (S)-pantoprazole magnesium dihydrate, a preparation of a second active ingredient, which is a NSAID or a COX-2 inhibitor or a NO-NSAID or a bisphosphonate or a corticosteroid selected from the group consisting of ACETYLSALICYLIC ACID, DICLOFENAC, DIFLUNISAL, ETODOLAC, FENOPROFEN, FLOCTAFENINE, FLURBIPROFEN, IBUPROFEN, INDOMETHACIN, KETOPROFEN, MECLOFENAMATE, MEFENAMIC ACID, MELOXICAM, NABUMETONE, NAPROXEN, OXAPROZIN, PHENYLBUTAZONE, PIROXICAM, SULINDAC, TENOXICAM, TIAPROFENIC ACID, TOLMETIN, CELECOXIB, ROFECOXIB, ALENDRONIC ACID, RISEDRONIC ACID, TILUDRONIC ACID, INCADRONIC ACID, OLPADRONIC ACID, MINODRONIC ACID, IBANDRONIC ACID, ZOLANDRONIC ACID, ETIDRONIC ACID, BETAMETHASONE, DEXAMETHASONE, FLUOCORTOLONE, METHYLPREDNISOLONE, PREDNISOLONE, PREDNISONE, HYDROCORTISONE, BUDESONIDE, TRIAMCINOLONE ACETONIDE and the pharmaceutically acceptable derivatives of these compounds, and instructions for simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

A selected particularly preferred aspect of the present invention to be especially emphasized is a pharmaceutical composition comprising, in admixture, a first active ingredient, which is (S)-pantoprazole magnesium dihydrate, and a second active ingredient, which is a NSAID or a COX-2 inhibitor or a NO-

NSAID selected from the group consisting of ACETYLSALICYLIC ACID, DICLOFENAC, DIFLUNISAL, ETODOLAC, FENOPROFEN, FLOCTAFENINE, FLURBIPROFEN, IBUPROFEN, INDOMETHACIN, KETOPROFEN, MECLOFENAMATE, MEFENAMIC ACID, MELOXICAM, NABUMETONE, NAPROXEN, OXAPROZIN, PHENYLBUTAZONE, PIROXICAM, SULINDAC, TENOXICAM, TIAPROFENIC ACID, TOLMETIN, CELECOXIB, ROFECOXIB and the pharmaceutically acceptable derivatives of these compounds.

A further selected particularly preferred aspect of the present invention to be especially emphasized is a pharmaceutical product comprising, in combination, a preparation of a first active ingredient, which is (S)-pantoprazole magnesium dihydrate, and a preparation of a second active ingredient, which is a NSAID or a COX-2 inhibitor or a NO-NSAID selected from the group consisting of ACETYLSALICYLIC ACID, DICLOFENAC, DIFLUNISAL, ETODOLAC, FENOPROFEN, FLOCTAFENINE, FLURBIPROFEN, IBUPROFEN, INDOMETHACIN, KETOPROFEN, MECLOFENAMATE, MEFENAMIC ACID, MELOXICAM, NABUMETONE, NAPROXEN, OXAPROZIN, PHENYLBUTAZONE, PIROXICAM, SULINDAC, TENOXICAM, TIAPROFENIC ACID, TOLMETIN, CELECOXIB, ROFECOXIB and the pharmaceutically acceptable derivatives of these compounds, for simultaneous, sequential or separate use in therapy, e.g. to prevent medicament induced gastric ulcer in a mammal.

A further selected particularly preferred aspect of the present invention to be especially emphasized is a kit comprising a preparation of a first active ingredient, which is (S)-pantoprazole magnesium dihydrate, a preparation of a second active ingredient, which is a NSAID or a COX-2 inhibitor or a NO-NSAID selected from the group consisting of ACETYLSALICYLIC ACID, DICLOFENAC, DIFLUNISAL, ETODOLAC, FENOPROFEN, FLOCTAFENINE, FLURBIPROFEN, IBUPROFEN, INDOMETHACIN, KETOPROFEN, MECLOFENAMATE, MEFENAMIC ACID, MELOXICAM, NABUMETONE, NAPROXEN, OXAPROZIN, PHENYLBUTAZONE, PIROXICAM, SULINDAC, TENOXICAM, TIAPROFENIC ACID, TOLMETIN, CELECOXIB, ROFECOXIB and the pharmaceutically acceptable derivatives of these compounds, and instructions for simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

A selected particularly preferred aspect of the present invention to be especially emphasized is a pharmaceutical composition comprising, in admixture, a first active ingredient, which is (S)-pantoprazole magnesium, and a second active ingredient, which is DICLOFENAC or a pharmaceutically acceptable derivative of this compound.

A further selected particularly preferred aspect of the present invention to be especially emphasized is a pharmaceutical product comprising, in combination, a preparation of a first active ingredient, which is (S)-pantoprazole magnesium, and a preparation of a second active ingredient, which is DICLOFENAC or a pharmaceutically acceptable derivative of this compound, for simultaneous, sequential or separate use in therapy, e.g. to prevent medicament induced gastric ulcer in a mammal.

A further selected particularly preferred aspect of the present invention to be especially emphasized is a kit comprising a preparation of a first active ingredient, which is (S)-pantoprazole magnesium, a preparation of a second active ingredient, which is DICLOFENAC or a pharmaceutically acceptable derivative of this compound, and instructions for simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

A selected particularly preferred aspect of the present invention to be especially emphasized is a pharmaceutical composition comprising, in admixture, a first active ingredient, which is (S)-pantoprazole magnesium dihydrate, and a second active ingredient, which is DICLOFENAC or a pharmaceutically acceptable derivative of this compound.

A further selected particularly preferred aspect of the present invention to be especially emphasized is a pharmaceutical product comprising, in combination, a preparation of a first active ingredient, which is (S)-pantoprazole magnesium dihydrate, and a preparation of a second active ingredient, which is DICLOFENAC or a pharmaceutically acceptable derivative of this compound, for simultaneous, sequential or separate use in therapy, e.g. to prevent medicament induced gastric ulcer in a mammal.

A further selected particularly preferred aspect of the present invention to be especially emphasized is a kit comprising a preparation of a first active ingredient, which is (S)-pantoprazole magnesium dihydrate, a preparation of a second active ingredient, which is DICLOFENAC or a pharmaceutically acceptable derivative of this compound, and instructions for simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

Within the scope of this invention, "inflammatory diseases" which may be mentioned are gastrointestinal inflammatory diseases such as, for example, inflammatory bowel disease, Crohn's disease, irritable bowel syndrome, gastroesophageal reflux disease (GERD) and ulcerative colitis, or non-gastrointestinal inflammatory diseases, in particular arthritis, including but not limited to rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis; or asthma, bronchitis and skin related disorders such as psoriasis, eczema, burns and dermatitis.

"Inflammation associated disorders" which may be mentioned are, for example, pain (both chronic and acute), migraine, fever and headaches.

Furthermore, the person skilled in the art knows on the basis of his/her expert knowledge which diseases, disorders or conditions can be treated, ameliorated or prevented by NSAIDs, COX-2 inhibitors, NO-NSAIDs, bisphosphonates and corticosteroids. According to the present invention, agents selected from the group consisting of NSAIDs, COX-2 inhibitors, NO-NSAIDs, bisphosphonates and corticosteroids can be combined beneficially with (S)-pantoprazole and/or its salts to enhance or to improve safety and tolerability of the mono therapy, i.e. the mono therapy using only said agents selected from

the group consisting of NSAIDs, COX-2 inhibitors, NO-NSAIDs, bisphosphonates and corticosteroids unpartnered with (S)-pantoprazole and/or its salts, by reducing the risk of adverse effects, such as medicament-associated gastrointestinal disorders or medicament-caused gastrointestinal diseases, associated conventionally with the mono therapy.

In this context, the skilled person knows therefore on the basis of his/her expert knowledge and/or on the basis of the disclosure of the present invention which diseases, disorders or conditions conventionally treated, ameliorated or prevented monotherapeutically with NSAIDs, COX-2 inhibitors, NO-NSAIDs, bisphosphonates or corticosteroids can be now beneficially treated, ameliorated or prevented with the combination therapy according to the present invention.

In more detail, the combination therapy according to this invention can be applied to treat diseases, disorders or conditions typically treated, ameliorated or prevented by NSAIDs and/or COX-2 inhibitors, such as, for example, inflammatory diseases (in particular all kind of arthritis, including rheumatosis arthritis or degenerative joint diseases including osteoarthritis) or inflammation associated disorders, and/or particularly symptoms caused by arthritis, such as inflammation, swelling, stiffness and joint pain, or other kinds of pain or painful conditions, such as gout attacks, bursitis, tendonitis, touthache, lower back and neck pain, myositis, sprains, strains or other injuries, or symptoms associated with influenza or other viral infections or common cold.

As further diseases, disorders or conditions, which can be treated, ameliorated or prevented by NSAIDs and/or, particularly, COX-2 inhibitors within the combination therapy according to this invention, can be mentioned, without being restricted thereto, neuropathic pains, (inflammatory) liver diseases, stroke, epilepsy, dysmenorrhoea, ophthalmic diseases, cognitive disorders such as dementia, particularly degenerative dementia (such e.g. Alzheimer's disease) or, in more particular, cellular and neoplastic transformation and metastatic tumour growth, such e.g. certain cancerous diseases, for example colonic cancer and prostate cancer, or cancer associated with overexpression of HER-2/neu (e.g. breast cancer), or adenomatous colorectal polyps (and to reduce herewith the risk of developing colon cancer), or other conditions mediated by COX-2.

As diseases, disorders or conditions, which can be treated, ameliorated or prevented by bisphosphonates within the combination therapy according to this invention, can be mentioned, without being restricted thereto, disorders associated with abnormal bone resorption such as, for example, osteoporosis, multiple myeloma or metastatic bone diseases.

Within the meaning of this invention the terms "use", "administration", "co-administration" or "administering" refer - with regard to the NSAIDs, COX-2 inhibitors, NO-NSAIDs, bisphosphonates or corticosteroids - preferably to oral application. However in some cases, parenterale (e.g. intravenous) or percutaneous application can be also advantageous. With regard to (S)-pantoprazole and/or its salts, oral or intravenous application is preferred.

The dosage of the active compounds is in a customary order of magnitude comparable with the mono dosage, whereby, due to the additive and/or super-additive synergism of the single effects, the relevant doses of the active compounds in the combined dosage can be reduced compared to norm, or whereby – while maintaining the customary doses of the single components – a surprisingly higher and prolonged effect is obtained.

The person skilled in the art is aware on the base of his expert knowledge of the total daily dosage of the NSAIDs, the COX-2 inhibitors, the NO-NSAIDs, the bisphosphonates or the corticosteroids, which are comprised in the abovementioned pharmaceutical compositions, pharmaceutical products, formulations, combinations, preparations, commercial packages or kits according to this invention. Said total daily dosage can vary within a wide range. For example, in the case of Diclofenac the daily doses are in a range from 100-2000 µg/kg.

In general, it has proven advantageous in human medicine to administer (S)-pantoprazole and/or its salts in the case of oral administration in a daily dose from approximately 10 to approximately 80, preferably 20 to 40 mg as calculated for the free acid (S)-pantoprazole. In the case of parenteral treatment, similar or [in particular in the case of intravenous administration of (S)-pantoprazole and/or its salts], as a rule, lower doses can be used.

The optimal dose and manner of administration of the active compounds necessary in each case can easily be determined by any person skilled in the art on the basis of his/her expert knowledge.

The person skilled in the art is familiar, on the basis of his/her knowledge, with carriers, diluents, adjuvants, auxiliaries or excipients which are suitable for the desired pharmaceutical formulations and/or preparations. Beside solvents, gel-forming agents, suppository bases, tablet auxiliaries and other active carriers, it is possible to use, for example, antioxidants, dispersants, emulsifiers, antifoams, flavor corrigents, preservatives, solubilizers, colorants or, in particular, permeation promoters and complexing agents (e.g. cyclodextrines).

In medicines, the active compounds are preferably employed in the form of tablets, coated tablets, capsules, suppositories, patches, emulsions, suspensions, gels or solutions, the active compound content advantageously being between 0.1 and 95%. Thus, for example with regard to the desired mode and site of action, the person skilled in the art can develop, on the basis of his/her knowledge, by appropriate choice of the excipients and the auxiliaries different galenic forms precisely tailored to the active ingredient(s) (such as, for example, retard forms or gastric acid resistant forms).

All patents and patent applications referred to herein are herein incorporated by reference into the specification in their entirety for all purposes.

It is to be understood that the invention covers all combinations of single aspects or embodiments of the invention as described herein.

It is to be understood that when used herein, 'medicament' or 'pharmaceutical composition' shall be taken to refer to a composition comprising both (S)-pantoprazole and/or its salts and the other active ingredient in a fixed combination (fixed unit dosage form), or a medicament pack comprising the two active ingredients as discrete separate dosage forms. In case of a medicament pack comprising the two active ingredients, the active ingredients are preferably packed into blister cards which are suited for improving compliance.

Each blister card preferably contains the medicaments to be taken on one day of treatment. If the medicaments are to be taken at different times of day, the medicaments can be disposed in different sections on the blister card according to the different ranges of times of day at which the medicaments are to be taken (for example morning and evening or morning, midday and evening). The blister cavities for the medicaments to be taken together at a particular time of day are accommodated in the respective range of times of day. The various times of day are, of course, also put on the blister in a clearly visible way. It is also possible, of course, for example to indicate a period in which the medicaments are to be taken, for example stating the times.

The daily sections may represent one line of the blister card, and the times of day are then identified in chronological sequence in this column.

Medicaments which must be taken together at a particular time of day are placed together at the appropriate time on the blister card, preferably a narrow distance apart, allowing them to be pushed out of the blister easily, and having the effect that removal of the dosage form from the blister is not forgotten.

Having described the invention in detail and by reference to the embodiments or aspects thereof, the scope of the present invention is not limited only to those described embodiments or aspects. As will be apparent to persons skilled in the art, modifications, analogies, variations, derivations, homologisations and adaptations to the above-described invention can be made on the base of art-known knowledge and/or on the base of the disclosure (e.g. the explicit, implicit or inherent disclosure) of the present invention without departing from the spirit and scope of this invention.

Examples

1. **Magnesium (-)-bis{[5-(difluoromethoxy)]-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazolide} dihydrate**

At 20-25°C, 20.2 g (52.7 mmol) of (-)-pantoprazole {(-)-[5-(difluoromethoxy)]-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole} were suspended in 200 ml of purified water. A solution of (55.2 mmol) sodium hydroxide in 10 ml of water was added, and the mixture was stirred at 20-30°C for 30 min. With addition of a filter aid (1g Hyflo-Super-Cel), the turbid solution was filtered. 6.32 g (31.2 mmol) of magnesium dichloride hexahydrate in 150 ml of water were then added drop by drop with stirring over a period of 30 min. After a further 30 min., the precipitated solid was filtered off with suction using a suction filter, stirred with water (2 x 50 ml) and again filtered off with suction. Drying under reduced pressure at 50-60°C gave, in a yield of 17.36 g (80%), a hydrate of magnesium (-)-bis{[5-(difluoromethoxy)]-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazolide} having a water content of 4.5-4.7 % as a colourless to beige powder (m. p. 158-161°C, with decomposition).

Specific rotation: $\alpha_D^{20°}$ = -114° (c = 0.5, measured in methanol)

For recrystallisation, 1.88 g of the hydrate were, at 55°C, dissolved in 6 ml of methanol, and 20 ml of water were added with stirring. A colourless to beige solid crystallized out. This gave the title compound of m. p. 160-163°C (with decomposition) having a water content of 4.3-4.4 %.

Alternatively, the title compound can also be prepared from organic-aqueous solvent mixtures. To this end, (-)-pantoprazole sodium, or (-)-pantoprazole together with one equivalent of aqueous, for example 2N, sodium hydroxide solution, is dissolved in an organic solvent, for example warm acetone. 0.5 to 0.55 equivalents of a magnesium salt (for example magnesium chloride hexahydrate), dissolved in water, are added drop by drop, and the mixture is cooled with stirring. The precipitated solid is filtered off, washed with the solvent mixture in question and dried at 50°C under reduced pressure until the weight remains constant. This gives the title compound as a colourless to beige powder.

2. **Magnesium (-)-bis{[5-(difluoromethoxy)]-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazolide} dihydrate**

A. (-)-Pantoprazole-Na

36 g of (-)-pantoprazole were suspended in 180 ml of methyl isobutyl ketone (MIBK) and 18 ml of 2-propanol and heated to an internal temperature of 45°C. The suspension was stirred at this temperature for 15 min. At 50°C, 11 g of 30% (w/w) aqueous sodium hydroxide solution were slowly added drop by drop to this suspension. A clear to slightly turbid solution resulted. This solution was stirred for a bit longer and then filtered to give a clear solution.

The clear filtrate was slowly cooled to room temperature. Between 45°C and 30°C, crystallization, which could be accelerated by seeding with (-)-pantoprazole sodium, began. The resulting suspension was stirred at an internal temperature of < 20°C for another 2 h. The suspension was then filtered, and the crystals were washed with 40 ml of MIBK.

Drying was carried out in a vacuum drying cabinet at < 50 mbar and 40-45°C. [It is also possible to dispense with drying and to use the moist product (having an MIBK content of 10-20 %) directly for step B]. The white-beige crystalline product obtained after drying was hygroscopic. The water content was from 2 to 12 %. The absorption and release of water were reversible. Yield: 34 g = 90 % of theory (based on anhydrous product). Specific rotation: $\alpha_D^{20°}$ = - 95 (c = 0.5, measured in methanol, sodium salt having a water content of 12%). m. p.: 145-165°C (decomposition, sodium salt having a water content of 2 %); 102-109°C (decomposition, sodium salt having a water content of 12 %).

B. (-)-Pantoprazole-Mg

30 g of (-)-pantoprazole sodium salt (calculated anhydrous substance) were suspended in 260 ml of water. The suspension was heated to 35-40°C and stirred at 35-40°C for another 10 min. This gave a clear solution. The clear solution was cooled to 22-27°C. 14.3 g of magnesium chloride hexahydrate were dissolved in 100 ml of water, and at room temperature and with stirring, the solution was slowly added dropwise to the (-)-pantoprazole sodium salt solution. The resulting suspension was then stirred at room temperature for another 4 h. The suspension was, under pressure, filtered through a Nutsche filter, and the product was, a little at a time, washed twice with 300 ml of water. Drying in a vacuum drying cabinet at < 50 mbar and 40-45°C gave 27.5 g (90 %) of the title compound of m. p. 160-163°C. Water content 4.3-4.4 %; specific rotation: $\alpha_D^{20°}$ = -129 (c= 0.5, measured in methanol).

Recrystallisation of (-)-pantoprazole-Mg

For recrystallisation, 6.0 g of the (-)-pantoprazole-Mg-dihydrate were, at 55°C, dissolved in 18 ml of methanol. After 15 min, 90 ml of water were added with stirring to the orange-brown-solution. A colourless to beige solid crystallised out. The resulting suspension was then stirred at 20-25°C for another 1 hour. The solid was filtered off, washed with 10 ml of water and dried under vacuum for 20 hours at 50°C. The yield for the title compound was 88 % (5.26 g) with the following data:

M.P.: 161-165°C (with decomposition)
Specific rotation: $\alpha_D^{20°}$ = -130° (c = 0.5, measured in methanol)

Patent Claims

1. A pharmaceutical composition comprising a first active ingredient, which is (S)-pantoprazole and/or its salt; and a second active ingredient, which is selected from a group consisting of NSAIDs, COX-2 inhibitors, NO-NSAIDs, bisphosphonates and corticosteroids.

2. A pharmaceutical composition according to claim 1, comprising in admixture for simultaneous administration a NSAID, a COX-2 inhibitor, a NO-NSAID, a bisphosphonate or a corticosteroid together with (S)-pantoprazole and/or its salt.

3. A pharmaceutical composition according to claim 1, comprising a first active ingredient, which is a NSAID or a COX-2 inhibitor or a NO-NSAID or a bisphosphonate or a corticosteroid, and a second active ingredient, which is (S)-pantoprazole and/or its salt, for simultaneous, sequential or separate use in therapy in any order.

4. A pharmaceutical composition according to any of the preceding claims, wherein (S)-pantoprazole is present in the form of its magnesium salt.

5. A pharmaceutical composition according to any of the preceding claims, wherein (S)-pantoprazole is present in the form of the dihydrate of its magnesium salt.

6. A pharmaceutical composition according to claim 1 or 2 or 3 or 4 or 5, wherein the second active ingredient is
- a NSAID selected from the group consisting of glycolic acid [o-(2,6-dichloroanilino)phenyl]acetate(ester) [INN: ACECLOFENAC]; 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid carboxymethyl ester [INN: ACEMETACIN]; 2-(acetyloxy)benzoic acid [ACETYLSALICYLIC ACID], 2-methoxyphenyl-alpha-methyl-4-(isobutyl)phenylacetate [Research Code: AF-2259], (4-allyloxy-3-chlorophenyl)acetic acid [INN: ALCLOFENAC], p-[(2-methylallyl)amino]hydratropic acid [INN: ALMINOPROFEN], 2-amino-3-benzoylphenylacetic acid [INN: AMFENAC], (plus/minus)-4-(1-hydroxyethoxy)-2-methyl-N-2-pyridyl-2H-1,2-benzothiazine-3-carboxamide ethylcarbonate (ester), 1,1-dioxide [INN: AMPIROXICAM], 2-methoxyphenyl-1-methyl-5-(p-methylbenzoyl)pyrrol-2-acetamido-acetate [INN: AMTOLMETINGUACIL], (plus/minus)-2,3-dihydro-5-(4-methoxybenzoyl)-1H pyrrolizine-1-carboxylic acid [INN: ANIROLAC], 2-[4-(alpha,alpha,alpha-trifluoro-m-tolyl)-1-piperazinyl]ethyl-N-(7-trifluoromethyl-4-quinolyl)anthranilate [INN: ANTRAFENINE], 5-(dimethylamino)-9-methyl-2-propyl-1H-pyrazolo[1,2-a][1,2,4]benzo-triazine-1,3(2H)-dione [INN: AZAPROPAZONE], 4-acetamidophenyl salicylate acetate [INN: BENORILATE], 2-(8-methyl-10,11-dihydro-11-oxodibenz[b,f]oxepin-2-yl)propionic acid [INN: BERMOPROFEN], 2-[(1-benzyl-1H-indazol-3-yl)methoxy]-2-methylpropionic acid [INN: BINDARIT], [2-amino-3-(p-bromobenzoyl)phenyl]acetic acid [INN: BROMFENAC], 3-(3-chloro-4-cyclohexylbenzoyl)propionic acid [INN: BUCLOXIC ACID], 5-butyl-1-cyclohexylbarbituric acid [INN: BUCOLOM], 4-butoxy-N-hydroxybenzeneacetamide [INN:

BUFEXAMAC], butylmalonic acid mono(1,2-diphenylhydrazide) [INN: BUMADIZONE], alpha-ethyl-4-(2-methylpropyl)benzeneacetic acid [INN: BUTIBUFEN], 2-(4-biphenylyl)butyric acid, trans-4-phenylcyclohexylamine salt (1:1) [INN: BUTIXIRATE], 2-(acetyloxy)-benzoic acid, calcium salt, compound with urea (1:1) [INN: CARBASALATE CALCIUM], (plus/minus)-6-chloro-alpha-methylcarbazole-2-acetic acid [INN: CARPROFEN], 1-cinnamoyl-5-methoxy-2-methylindole-3-acetic acid [INN: CINMETACIN], N-(2-pyridyl)-2-methyl-4-cinnamoyloxy-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide [INN: CINNOXICAM], 6-chloro-5-cyclohexyl-1-indancarboxylic acid [INN: CLIDANAC], 2-[4-(p-chlorophenyl)benzyloxy]-2-methylpropionic acid [INN: CLOBUZARIT], 5-methoxy-2-methyl-3-indolylacetohydroxamic acid [INN: DEBOXAMET], (S)-(+)-p-isobutylhydratropic acid [INN: DEXIBUPROFEN], (+)-(S)-m-benzoylhydratropic acid [INN: DEXKETOPROFEN], 2-[(2,6-dichlorophenyl)amino]benzeneacetic acid [INN: DICLOFENAC], 2',4'-Difluoro-4-hydroxy-3-biphenylcarboxylic acid [INN: DIFLUNISAL], 4-(2,6-dichloroanilino)-3-thiopheneacetic acid [INN: ELTENAC], N-beta-phenethyl-anthranilic acid [INN: ENFENAMIC ACID] salicylic acid acetate, ester with beta-hydroxy p-acetophenetidide [INN: ETERSALATE], 1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid [INN: ETODOLAC], 2-[[3-(trifluoromethyl)phenyl]amino]benzoic acid 2-(2-hydroxyethoxy)-ethyl ester [INN: ETOFENAMATE], p-chlorobenzoic acid, ester with 4-butyl-4-(hydroxymethyl)-1,2-diphenyl-3,5-pyrazolidinedione [INN: FECLOBUZONE], 4-biphenylacetic acid [INN: FELBINAC], 3-(4-biphenylylcarbonyl)propionic acid [INN: FENBUFEN], [o-(2,4-dichlorophenoxy)phenyl]acetic acid [INN: FENCLOFENAC], (plus/minus)-m-phenoxyhydratropic acid [INN: FENOPROFEN], 4-(p-chlorophenyl)-2-phenyl-5-thiazoleacetic acid [INN: FENTIAZAC], (plus/minus)-alpha-[[(2-hydroxy-1,1-dimethylethyl)amino]methyl]-benzyl alcohol [INN: FEPRADINOL], 4-(2',4'-difluorobiphenylyl)-4-oxo-2-methylbutanoic acid [INN: FLOBUFEN], 2,3-dihydroxypropyl N-[8-(trifluoromethyl)-4-quinoly]anthranilate [INN: FLOCTAFENINE], N-(alpha,alpha,alpha-trifluoro-m-tolyl)anthranilic acid [INN: FLUFENAMIC ACID], (plus)-2-(p-fluorophenyl)-alpha-methyl-5-benzoxazoleacetic acid [INN: FLUNOXAPROFEN], 2-fluoro-alpha-methyl-4-biphenylacetic acid [INN: FLURBIPROFEN], (plus/minus)-2-(2-fluoro-4-biphenylyl)propionic acid 1 (acetoxy)ethyl ester [INN: FLURBIPROFEN AXETIL], 2-ethyl-2,3-dihydro-5-benzofuranacetic acid [INN: FUROFENAC], 2-[4-(2'-furoyl)phenyl]propionic acid [INN: FURPROFEN], 2-[2-[1-(p-chlorobenzoyl)-5-methoxy-2-methylindol-3-yl]acetamido]-2-deoxy-D-glucose [INN: GLUCAMETACIN], 2-(2-fluorobiphenyl-4-yl)propionic acid 4-nitrooxybutylester [Research Code: HCT-1026], (p-isobutylphenyl)acetic acid [INN: IBUFENAC], alpha-p-isobutylphenylpropionic acid [INN: IBUPROFEN], methyl 4-(3-thienyl)phenyl-alpha-methylacetate [Research Code: IDPH-8261], (plus/minus)-2-[p-(1-oxo-2-isoindolinyl)phenyl]butyric acid [INN: INDOBUFEN], 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid [INN: INDOMETACIN], 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid, 3,7,11-trimethyl-2,6,10-dodecatrienyl ester [INN: INDOMETACIN FARNESIL], p-(1-oxo-2-isoindolinyl)hydratropic acid [INN: INDOPROFEN], 2-(10-methoxy-4H-benzo[4,5]cyclohepta[1,2-b]thiophen-4-ylidene)-acetic acid [Research Code: IX-207-887], m-benzoylhydratropic acid [INN: KETOPROFEN], (DL)-5-benzoyl-3H-1,2-dihydropyrrolo[1,2-a]pyrrole-1-carboxylic acid [INN: KETOROLAC], 2,3-dihydro-5-hydroxy-6-[2-(hydroxymethyl)cinnamyl]benzofuran [Research Code: L-651896], N-(2-carboxyphenyl)-4-chloroanthranilic acid [INN: LOBENZARIT], 3-(p-chlorophenyl)-1-phenylpyrazole-4-acetic acid [INN:

LONAZOLAC], 6-chloro-4-hydroxy-2-methyl-N-2-pyridyl-2H-thieno[2,3-e]-1,2-thiazine-3-carboxamide 1,1-dioxide [INN: LORNOXICAM], 2-[4-(2-oxocyclopentan-1-ylmethyl)phenyl]-propionate [INN: LOXOPROFEN], 2(R)-[4-(3-methyl-2-thienyl)phenyl]propionic acid [Research Code: M-5010], N-(2,3-xylyl)anthranilic acid [INN: MEFENAMIC ACID], 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide [INN: MELOXICAM], 5-aminosalicylic acid [INN: MESALAZINE], (2,2-dimethyl-6-(4-chlorophenyl)-7-phenyl-2,3-dihydro-1H-pyrrolizin-5-yl)-acetic acid [Research Code: ML-3000], 3,4-bis(4-methoxyphenyl)-5-isoxazoleacetic acid [INN: MOFEZOLAC], 4-(6-methoxy-2-naphthyl)-2-butanone [INN: NABUMETONE], (plus)-6-methoxy-alpha-methyl-2-naphthalineacetic acid [INN: NAPROXEN], 2-[3-(trifluoromethyl)anilino]nicotinic acid [INN: NIFLUMIC ACID], 5,5'-azodisalicylic acid [INN: OLSALAZINE], 4,5-diphenyl-2-oxazolepropionic acid [INN: OXAPROZIN], alpha-methyl-4-[(2-oxocyclohexylidene)methyl]benzene acetic acid [INN: PELUBIPROFEN], 4-butyl-1,2-diphenyl-3,5-pyrazolidinedione [INN: PHENYLBUTAZONE], 2-(p-isobutylphenyl)propionic acid 2-pyridyl-methyl ester [INN: PIMEPROFEN], 4-(p-chlorophenyl)-1-(p-fluorophenyl)pyrazole-3-acetic acid [INN: PIRAZOLAC], 4-hydroxy-2-methyl-N-2-pyridyl-2H-1,2-benzothiadiazin-3-carboxamide 1,1-dioxide [INN: PIROXICAM], 3-chloro-4-(3-pyrrolin-1-yl)hydratropic acid [INN: PIRPROFEN], 2-[5H-(1)benzopyrano]2,3-b]pyridin-7-yl]propionic acid [INN: PRANOPROFEN], 2,6-di-tert-butyl-4-(2'-thenoyl)phenol [INN: PRIFELONE], alpha-cyano-1-methyl-beta-oxopyrrole-2-propionanilide [INN: PRINOMIDE], 3-[4-(2-hydroxyethyl)-1-piperazinyl]-propyl-D,L-4-benzamido-N,N-dipropylglutaramat 1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetate (ester) [INN: PROGLUMETACIN], 7-methyl-1-(1-methylethyl)-4-phenyl-2(1H)quinazolinone [INN: PROQUAZONE], 7-methoxy-alpha,10-dimethylphenothiazine-2-acetic acid [INN: PROTIZINIC ACID], 2-[[2-(p-chlorophenyl)-4-methyl-5-oxazolyl]methoxy]-2-methylpropionic acid [INN: ROMAZARIT], o-hydroxybenzamide [SALICYLAMIDE], 2-hydroxybenzoic acid [SALICYLIC ACID], N-acetyl-L-cysteine salicylate (ester), acetate (ester) [INN: SALMISTEINE], N-acetyl-L-cysteine salicylate (ester) [INN: SALNACEDIN], 2-hydroxybenzoic acid 2-carboxyphenyl ester [INN: SALSALATE], 4-[1-(2-fluorobiphenyl-4-yl)ethyl]-N-methylthiazole-2-amine [Research Code: SM-8849], (Z)-5-fluoro-2-methyl-1-[p-(methylsulfinyl)benzylidene]indene-3-acetic acid [INN: SULINDAC], p-2-thenoylhydratropic acid [INN: SUPROFEN] 2-(4-(3-methyl-2-butenyl)phenyl)propionic acid [Research Code: TA-60], phthalidyl 2-(alpha,alpha,alpha-trifluoro-m-toluidino)nicotinate [INN: TALNIFLUMATE], (Z)-5-chloro-3-(2-thenoyl)-2-oxoindole-1-carboxamide [INN: TENIDAP], 2-thiophenecarboxylic acid, ester with salicylic acid [INN: TENOSAL], 4-hydroxy-2-methyl-N-2-pyridyl-2H-thieno[2,3-e]-1,2-thiazine-3-carboxamide [INN: TENOXICAM], 5-(4-chlorophenyl)-N-hydroxy-1-(4-methoxyphenyl)-N-methyl-1H-pyrazole-3-propionamide [INN: TEPOXALIN], alpha-(5-benzoyl-2-thienyl)propionic acid [INN: TIAPROFENIC ACID], 5-chloro-3-[4-(2-hydroxyethyl)-1-piperazinyl]carbonylmethyl-2-benzo-thiazolin one [INN: TIARAMIDE], 2-(2-methyl-5H-[1]benzopyrano[2,3-b]pyridin-7-yl)-propionic acid N,N-dimethylcarbamoylmethyl ester [INN: TILNOPROFEN ARBAMEL], 1-Cyclohexyl-2-(2-methyl-4-quinolyl)-3-(2-thiazolyl)guanidine [INN: TIMEGADINE], 2-amino-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine [INN: TINORIDINE], N-(3-chloro-o-tolyl)anthranilic acid [INN: TOLFENAMIC ACID], 1-methyl-5-(4-methylbenzoyl)-1H-pyrrole-2-acetic acid [INN: TOLMETIN], hydroxybis[alpha-methyl-4-(2-methylpropyl)benzene acetato-O]-aluminium [Research Code: U-18573-G], N-(3-

trifluoromethylphenyl)-anthranilic acid n-butyl ester [INN: UFENAMATE], 2-[4-[3-(hydroxyimino)cyclohexyl]phenyl]propionic acid [INN: XIMOPROFEN], 2-(10,11-dihydro-10-oxo-dibenz[b,f]thiepin-2-yl-propionic acid [INN: ZALTOPROFEN] and 2-[4-(2-thiazolyloxy)phenyl]-propionic acid [INN: ZOLIPROFEN]; or

- a NO-NSAID such as, for example, a NO-NSAID selected from the group consisting of those NO-NSAIDs which are disclosed in WO 96/32946, WO 96/35416, WO 96/38136, WO 96/39409, WO 00/50037, US 6,057,347, WO 94/04484, WO 94/12463, WO 95/09831, WO 95/30641, WO 97/31654, WO 99/44595, WO 99/45004 or WO 01/45703; or

- a COX-2 inhibitor selected from the group consisting of 5-chloro-6'-methyl-3-[4-(methylsulfonyl)phenyl]-2,3'-bipyridine [INN: ETORICOXIB], 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzene-sulfonamide [INN: CELECOXIB], 4-[p-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone [INN: ROFECOXIB], N-[[p-(5-methyl-3-phenyl-4-isoxazolyl)phenyl]sulfonyl]propion-amide [INN: PARECOXIB], p-(5-methyl-3-phenyl-4-isoxazolyl)benzenesulfonamide [INN: VALDECOXIB], 2-[2-(2-chloro-6-fluorophenylamino)-5-methylphenyl]acetic acid [INN: LUMIRACOXIB], 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzene-sulfonamide [INN: TILMACOXIB], 4-[4-chloro-5-(3-fluoro-4-methoxyphenyl)-1H-imidazol-1-yl]benzene-sulfonamide [INN: CIMICOXIB], 4'-nitro-2'-phenoxymethanesulfonanilide [INN: NIMESULIDE], 6-(2,4-difluorophenoxy)-5-methylsulfonylamino-1-indanone [INN: FLOSULIDE], 5-bromo-2-(4-fluoro-phenyl)-3-(4-methanesulfonyl-phenyl)-thiophene [DUP-697], 4-acetyl-2-(2,4-difluorophenoxy)methanesulfonanilide [FK-3311], N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide [NS-398], 5-methanesulfonamido-6-(2,4-difluorophenylthio)-1-indanone [L-745337], 8-acetyl-3-(4-fluorophenyl)-2-[4-(methanesulfonyl)phenyl]imidazo[1,2-a]-pyridine [GR-253035], 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)pyrazol-1-yl]benzenesulfon-amide [SC-58236], 4-(2,3-dihydro-2-oxo-3-phenyl-4-oxazolyl)-benzenesulfonamide [LAS-33815], CS-502, 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methyl-sulfonyl)phenyl]-3(2H)-pyridazinone [ABT-963], and GW-406381, and those COX-2 inhibitors disclosed in WO 02096427, WO 02096886 or WO 02096885; or

- a bisphosphonate selected from the group consisting of ALENDRONIC ACID, RISEDRONIC ACID, TILUDRONIC ACID, IBANDRONIC ACID, ZOLANDRONIC ACID, CLODRONIC ACID, INCADRONIC ACID, OLPADRONIC ACID, MINODRONIC ACID, PAMIDRONIC ACID and ETIDRONIC ACID; or

- a corticosteroid selected from the group consisting of HYDROCORTISONE, PREDNISONE, PREDNISOLONE, METHYLPREDNISOLONE, TRIAMCINOLONE ACETONIDE, AMCINONIDE, CLOBETASONE, CLOBETASOL, DEFLAZACORT, DESONIDE, CLOPREDNOL, DEXAMETHASONE, DIFLORASONE, DIFLUCORTOLONE, DIFLUPREDNATE, FLUDROXYCORTIDE, FLUDROCORTISONE, FLUMETASONE, TIXOCORTOL PIVALATE, FLUOCORTIN BUTYL, CLOCORTOLONE, FLUOCINOLONE ACETONIDE, FLUOCORTOLONE, FLUOROMETHOLONE, FLUPREDNIDENE, FLUPREDNISOLONE, BETAMETHASONE, HALCINONIDE, BUDESONIDE, HALOMETASONE, RIMEXOLONE, PARAMETHASONE, PREDNYLIDENE, LOTEPREDNOL ETABONATE, PREDNICARBATE,

or a pharmaceutically acceptable derivative of any of these second ingredients.

7. A pharmaceutical composition according to claim 1 or 2 or 3 or 4 or 5, wherein the second active ingredient is selected from the group consisting of
glycolic acid [o-(2,6-dichloroanilino)phenyl]acetate(ester) [INN: ACECLOFENAC]; 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid carboxymethyl ester [INN: ACEMETACIN]; 2-(acetyloxy)benzoic acid [ACETYLSALICYLIC ACID], 2-methoxyphenyl-alpha-methyl-4-(isobutyl)phenylacetate [Research Code: AF-2259], (4-allyloxy-3-chlorophenyl)acetic acid [INN: ALCLOFENAC], p-[(2-methylallyl)amino]hydratropic acid [INN: ALMINOPROFEN], 2-amino-3-benzoylphenylacetic acid [INN: AMFENAC], (plus/minus)-4-(1-hydroxyethoxy)-2-methyl-N-2-pyridyl-2H-1,2-benzothiazine-3-carboxamide ethylcarbonate (ester), 1,1-dioxide [INN: AMPIROXICAM], 2-methoxyphenyl-1-methyl-5-(p-methylbenzoyl)pyrrol-2-acetamido-acetate [INN: AMTOLMETINGUACIL], (plus/minus)-2,3-dihydro-5-(4-methoxybenzoyl)-1H pyrrolizine-1-carboxylic acid [INN: ANIROLAC], 2-[4-(alpha,alpha,alpha-trifluoro-m-tolyl)-1-piperazinyl]ethyl-N-(7-trifluoromethyl-4-quinolyl)anthranilate [INN: ANTRAFENINE], 5-(dimethylamino)-9-methyl-2-propyl-1H-pyrazolo[1,2-a][1,2,4]benzo-triazine-1,3(2H)-dione [INN: AZAPROPAZONE], 4-acetamidophenyl salicylate acetate [INN: BENORILATE], 2-(8-methyl-10,11-dihydro-11-oxodibenz[b,f]oxepin-2-yl)propionic acid [INN: BERMOPROFEN], 2-[(1-benzyl-1H-indazol-3-yl)methoxy]-2-methylpropionic acid [INN: BINDARIT], [2-amino-3-(p-bromobenzoyl)phenyl]acetic acid [INN: BROMFENAC], 3-(3-chloro-4-cyclohexylbenzoyl)propionic acid [INN: BUCLOXIC ACID], 5-butyl-1-cyclohexylbarbituric acid [INN: BUCOLOM], 4-butoxy-N-hydroxybenzeneacetamide [INN: BUFEXAMAC], butylmalonic acid mono-(1,2-diphenylhydrazide) [INN: BUMADIZONE], alpha-ethyl-4-(2-methylpropyl)benzeneacetic acid [INN: BUTIBUFEN], 2-(4-biphenylyl)butyric acid, trans-4-phenylcyclohexylamine salt (1:1) [INN: BUTIXIRATE], 2-(acetyloxy)-benzoic acid, calcium salt, compound with urea (1:1) [INN: CARBASALATE CALCIUM], (plus/minus)-6-chloro-alpha-methylcarbazole-2-acetic acid [INN: CARPROFEN], 1-cinnamoyl-5-methoxy-2-methylindole-3-acetic acid [INN: CINMETACIN], N-(2-pyridyl)-2-methyl-4-cinnamoyloxy-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide [INN: CINNOXICAM], 6-chloro-5-cyclohexyl-1-indancarboxylic acid [INN: CLIDANAC], 2-[4-(p-chlorophenyl)benzyloxy]-2-methylpropionic acid [INN: CLOBUZARIT], 5-methoxy-2-methyl-3-indolylacetohydroxamic acid [INN: DEBOXAMET], (S)-(+)-p-isobutylhydratropic acid [INN: DEXIBUPROFEN], (+)-(S)-m-benzoylhydratropic acid [INN: DEXKETOPROFEN], 2-[(2,6-dichlorophenyl)amino]benzeneacetic acid [INN: DICLOFENAC], 2',4'-Difluoro-4-hydroxy-3-biphenylcarboxylic acid [INN: DIFLUNISAL], 4-(2,6-dichloroanilino)-3-thiopheneacetic acid [INN: ELTENAC], N-beta-phenethyl-anthranilic acid [INN: ENFENAMIC ACID] salicylic acid acetate, ester with beta-hydroxy p-acetophenetidide [INN: ETERSALATE], 1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid [INN: ETODOLAC], 2-[[3-(trifluoromethyl)phenyl]amino]benzoic acid 2-(2-hydroxyethoxy)-ethyl ester [INN: ETOFENAMATE], p-chlorobenzoic acid, ester with 4-butyl-4-(hydroxymethyl)-1,2-diphenyl-3,5-pyrazolidinedione [INN: FECLOBUZONE], 4-biphenylacetic acid [INN: FELBINAC], 3-(4-biphenylylcarbonyl)propionic acid [INN: FENBUFEN], [o-(2,4-dichlorophenoxy)phenyl]acetic acid [INN: FENCLOFENAC], (plus/minus)-m-phenoxyhydratropic acid [INN: FENOPROFEN], 4-(p-chlorophenyl)-2-phenyl-5-thiazoleacetic acid [INN: FENTIAZAC], (plus/minus)-alpha-[[(2-hydroxy-1,1-

dimethylethyl)amino]methyl]-benzyl alcohol [INN: FEPRADINOL], 4-(2',4'-difluorobiphenylyl)-4-oxo-2-methylbutanoic acid [INN: FLOBUFEN], 2,3-dihydroxypropyl N-[8-(trifluoromethyl)-4-quinolyl]anthranilate [INN: FLOCTAFENINE], N-(alpha,alpha,alpha-trifluoro-m-tolyl)anthranilic acid [INN: FLUFENAMIC ACID], (plus)-2-(p-fluorophenyl)-alpha-methyl-5-benzoxazoleacetic acid [INN: FLUNOXAPROFEN], 2-fluoro-alpha-methyl-4-biphenylacetic acid [INN: FLURBIPROFEN], (plus/minus)-2-(2-fluoro-4-biphenylyl)propionic acid 1 (acetoxy)ethyl ester [INN: FLURBIPROFEN AXETIL], 2-ethyl-2,3-dihydro-5-benzofuranacetic acid [INN: FUROFENAC], 2-[4-(2'-furoyl)phenyl]propionic acid [INN: FURPROFEN], 2-[2-[1-(p-chlorobenzoyl)-5-methoxy-2-methylindol-3-yl]acetamido]-2-deoxy-D-glucose [INN: GLUCAMETACIN], 2-(2-fluorobiphenyl-4-yl)propionic acid 4-nitrooxybutylester [Research Code: HCT-1026], (p-isobutylphenyl)acetic acid [INN: IBUFENAC], alpha-p-isobutylphenylpropionic acid [INN: IBUPROFEN], methyl 4-(3-thienyl)phenyl-alpha-methylacetate [Research Code: IDPH-8261], (plus/minus)-2-[p-(1-oxo-2-isoindolinyl)phenyl]butyric acid [INN: INDOBUFEN], 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid [INN: INDOMETACIN], 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid, 3,7,11-trimethyl-2,6,10-dodecatrienyl ester [INN: INDOMETACIN FARNESIL], p-(1-oxo-2-isoindolinyl)hydratropic acid [INN: INDOPROFEN], 2-(10-methoxy-4H-benzo[4,5]cyclohepta[1,2-b]thiophen-4-ylidene)-acetic acid [Research Code: IX-207-887], m-benzoylhydratropic acid [INN: KETOPROFEN], (DL)-5-benzoyl-3H-1,2-dihydropyrrolo[1,2-a]pyrrole-1-carboxylic acid [INN: KETOROLAC], 2,3-dihydro-5-hydroxy-6-[2-(hydroxymethyl)cinnamyl]benzofuran [Research Code: L-651896], N-(2-carboxyphenyl)-4-chloroanthranilic acid [INN: LOBENZARIT], 3-(p-chlorophenyl)-1-phenylpyrazole-4-acetic acid [INN: LONAZOLAC], 6-chloro-4-hydroxy-2-methyl-N-2-pyridyl-2H-thieno[2,3-e]-1,2-thiazine-3-carboxamide 1,1-dioxide [INN: LORNOXICAM], 2-[4-(2-oxocyclopentan-1-ylmethyl)phenyl]-propionate [INN: LOXOPROFEN], 2(R)-[4-(3-methyl-2-thienyl)phenyl]propionic acid [Research Code: M-5010], N-(2,3-xylyl)anthranilic acid [INN: MEFENAMIC ACID], 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide [INN: MELOXICAM], 5-aminosalicylic acid [INN: MESALAZINE], (2,2-dimethyl-6-(4-chlorophenyl)-7-phenyl-2,3-dihydro-1H-pyrrolizin-5-yl)-acetic acid [Research Code: ML-3000], 3,4-bis(4-methoxyphenyl)-5-isoxazoleacetic acid [INN: MOFEZOLAC], 4-(6-methoxy-2-naphthyl)-2-butanone [INN: NABUMETONE], (plus)-6-methoxy-alpha-methyl-2-naphthalineacetic acid [INN: NAPROXEN], 2-[3-(trifluoromethyl)anilino]nicotinic acid [INN: NIFLUMIC ACID], 5,5'-azodisalicylic acid [INN: OLSALAZINE], 4,5-diphenyl-2-oxazolepropionic acid [INN: OXAPROZIN], alpha-methyl-4-[(2-oxocyclohexylidene)methyl]benzene acetic acid [INN: PELUBIPROFEN], 4-butyl-1,2-diphenyl-3,5-pyrazolidinedione [INN: PHENYLBUTAZONE], 2-(p-isobutylphenyl)propionic acid 2-pyridyl-methyl ester [INN: PIMEPROFEN], 4-(p-chlorophenyl)-1-(p-fluorophenyl)pyrazole-3-acetic acid [INN: PIRAZOLAC], 4-hydroxy-2-methyl-N-2-pyridyl-2H-1,2-benzothiadiazin-3-carboxamide 1,1-dioxide [INN: PIROXICAM], 3-chloro-4-(3-pyrrolin-1-yl)hydratropic acid [INN: PIRPROFEN], 2-[5H-(1)benzopyrano]2,3-b]pyridin-7-yl]propionic acid [INN: PRANOPROFEN], 2,6-di-tert-butyl-4-(2'-thenoyl)phenol [INN: PRIFELONE], alpha-cyano-1-methyl-beta-oxopyrrole-2-propionanilide [INN: PRINOMIDE], 3-[4-(2-hydroxyethyl)-1-piperazinyl]-propyl-D,L-4-benzamido-N,N-dipropylglutaramat 1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetate (ester) [INN: PROGLUMETACIN], 7-methyl-1-(1-methylethyl)-4-phenyl-2(1H)quinazolinone [INN: PRO-

QUAZONE], 7-methoxy-alpha,10-dimethylphenothiazine-2-acetic acid [INN: PROTIZINIC ACID], 2-[[2-(p-chlorophenyl)-4-methyl-5-oxazolyl]methoxy]-2-methylpropionic acid [INN: ROMAZARIT], o-hydroxybenzamide [SALICYLAMIDE], 2-hydroxybenzoic acid [SALICYLIC ACID], N-acetyl-L-cysteine salicylate (ester), acetate (ester) [INN: SALMISTEINE], N-acetyl-L-cysteine salicylate (ester) [INN: SALNACEDIN], 2-hydroxybenzoic acid 2-carboxyphenyl ester [INN: SALSALATE], 4-[1-(2-fluorobiphenyl-4-yl)ethyl]-N-methylthiazole-2-amine [Research Code: SM-8849], (Z)-5-fluoro-2-methyl-1-[p-(methylsulfinyl)benzylidene]indene-3-acetic acid [INN: SULINDAC], p-2-thenoylhydratropic acid [INN: SUPROFEN] 2-(4-(3-methyl-2-butenyl)phenyl)propionic acid [Research Code: TA-60], phthalidyl 2-(alpha,alpha,alpha-trifluoro-m-toluidino)nicotinate [INN: TALNIFLUMATE], (Z)-5-chloro-3-(2-thenoyl)-2-oxoindole-1-carboxamide [INN: TENIDAP], 2-thiophenecarboxylic acid, ester with salicylic acid [INN: TENOSAL], 4-hydroxy-2-methyl-N-2-pyridyl-2H-thieno[2,3-e]-1,2-thiazine-3-carboxamide [INN: TENOXICAM], 5-(4-chlorophenyl)-N-hydroxy-1-(4-methoxyphenyl)-N-methyl-1H-pyrazole-3-propionamide [INN: TEPOXALIN], alpha-(5-benzoyl-2-thienyl)propionic acid [INN: TIAPROFENIC ACID], 5-chloro-3-[4-(2-hydroxyethyl)-1-piperazinyl]carbonylmethyl-2-benzo-thiazolin one [INN: TIARAMIDE], 2-(2-methyl-5H-[1]benzopyrano[2,3-b]pyridin-7-yl)-propionic acid N,N-dimethylcarbamoylmethyl ester [INN: TILNOPROFEN ARBAMEL], 1-Cyclohexyl-2-(2-methyl-4-quinolyl)-3-(2-thiazolyl)guanidine [INN: TIMEGADINE], 2-amino-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine [INN: TINORIDINE], N-(3-chloro-o-tolyl)anthranilic acid [INN: TOLFENAMIC ACID], 1-methyl-5-(4-methylbenzoyl)-1H-pyrrole-2-acetic acid [INN: TOLMETIN], hydroxybis[alpha-methyl-4-(2-methylpropyl)benzene acetato-O]-aluminium [Research Code: U-18573-G], N-(3-trifluoromethylphenyl)-anthranilic acid n-butyl ester [INN: UFENAMATE], 2-[4-[3-(hydroxyimino)cyclohexyl]phenyl]propionic acid [INN: XIMOPROFEN], 2-(10,11-dihydro-10-oxo-dibenz[b,f]thiepin-2-yl-propionic acid [INN: ZALTOPROFEN], 2-[4-(2-thiazolyloxy)phenyl]-propionic acid [INN: ZOLIPROFEN], and

5-chloro-6'-methyl-3-[4-(methylsulfonyl)phenyl]-2,3'-bipyridine [INN: ETORICOXIB], 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzene-sulfonamide [INN: CELECOXIB], 4-[p-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone [INN: ROFECOXIB], N-[[p-(5-methyl-3-phenyl-4-isoxazolyl)phenyl]sulfonyl]propion-amide [INN: PARECOXIB], p-(5-methyl-3-phenyl-4-isoxazolyl)benzenesulfonamide [INN: VALDECOXIB], 2-[2-(2-chloro-6-fluorophenylamino)-5-methylphenyl]acetic acid [INN: LUMIRACOXIB], 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzene-sulfonamide [INN: TILMACOXIB], 4-[4-chloro-5-(3-fluoro-4-methoxyphenyl)-1H-imidazol-1-yl]benzene-sulfonamide [INN: CIMICOXIB], 4'-nitro-2'-phenoxymethanesulfonanilide [INN: NIMESULIDE], 6-(2,4-difluorophenoxy)-5-methylsulfonylamino-1-indanone [INN: FLOSULIDE], 5-bromo-2-(4-fluoro-phenyl)-3-(4-methanesulfonyl-phenyl)-thiophene [DUP-697], 4-acetyl-2-(2,4-difluorophenoxy)methanesulfonanilide [FK-3311], N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide [NS-398], 5-methanesulfonamido-6-(2,4-difluorophenylthio)-1-indanone [L-745337], 8-acetyl-3-(4-fluorophenyl)-2-[4-(methanesulfonyl)phenyl]imidazo[1,2-a]-pyridine [GR-253035], 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)pyrazol-1-yl]benzenesulfon-amide [SC-58236], 4-(2,3-dihydro-2-oxo-3-phenyl-4-oxazolyl)-benzenesulfonamide [LAS-33815], CS-502, 2-(3,4-

difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methyl-sulfonyl)phenyl]-3(2H)-pyridazinone [ABT-963], GW-406381, and
ALENDRONIC ACID, RISEDRONIC ACID, TILUDRONIC ACID, INCADRONIC ACID, OLPADRONIC ACID, MINODRONIC ACID, IBANDRONIC ACID, ZOLANDRONIC ACID, CLODRONIC ACID, PAMIDRONIC ACID and ETIDRONIC ACID;
or a pharmaceutically acceptable derivative of any of these second ingredients.

8. A pharmaceutical composition according to claim 1 or 2 or 3 or 4 or 5, wherein the second active ingredient is selected from the group consisting of
ACETYLSALICYLIC ACID, DICLOFENAC, DIFLUNISAL, ETODOLAC, FENOPROFEN, FLOCTAFENINE, FLURBIPROFEN, IBUPROFEN, INDOMETHACIN, KETOPROFEN, ME-CLOFENAMATE, MEFENAMIC ACID, MELOXICAM, NABUMETONE, NAPROXEN, OXAPROZIN, PHENYLBUTAZONE, PIROXICAM, SULINDAC, TENOXICAM, TIAPROFENIC ACID, TOLMETIN, ETORICOXIB, CELECOXIB, ROFECOXIB, PARECOXIB, VALDECOXIB, LUMIRACOXIB, TILMACOXIB, CIMICOXIB, ALENDRONIC ACID, RISEDRONIC ACID, TILUDRONIC ACID, IBANDRONIC ACID, ZOLANDRONIC ACID, INCADRONIC ACID, OLPADRONIC ACID, MINODRONIC ACID, CLODRONIC ACID, PAMIDRONIC ACID and ETIDRONIC ACID,
or a pharmaceutically acceptable derivative of any of these second ingredients.

9. A pharmaceutical composition according to claim 1 or 2 or 3 or 4 or 5, wherein the second active ingredient is DICLOFENAC or a pharmaceutically acceptable derivative of this compound.

10. A method for prevention of gastrointestinal diseases caused by NSAIDs, COX-2 inhibitors, NO-NSAIDs, bisphosphonates and/or corticosteroids, which comprises administering to a mammal being in need of a NSAID, COX-2 inhibitor, NO-NSAID, bisphosphonate and/or corticosteroid therapy, a therapeutically effective amount of (S)-pantoprazole and/or its salt, simultaneously, separately or sequentially with the NSAID, COX-2 inhibitor, NO-NSAID, bisphosphonate and/or corticosteroid.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/050335

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4439 A61K31/00 A61P1/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 544 556 B1 (KOSITPRAPA UNCHALEE ET AL) 8 April 2003 (2003-04-08) column 2, line 8 - line 49 column 2, line 61 - column 3, line 10 column 3, line 23 - column 4, line 29 column 5, line 38 - column 6, line 31 column 6, line 32 - line 40 claims 1,2,7,8,31,32	1-10
X	EP 1 352 660 A (ASTRAZENECA AB) 15 October 2003 (2003-10-15) claims 7-9,11	1-10
Y	US 2003/069255 A1 (PLACHETKA JOHN R) 10 April 2003 (2003-04-10) claims 5-9	1-10

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 May 2005	27/05/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Giacobbe, S

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/050335

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 03/075884 A (LIFIZZ INC) 18 September 2003 (2003-09-18) paragraph '0023! claims 1,2,8	1-10
Y	US 5 888 535 A (GRAY NANCY M) 30 March 1999 (1999-03-30) the whole document	1-10
Y	US 6 410 569 B1 (KOHL BERNHARD) 25 June 2002 (2002-06-25) the whole document	1-10

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/050335

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6544556 B1	08-04-2003	AU 8899801 A	26-03-2002
		EP 1330238 A1	30-07-2003
		JP 2004508396 T	18-03-2004
		WO 0222108 A1	21-03-2002
		US 2003129235 A1	10-07-2003
EP 1352660 A	15-10-2003	EP 1352660 A1	15-10-2003
		SI 814839 T1	31-12-2003
		AT 242006 T	15-06-2003
		AU 712571 B2	11-11-1999
		AU 1323997 A	01-08-1997
		BR 9607476 A	23-12-1997
		CA 2213987 A1	17-07-1997
		CN 1183048 A ,C	27-05-1998
		CZ 9702748 A3	14-01-1998
		DE 69628551 D1	10-07-2003
		DE 69628551 T2	06-05-2004
		DK 814839 T3	22-09-2003
		EE 9700194 A	16-02-1998
		EP 0814839 A1	07-01-1998
		ES 2201211 T3	16-03-2004
		HK 1001761 A1	10-10-2003
		HK 1017991 A1	23-04-2004
		HU 9904095 A2	28-06-2000
		IL 121650 A	12-03-2003
		JP 11501948 T	16-02-1999
		NO 974069 A	17-10-1997
		NZ 325975 A	25-02-1999
		PL 322174 A1	19-01-1998
		PT 814839 T	31-10-2003
		RU 2158138 C2	27-10-2000
		WO 9725064 A1	17-07-1997
		SK 117797 A3	08-04-1998
		TR 9700915 T1	21-11-1997
		TW 452495 B	01-09-2001
		US 2002155153 A1	24-10-2002
		US 6365184 B1	02-04-2002
		US 2004022846 A1	05-02-2004
		ZA 9610936 A	08-07-1997
US 2003069255 A1	10-04-2003	CA 2449098 A1	12-12-2002
		EP 1411900 A2	28-04-2004
		JP 2004536809 T	09-12-2004
		WO 02098352 A2	12-12-2002
WO 03075884 A	18-09-2003	AU 2003219999 A1	22-09-2003
		CA 2495886 A1	18-09-2004
		EP 1490024 A1	29-12-2004
		WO 03075884 A1	18-09-2003
		US 2003175340 A1	18-09-2003
US 5888535 A	30-03-1999	US 2003086968 A1	08-05-2003
		US 2004142032 A1	22-07-2004
		US 2001008899 A1	19-07-2001
		AU 6713194 A	21-11-1994
		AU 6904498 A	16-07-1998
		CA 2161256 A1	10-11-1994
		EP 0695123 A1	07-02-1996

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/050335

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5888535 A		JP 8509736 T	15-10-1996
		WO 9424867 A1	10-11-1994
US 6410569 B1	25-06-2002	DE 19843413 C1	30-03-2000
		AT 219074 T	15-06-2002
		AU 761715 B2	05-06-2003
		AU 5515699 A	14-03-2000
		BG 105173 A	30-11-2001
		BR 9914288 A	19-06-2001
		CA 2341031 A1	02-03-2000
		CN 1318065 A ,C	17-10-2001
		CZ 20010621 A3	15-08-2001
		DE 69901840 D1	18-07-2002
		DE 69901840 T2	22-05-2003
		DK 1105386 T3	30-09-2002
		EA 4431 B1	29-04-2004
		EE 200100054 A	17-06-2002
		WO 0010995 A1	02-03-2000
		EP 1105386 A1	13-06-2001
		ES 2178896 T3	01-01-2003
		HK 1037616 A1	25-10-2002
		HR 20010117 A1	28-02-2002
		HU 0103257 A2	28-02-2002
		JP 2002523411 T	30-07-2002
		MX PA01001758 A	17-04-2002
		NO 20010718 A	12-02-2001
		NZ 509761 A	29-08-2003
		PL 345993 A1	14-01-2002
		PT 1105386 T	29-11-2002
		SI 1105386 T1	31-12-2002
		SK 2362001 A3	11-09-2001
		TR 200100287 T2	23-07-2001
		US 2002188008 A1	12-12-2002
		ZA 200100934 A	04-03-2002

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 April 2006 (27.04.2006)

PCT

(10) International Publication Number
WO 2006/044202 A2

(51) International Patent Classification:
A61K 9/56 (2006.01)

(21) International Application Number:
PCT/US2005/035787

(22) International Filing Date: 3 October 2005 (03.10.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/620,482 19 October 2004 (19.10.2004) US

(71) Applicant *(for all designated States except US)*: **STATE OF OREGON acting by and through THE STATE BOARD OF HIGHER EDUCATION ON BEHALF OF OREGON STATE UNIVERSITY** [US/US]; Office of Technology Transfer, 312 Kerr Administrative Building, Corvallis, OR 97331-2140 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **AYRES, James, W.** [US/US]; 1173 Charlemagne, Corvallis, OR 97330 (US).

(74) Agent: **SLATER, Stacey, C.**; Klarquist Sparkman, LLP, One World Trade Center, Suite 1600, 121 S.W. Salmon Street, Portland, OR 97204 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv))*

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ENTERIC COATED COMPOSITIONS THAT RELEASE ACTIVE INGREDIENT(S) IN GASTRIC FLUID AND INTESTINAL FLUID

(57) Abstract: Embodiments of a pharmaceutical formulation comprising an enteric material are disclosed. The embodiments release at least a portion of an active ingredient upon contacting gastric fluid. The remaining portion of the formulation releases active ingredient upon contacting intestinal fluid. Certain embodiments of the pharmaceutical composition comprise at least one active ingredient in a core and a leaky enteric coating, such as an enteric coating comprising a gastric fluid channeling agent. Other embodiments of the pharmaceutical composition comprise at least one active ingredient substantially homogeneously admixed with at least one enteric material, such as an enteric material comprising a gastric fluid channeling agent. Disclosed embodiments of the pharmaceutical composition may comprise a single active ingredient, or may comprise plural active ingredients. Generally, but not necessarily, the active ingredient has a window of absorption. The present disclosure also describes a method for treating a subject having a condition treatable by an active ingredient. The method comprises providing one or more embodiments of the pharmaceutical composition disclosed herein comprising an active ingredient suitable for treating the condition. The pharmaceutical composition is administered to the subject. A method for making embodiments of the disclosed composition also is described. The method comprises providing a core comprising an active ingredient. An enteric material is applied to at least a portion of the core, and generally on or about a substantial portion of the core, to form a coat. The composition is then made leaky.

WO 2006/044202 A2

ENTERIC COATED COMPOSITIONS THAT RELEASE ACTIVE INGREDIENT(S) IN GASTRIC FLUID AND INTESTINAL FLUID

CROSS REFERENCE TO RELATED APPLICATION

This application claims the benefit of the earlier filing date of U.S. Provisional Application No. 60/620,482, filed on October 19, 2004. The entire disclosure of provisional application No. 60/620,482 is considered to be part of the disclosure of the accompanying application and is incorporated herein by reference.

FIELD

The present disclosure concerns pharmaceutical compositions, methods for preparing such compositions, and methods for their use, particularly orally administered dosage forms having active agents with site specific absorption and enteric coats that release at least a portion of the active agents in acidic gastric fluids.

BACKGROUND

Enteric coating of dosage forms that contain drugs is well known in the pharmaceutical sciences literature. Enteric coatings are coatings designed to prevent release of the enteric-coated drug in gastric fluid of the stomach and prevent exposure of the drug to the acidity of the gastric contents while the enteric coated drug composition is in the stomach. After passing from the stomach into the intestine, the enteric coating dissolves and releases the drug into intestinal fluids.

The Food and Drug Administration (FDA) defines drug dosage forms that are enteric coated as "delayed-release" dosage forms. Delayed-release (enteric coated) dosage forms are differentiated from controlled-release or sustained-release dosage forms, which are intended to provide drug input over an extended period of time, thereby reducing administration frequency. FDA guidelines for enteric-coated dosage forms state: "*In vitro* dissolution tests for these products should document that they are stable under acidic conditions and that they release the drug only in a neutral medium (e.g., pH 6.8)."

A. Drugs with an Absorption Window

Site specific absorption for orally administered therapeutics refers to therapeutic agents that are absorbed only from or better from one region or area of the intestinal tract relative to other areas or regions of the intestinal tract. Most drugs are not well absorbed from the stomach and are well absorbed from the small intestine. Many drugs also are well absorbed from the colon. Drugs that are absorbed throughout the intestine, including the

colon, often are good candidates for sustained drug release formulations, especially if such drugs have a relatively short biological half-life. Sustained-release, drug formulation product literature provides numerous examples of such formulations.

Some drugs that undergo site specific absorption are only absorbed or are best absorbed in the small intestine. Such drugs may pass the absorption site without being available such as, for example, when trapped inside a dosage formulation or the drug is slowly soluble and has not yet had time to dissolve. Any drug that has not been absorbed at the adsorption site will not be absorbed, or is absorbed so slowly or so poorly that it is not therapeutically effectively available to the body. In these cases the bioavailability of the drug is incomplete. Some drugs undergo site specific drug absorption because their absorption involves transporter systems that are concentrated in certain regions of the intestinal tract. In this case if the drug is delivered into the absorption site area faster than drug can be absorbed, then the transporter system may become saturated. Any additional drug that is present is not carried across the membrane by the transporter system but travels on unabsorbed. The result is incomplete bioavailability. Such site specific absorption drugs, regardless of the mechanism associated with site specific absorption, are said to have an absorption window. The absorption window may be, and commonly is, in the jejunum, the duodenum, or a combination thereof.

B. <u>Discussion of Patents and Publications</u>

U. S. patent No. 6,399,086 teaches that β-lactam antibiotics have a specific absorption site in the small intestine. The '086 patent also teaches that there is a need for a dosage form that provides about 50% of the drug within 3-4 hours of administration, and releases the remainder of the drug at a controlled rate. Such dosage form may comprise a β-lactamase inhibitor. The "Background" section of the '086 patent teaches that enteric coating controlled release amoxicillin trihydrate suppresses drug release at gastric pH, but that this result is not useful. The '086 patent states that:

> Hilton and Deasy [J. Pharm. Sci. 82(7):737-743 (1993)] described a controlled-release tablet of amoxicillin trihydrate based on the enteric polymer hydroxy-propylmethyl cellulose acetate succinate. This polymer suppressed the release of the drug in the presence of gastric pH but could enhance its release in the small intestine. Therefore, such a formulation cannot give the desired burst effect discussed below. Single dose studies with a panel of fasting subjects showed that the tablets had a relative bioavailability of only 64.4%, probably because the poorer absorption of amoxicillin from the distal jejunum and ileum than from the

duodenum and proximal jejunum. Other pharmacokinetic parameters confirmed a lack of therapeutic advantage of these factors over an equivalent dose of conventional capsule.

The '086 patent provides additional information about drugs that have an absorption window and gives examples of some drugs that are useful in the instant invention disclosed herein. The '086 patent is incorporated herein by reference in its entirety. The '086 patent further states that:

> The term "drugs which have an absorption window" as currently used in the art refers to drugs which are absorbed at specific sites in the gastrointestinal tract, for example drugs which are absorbed by carrier-mediated mechanisms. Such mode of absorption is suggested for compounds like dipeptides [Matthews, D. M., Biochem. Soc. Trans. 11:808-810 (1983)], riboflavin [Levy, J. & W. Jusko, J., J. Pharm. Sci. 55:285-289 (1966)], folic acid [Hepner, G. W. et al., Lancet 2:302-306 (1968)] and ascorbic acid [Mayersohn M., Eur. J. Pharmacol. 19:140-142 (1972)]. Penicillin may be regarded as a dipeptide derived from cysteine and valine [Doyle, F. P. & Nayler, J. H. C., Advances in Drug Research 1:8-13, (1964); Harper, N.J. & Simmonds, A.B. Eds. Academic Press] and is thus absorbed by a special transport mechanism common to the absorption mechanism of dipeptides, for which a suitable transport system has been demonstrated in man [Matthews, D. M., ibid.; Silk, D. B. A. et al., Ann. Nutr. Metab. 26:337-352 (1982)].
>
> Another mechanism for drugs which are absorbed at a specific absorption site is associated with drugs which are solubilized at a specific locus in the gastrointestinal tract, for examples fats. A specific illustrative example for this mechanism is tocopherol which is solubilized by bile acid micelles [Guyton, A. C., Textbook of Medical Physiology, W.B. Saunders Company, (1986)]. Further examples of drugs which are absorbed by carriers are salts [Guyton, A. C., (1986) ibid.] AZT, 5-FU, .alpha.-methyl-Dopa and L-Dopa, riboflavin [Gibaldi, M., Biopharmaceutics and Clinical Pharmacokinetics, 3rd Edition, (1984); Evans, W.E. et al., Applied Pharmacokinetics 19:1-14 (1992); Rowland, M. & Tozer, T.N., Clinical Pharmacokinetics, concepts and applications, pp 23-24, (1988), Lea & Febiger, Philadelphia]. According to the preferred embodiments of the present invention, the β-lactam antibiotic drug capable of providing the desired burst effect, is

cephalosporin and/or a penicillin. Examples of cephalosporins which may be used with the delivery system of the invention are cefadroxil, cefalexin, cefaclor, cefprozil, cefuroxime, cefoxitin, cefpodoxime, cefixime, pharmaceutically acceptable salts thereof or pharmaceutically acceptable derivatives thereof. Examples of penicillins which may be used in the delivery system of the invention are penicillin G, penicillin V, amoxicillin, ampicillin, nafcillin, oxacillin, cloxacillin, dicloxacillin, or pharmaceutically acceptable salts thereof. Examples for pharmaceutically acceptable cephalosporin derivatives, which may be used in the delivery system of the invention, are cefpodoxime proxetil and cefuroxime axetil.

In a particularly preferred embodiment of the present invention the drug delivery system of the invention contains as the β-lactam agent amoxicillin trihydrate or pharmaceutically acceptable salts thereof. A mixture of the active antibiotic agent with a pharmaceutically acceptable salt thereof can also be used as the active pharmaceutical agent in the delivery system of the invention. Thus, for example, it may be advantageous to use a mixture of amoxicillin with amoxicillin sodium salt in order to provide the desired burst effect.

It may be advantageous to add to the drug delivery systems of the invention a β-lactamase inhibitor. Suitable β-lactamase inhibitors are clavulonic acid or sulbactam. β-lactamase inhibitors themselves have poor antibacterial activity. However, when given in combination with penicillins, to treat infections involving β-lactamase producing bacteria, they enhance the antibiotic effect [Kalant, H. & Roschlau, W. A. E., Principles of Medical Pharmacology, 5th Ed., pp 549 (1989) B. C. Decker Inc.].

The drug delivery system of the invention may further optionally contain additional pharmaceutical agents having a specific absorption site in the small intestine, for example, vitamins such as riboflavin, folic acid, ascorbic acid, thiamin or tocopherol or mixtures thereof, anti-viral agents such as AZT, antitumor agents, therapeutic metal inorganic salts such as iron salt, lithium salt or potassium salt, antihypertensive agents such as .alpha.-methyl Dopa and antiparkinsonian agents such as L-Dopa. The drug delivery system of the invention may also fiber contain a

mixture of such agents, e.g. a mixture of vitamin/s with other therapeutic agents, for example metals. A specific example may be a mixture of iron and folic acid."

International patent application No. PCT/US01/20134 provides information concerning oral sustained release formulations (SR) that are designed to provide slow drug release over time periods of 4 or 6 or more hours, such as well-known, ethyl-cellulose-coated bead formulations, osmotic pump tablets, hydrophilic matrix compressed tablets and the like, and further teaches that such formulations are not suitable for drugs that have an absorption window. Such sustained release dosage formulations are well known to be transported, after leaving the stomach, through the small intestine and past known absorption window areas in about 3-5 hours. International patent application No. PCT/US01/20134 states that:

> That is, after transiting the stomach, there is an approximately 3-5 hour window of bioavailability before the dosage form reaches the colon. Sustained or delayed release vehicles that are not retained in the stomach before and during release of the drug may release a significant portion of the drug after the window of bioavailability has passed.

Thus, any drug with an absorption window trapped in the dosage formulation is likely to not be bioavailable. Total transit times from stomach-to-colon after swallowing a drug dosage formulation are variable, depending mostly on whether or not there is food in the stomach, and stomach emptying time. Transit times in the small intestine are relatively uniform. Even if a patient might eat frequently enough to interrupt the body's "house keeper wave" that empties the stomach, drugs with an absorption window still are not suitable for known sustained release formulations because it is too likely that the drug formulation will be trapped in the stomach. Alternatively, the drug formulation will leave the stomach quickly. These release patterns result in highly variable bioavailability from dose-to-dose or day-to-day, and increase the occurrence of drug toxicity or clinical failure.

Thus, a need exists for a composition that will provide good bioavailability of drugs that have an absorption window. There is an additional need for compositions that increase the duration of action or decrease the frequency of dosing of absorption-window drugs even if they do not increase or maintain bioavailability for drugs with a window of absorption. Such compositions have not been known but are disclosed herein. And, it is additionally surprising that the new compositions are useful for drugs with an absorption window not

only if the absorption is known to be limited by transporter systems saturation or because the drug is slowly soluble.

WO 02/00213 A1 PCT/US01/2013 describes a rapidly expanding composition for gastric retention that can provide controlled release of therapeutic agents in the stomach. The primary feature of such an expanding dosage form is that it is retained in the stomach because of its large size. The primary value of such an expanding dosage form is delivery of drugs that are most readily absorbed by the jejunum and duodenum, i.e., drugs with an absorption window. A disadvantage of such dosage forms is that they are "single unit", i.e., a single tablet or a single capsule. It is well known that single-unit dosage forms often provide a "partial or none" effect. Single-unit tablet or capsule gastric retention devices may provide the desired effect when administered with food but have been shown to be removed from the stomach by the Intermittent Migrating Myoelectric Complex, commonly known as the "housekeeper wave". Multiple-unit drug dosage forms such as multiple pellets or beads inside a capsule provide a distinct advantage over single-unit dosage forms because the average effect of the beads is to release drug even if a single bead fails to be an effective delivery unit.

C. **Enteric Coated Formulations**

Enteric formulations and enteric coated formulations are well known in the pharmaceutical sciences and medical practice. Enteric coatings are intended to protect the therapeutic agent from destruction or degradation by the acid contents of the stomach or to prevent the therapeutic from irritating the stomach, and delays release of the therapeutic until such time as the enteric-coated formulation reaches the intestine. Enteric formulations then allow the therapeutic to be released into the less acidic fluids of the intestinal tract. See, for example, Remington's Pharmaceutical Sciences, 18th Ed., page 1634 (Mack Publishing, 1990), which states: "Enteric-Coated Tablets (ECT)- These are compressed tablets coated with substances that resist solution in gastric fluid but disintegrate in the intestine." Enteric coating is not only applied to tablets, but also is commonly applied to beads to prevent exposing therapeutic to gastric acid as is shown in U.S. patent No. 4,786,505.

The FDA publishes industry guidelines. For example, Guidance for Industry, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations (http://63.75.126.224/Google/fda_search.pl?client=fdagov&site=fdagov&searchselector=&q=enteric%2C+delayed&sa=Search&restrict=cder_guidance) states that:

As defined in the *U.S. Pharmacopeia* (USP), delayed-release drug products are dosage forms that release the drugs at a time later than immediately after administration (i.e., these drug products exhibit a lag time in quantifiable plasma concentrations). Typically, coatings (e.g., enteric coatings) are intended to delay the release of medication until the dosage form has passed through the acidic medium of the stomach. *In vitro* dissolution tests for these products should document that they are stable under acidic conditions and that they release the drug only in a neutral medium (e.g., pH 6.8).

The literature clearly teaches that a sufficient amount of enteric coating must be utilized to produce an acceptable enteric-coated drug product that does not release drug in gastric fluid. An insufficient amount of enteric coating material is taught to be unacceptable. A leading manufacturer of enteric coating polymers, Rohm Pharma Polymers, recommends a 30- to 50-micron thickness coating in order to obtain adequate enteric coating protection (Eudragit® technical sheets, Rohm Tech Inc., MA).

Also, U.S. Patent No. 6,605,300 and WO 2000023055 A1 teach that:

Typical enteric coating levels did not meet the above requirements for the desired dosage profile of amphetamine salts. Using the typical amount of enteric coating (10-20.mu.) resulted in undesired premature leakage of the drug from the delivery system into the upper gastrointestinal tract and thus no drug delivery at the desired location in the gastrointestinal tract after the appropriate lag time. The unacceptable premature drug release from the delivery system in gastric fluid and no drug delivery to the desired location in the gastrointestinal tract after an appropriate delay time teaches such coatings are not acceptable.

"EUDRAGIT.RTM. L 30D-55 (Rohm Pharma, Germany) coating dispersion" was used in the first example. An enteric layer 20-microns thick on drug-loaded beads resulted in unacceptable premature drug release from the delivery system in gastric fluid and no drug delivery to the desired location in the gastrointestinal tract after an appropriate delay time. Thus this coating did not meet the requirements of an enteric coating. Applicants then report that a thicker application of an enteric coating having a thickness of greater than 25 microns was required to provide an effective enteric coat.

For pharmaceutical formulations known prior to the present invention, enteric coatings must protect drug and drug must not be released in gastric fluid for particular

periods of time to be considered effective. For example, Jorg Brietkreutz concludes that "[t]he criteria of the pharmacopeias are usually set to 2 or 3 hours of gastric juice resistance. Sometimes 1 hour is accepted in exceptional cases." See, Jorg Brietkreutz, *Leakage of enteric (Eudragit L)-coated dosage forms in simulated gastric juice in the presence of poly(ethylene glycol)*, **Journal of Controlled Release,** 67 (2000) 79-88). Brietkreutz also states that "recently, 40-55 mm was reported to be the minimum coating thickness for Eudragit L". And, commercially available enteric coated products containing omeprazole are reported unstable when both PEG and enteric coated products are in gastric fluid because "In the case of the tablet with micropellets, omeprazole release starts at about 100 min, whereas the capsule formulation releases the drug after 150 minutes." The amount of drug released in gastric fluid for the authors to conclude the products are unstable is less than 10%. This teaching that less than 10% drug release in gastric fluid indicates an unstable or unsuitable enteric coat is consistent with FDA guidelines requiring that enteric coats only release drug in neutral medium and not acidic medium. Further, United States Pharmacopea indicates that the maximum amount of drug release allowable from an enteric-coated product is 10% for dissolution testing in simulated gastric fluid for 2 hours. U.S. Pharmacopeia, 23, U.S. Pharmacopeial Convention: Rockville, Maryland, 1994, pp. 1795-1796.

Riboflavin, a drug with an absorption window, has been formulated as enteric-coated pellets (HX Guo, J Heinamaki, and J Yliruusi, *Diffusion of a Freely Water-Soluble Drug in Aqueous Enter-Coated Pellets*, **AAPS Pharm Sci Tech**, 2003:3(2) article 16 (http://www.aapspharmscitech.org). The effects of pellet filler and enteric-coating thickness on drug release in gastric fluid were studied. When the core pellet contained waxy cornstarch, a 20% weight gain of traditional enteric coating was reported to have "failed the test" by releasing about 20% drug in gastric fluid in 1 hour, but 30% enteric coating did prevent drug release. The authors state that "[n]either the 20% nor the 30% enteric-coated lactose pellets gave acidic resistance", releasing about 45% and 55% drug in gastric fluid in 1 hour. The authors go to great lengths to study the reasons and mechanisms involved in how the pellet core composition causes the enteric coating to fail and conclude that diffusion of a water-soluble drug and excipient into an enteric coating can result in "coating failure and, subsequently, premature dissolution of enteric-coated pellets in an acidic environment". Clearly, persons of ordinary skill in the art regard "coating failure" and "premature dissolution" as results to be avoided.

Beckert *et al.* describe sucrose pellets having a coating of bisacodyl admixed with Eudragit L 30 D-55. This formulation may further include a coating of methyl

methacrylate/methacrylic acid polymers. Beckert *et al.*, *Compression of Enteric-Coated Pellets to Disintegrating Tablets,"* **International Journal of Pharmaceutics** 143, pp. 13-23 (1996). With reference to Eudagrit L 30 D-55, the authors conclude that films made from such materials "are so brittle that even the double amount of coating does not reduce the damage with the coatings." *Id.* at 21. Beckert *et al.* apparently desired compounds that release less than 10% bisacodyl in gastric fluid to comply with USP 23, but which release "sufficient bisacodyl between pH 6.8 and 7.5," i.e. at intestinal pH levels. Beckert *et al.* state that:

> The amount of bisacodyl liberated is reduced with thicker films if coatings containing a mixture of Eudagrit L and Eudgrit NE are applied. The liberation of bisacodyl in 0.1 M HCl from this film is approximately 4% w/w of the total bisacodyl content. As these coatings do not dissolve and release sufficient bisacodyl between pH 6.8 and 7.5, two new polymers (Table 4) showing high elasticity combined with sufficient dissolution in the pH range 6.8-7.0 (Fig. 7) have been developed by Lehmann and Sufke. Emphasis added.

Id. Thus, Beckert *et al.* concluded that sucrose beads coated with Eudagrit L admixed with bisacodyl required too thick a coating to provide a useful formulation. The authors therefore further coated the formulation with methyl methacrylate/methacrylic acid polymers. With reference to these formulations, Beckert *et al.* conclude that:

> Pellets coated with 25% w/w of one of the new polymers liberate only 4-5% w/w bisacodyl in acidic media after tableting. The liberation of bisacodyl in phosphate buffer within 45 min at pH 6.8 is 100% for polymer 1 and 40% for polymer 2 and rises to 100% at pH 7.2. Thus, tablets comprising enteric-coated bisacodyl pellets are available which comply with all recommendations of USP 23.

Id.

Further, the authors conclude that:

> The remaining deformation of pellets needs to be neutralized by elastic coatings which can follow the deformation without rupturing. The most important parameters are the type and the applied thickness of the film forming polymer. Disintegrating tablets can be obtained from enteric–coated pellets which do not

liberate more than 10% bisacodyl after 2 h in 0.1 m HCl, thus complying with USP 23.

Id. at 22. Thus, these authors conclude that rupturing coatings so that gastric release of therapeutic, particularly release in excess of the 10% level recited in USP 23, is an undesirable result. Beckert *et al.* also refer to the work of other authors concerning gastric release of acetylsalicylic acid and indometacin coated with Eudragit L and sulfametoxazole coated with cellulose acetate phthalate. Acetylsalicylic acid and indometacin pellets have been made that release less than 10% w/w of the active ingredient within 2 hours in 0.1 M HCl. These tablets conformed to the requirement of USP 23 for enteric coated preparations. See, Lehmann, *et al.*, **Acta Pharm. Technol.**, 36, 7S (1990); Lehmann *et al.*, *Schnellzerfallende Tabletten mit Gesteurter Wirkstoffabgabe, Pharm. Ind.*, 55, 940-947 (1993). With reference to sulfametoxozole Beckert *et al.* state that:

> Disintegrating tablets from sulfametoxazole pellets coated with cellulose acetate phthalate were described by Takenaka *et al.* [*Preparation of Enteric-Coated Microcapsules for Tableting by Spray-drying Technique and in vitro Simulation of Drug Release from the Tablet in GI-tract*, **J. Pharm. Sci** 9, 1388-1392 (1980)], but liberated more than 10% of the drug within 2 hours in artificial gastric fluid and thus did not conform to the requirement of USP 23.

Id, at 14.

Thus, the literature teaches that an insufficient amount, or an enteric coating layer that is too "thin" produces an unacceptable, defective enteric coat that allows contact of acidic gastric fluids with therapeutic agents inside the enteric coating and/or allows release of the enteric-coated therapeutic agents into acidic fluid. It also is generally well known in the field that coating drug dosage forms to sustain or delay drug release may reduce the amount of drug absorbed into the body.

U.S. Patent Publication No. 20030021845 A1 discloses a very complex, multilayered, single-unit gastroretentive divice that must be folded prior to administration. The device has multiple layers of polymer sheets, generally glued together by solvent softening. The device is too large to swallow without folding and too large to pass through the pyloric sphincter until delaminated, dissolved, or disintegrated. In the stomach, the device unfolds and slowly degrades or dissolves such that the device is retained in the stomach longer than a conventional dosage form, for a minimum of 3 hours and preferably

about 8-12 hours. In some cases a polymer combination involved may be a "shielding layer" optionally covering part or all of the face of other polymer sheets of the device. According to U.S. patent publication No. 20030021845 the shielding layer polymer is selected from "(a) a hydrophilic polymer which is not instantly soluble in gastric fluids; (b) an enteric polymer substantially insoluble at pH less than 5.5; (c) a hydrophobic polymer; and (d) any mixture of at least two polymers as defined in any of (a), (b), or (c)." U.S. Patent Publication No. 20030021845 also states that:

> There are several advantages in including an enteric polymer in the matrix or the shielding layer, as enteric polymers have improved mechanical properties (e.g. Young's modulus and yield strength). The addition of an enteric polymer to the shielding layer prevented rapid rupture of the shielding layer *in vitro*. A further advantage of using an enteric polymer is to ensure the complete dissolution and/or disintegration of the components of the device, e.g. the matrix, the shielding layer or the membrane, in the intestine, had it not already occurred in the stomach. A preferred enteric polymer incorporated into the shielding layer may be methylmethacrylate-methacrylic acid copolymer, at a ratio of 2:1 ester to free carboxylic groups.

The device described by U.S. Patent Publication No. 20030021845 A1 is intended to be retained in the stomach and to release drug into gastric fluids of the stomach. Thus, the shielding polymer layer must necessarily allow release of drug into gastric fluid even though it comprises an enteric polymer as one of the multilaminated films but such compositions are not known for multiparticulates, such as beads or granules, or for tablets or capsules. The compositions disclosed by U.S. Patent Publication No. 20030021845 A1 differ substantially from the new compositions disclosed herein. For example, the shielding layer of U.S. Patent Publication No. 20030021845 A1 were prepared by casting the polymers in a mixture of 50% ethyl alcohol and 50% NaOH followed by evaporative drying. Dried films were than affixed to other dried films to produce multilaminate sheets using ethyl alcohol to partially "melt" the films together. Polymer films formed by casting as taught could be glued to one or two faces of a tablet and folded like wings to promote gastric retention. But it is not practical or even possible to uniformly coat the entire surface of tablets or particulates, such as beads and granules, using the method taught by the published application.

Tablets, beads, granules, capsules, and active ingredients would dissolve and/or degrade if mixed into such a solution for casting. There is no known useful commercial

way to affix such films to uniformly coat the substantially round or irregularly shaped tablets, beads, granules, or capsules.

Gastroretentive devices can be sustained-release dosage forms because they reduce the required frequency of dosing for some drugs. Another way to reduce drug dosing frequency is to formulate what has been called a "pulse" drug delivery system using a mixture of a fixed ratio of immediate release and enteric-coated drug. In this system, 50% of the dose is released immediately in gastric fluid (the first pulse) and 50% is enteric coated and then released after transfer from the stomach into the intestine (the second pulse). U.S. Patent No. 6,322,819 teaches a "pulsed dose delivery" is important for amphetamines. The '819 patent teaches that typical enteric coating levels on amphetamine-loaded pellets resulted in undesired premature leakage of drug in the upper intestinal tract, and thus did not provide drug delivery at the desired location in the gastrointestinal tract after the appropriate lag time. An enteric coating thickness of at least 25 μm was required to prevent premature drug leakage. Then, essentially all the enteric-coated drug was released within 1 hour after transfer into intestinal fluid. This combination of 50% immediate release of drug and 50% enteric-coated drug that did not release in gastric fluid resulted in a pharmacokinetic drug pattern that allows a reduction in dosing frequency. The '819 patent states that "it will be appreciated that the multiple dosage form of the present invention can deliver rapid and complete dosages of pharmaceutically active amphetamine salts to achieve the desired levels of the drug in a recipient over the course of about 8 hours with a single oral administration." Similar results have been obtained for cyclosporine, a drug with a window of absorption, when formulated as 50% dried microemulsion and 50% dried enteric coated micoemulsion. See, Chong-Kook Kim, Hee-Jong Shin, Su-Geun Yang, Jae-Hyun Kim and Yu-Kyoung Oh, *Once-a-Da Oral Dosing Regimin of Cyclosporin A: Combined Therapy of Cyclosporin A Premicoemulsion Concentrates and Enteric Coated Solid-State Premicoemulsion Concentrates*, **Pharmaceutical Research**, Vol. 18, No. 4, 2001 (454-459)). Enteric coated compositions deemed acceptable by the authors prevented all drug release during 2 hours of exposure to gastric fluid.

D. Gastrointestinal Tract Transit Times

GI transit time of drug pellets has been extensively studied. Food was shown to have a profound effect on gastric emptying rate of drug pellets. Davis, S.S.; Hardy, J.G.; Taylor, M.J.; Whalley, D.R.; Wilson, C.G. The effect of food on the gastrointestinal transit of pellets and an osmotic device (Osmet). Int. J. Pharm. **1984**. *21*, 331-340.; Davis, S.S.; Khosla, R.; Wilson, C.G.; Washington, N. Gastrointestinal transit of a controlled-release

pellet formulation of tiaprofenic acid and the effect of food. Int. J. Pharm. **1987**. *35*, 253-258.; Hardy, J.G.; Lamont, G.L.; Evans, D.F.; Haga, A.K.; Gamst, O.N. Evaluation of an enteric-coated naproxen pellet formulation. Aliment. Pharmacol. Ther. **1991**. *5*, 69-75.)

In the fed condition, the gastric emptying rate of pellets appears to be zero order over 5 to 8 hours. (Hardy, J.G.; Lamont, G.L.; Evans, D.F.; Haga, A.K.; Gamst, O.N. Evaluation of an enteric-coated naproxen pellet formulation. Aliment. Pharmacol. Ther. **1991**. *5*, 69-75.; Fischer, W.; Boertz, A.; Davis, S.S.; Khosla, R.; Cawello, W.; Sandrock, K.; Cordes, G. Investigation of the gastrointestinal transit and in vivo drug release of isosorbide-5-nitrate pellets. Pharm. Res. **1987**. *4* (6), 480-485.; Bechgaard, H.; Christensen, F.N.; Davis, S.S.; Hardy, J.G.; Taylor, M.J.; Whalley, D.R.; Wilson, C.G. Gastrointestinal transit of pellet systems in ileostomy subjects and the effect of density. J. Pharm. Pharmacol. **1985**. *37*, 718-721.)

These findings are consistent with another study that found emptying of solids is approximately a zero-order function. (Collins, P.J.; Horowitz, M.; Cook, D.J.; Harding, P.E.; Shearman, D.J.C. Gastric emptying in normal subjects--a reproducible technique using a single scintillation camera and computer system. Gut **1983**. *24*, 1117-1125.)

Meal size influences the half-time by which pellets are emptied gastrically. The mean half-time was 78 minutes after a light meal (1,500 kJ or 358.5 kcal) compared to 170 minutes for a heavy meal (3,600 kJ or 860.4 kcal). (Davis, S.S.; Khosla, R.; Wilson, C.G.; Washington, N. Gastrointestinal transit of a controlled-release pellet formulation of tiaprofenic acid and the effect of food. Int. J. Pharm. **1987**. *35*, 253-258.) In the fasted condition, fifty percent of ingested pellets were emptied from the stomach within an hour with a range of less than 0.3 to 0.9 hour (Hardy, J.G.; Lamont, G.L.; Evans, D.F.; Haga, A.K.; Gamst, O.N. Evaluation of an enteric-coated naproxen pellet formulation. Aliment. Pharmacol. Ther. **1991**. *5*, 69-75.) depending upon the time of administration relative to an occurrence of phase 3 of the migrating myoelectric complex (MMC). (Mayer, E.A. The physiology of gastric storage and emptying. In *Physiology of the gastrointestinal tract*; Johnson, L.R., Ed.; Raven Press: New York, 1994; 929-976.)

It is known that emptying of non-nutrient-containing liquid appears to be first order and volume-sensitive mechanisms play the major role in the regulation of gastric emptying. (Mayer, E.A. The physiology of gastric storage and emptying. In *Physiology of the gastrointestinal tract*; Johnson, L.R., Ed.; Raven Press: New York, 1994; 929-976.)

Patterns of gastric emptying of pellets taken before a meal were shown to be approximately exponential, i.e., typical of gastric emptying of liquid. (O'Reilly, S.; Wilson,

C.G.; Hardy, J.G. The influence of food on the gastric emptying of multiparticulate dosage forms. Int. J. Pharm. **1987**. *34*, 213-216.)

Lag time of gastric emptying for solid food also differs from that for liquid. The initial lag phase has been observed for gastric emptying of solid food and the average values range from 21 to 60 minutes. (Hardy, J.G.; Lamont, G.L.; Evans, D.F.; Haga, A.K.; Gamst, O.N. Evaluation of an enteric-coated naproxen pellet formulation. Aliment. Pharmacol. Ther. **1991**. *5*, 69-75.; Collins, P.J.; Horowitz, M.; Cook, D.J.; Harding, P.E.; Shearman, D.J.C. Gastric emptying in normal subjects--a reproducible technique using a single scintillation camera and computer system. Gut **1983**. *24*, 1117-1125.; Mayer, E.A.; Thomson, J.B.; Jehn, D.; Reedy, T.; Elashoff, J.; Deveny, C.; Meyer, J.H. Gastric emptying and seiving of solid food and pancreatic and biliary secretions after solid meals in patients with nonresective ulcer surgery. Gastroenterology **1984**. *87*, 1264-1271.)

This lag time reflects primarily the time required to reduce the solid food to smaller sizes. (Weiner, K.; Graham, L.S.; Reedy, T.; Elashoff, J.; Meyer, J.H. Simultaneous gastric emptying of two solid foods. Gastroenterology **1981**. *81*, 257-266.) After a capsule containing drug pellets was administered in the fed condition, seven of eight subjects showed no gastric emptying of the pellets during the first hour. (Hardy, J.G.; Lamont, G.L.; Evans, D.F.; Haga, A.K.; Gamst, O.N. Evaluation of an enteric-coated naproxen pellet formulation. Aliment. Pharmacol. Ther. **1991**. *5*, 69-75.) This observed pellet emptying delay suggests that, following capsule disintegration, the pellets became dispersed within the stomach and were mixed with food content before being emptied along with the meal. (O'Reilly, S.; Wilson, C.G.; Hardy, J.G. The influence of food on the gastric emptying of multiparticulate dosage forms. Int. J. Pharm. **1987**. *34*, 213-216.) Lag time of gastric emptying in these subjects causes lag time of absorption for drug in enteric-coated pellets. (Hardy, J.G.; Lamont, G.L.; Evans, D.F.; Haga, A.K.; Gamst, O.N. Evaluation of an enteric-coated naproxen pellet formulation. Aliment. Pharmacol. Ther. **1991**. *5*, 69-75.) Unlike solid food, liquid emptying has minimal observable lag time. (Collins, P.J.; Horowitz, M.; Cook, D.J.; Harding, P.E.; Shearman, D.J.C. Gastric emptying in normal subjects--a reproducible technique using a single scintillation camera and computer system. Gut **1983**. *24*, 1117-1125.) Thus, the drug onset action rate is faster for drug dissolved in liquids in the stomach than when drug is trapped inside enteric coated pellets or tablets.

While the presence of food increases the mean gastric emptying time of pellets, the small intestinal transit time is unaffected. (Davis, S.S.; Hardy, J.G.; Taylor, M.J.; Whalley, D.R.; Wilson, C.G. The effect of food on the gastrointestinal transit of pellets and an osmotic device (Osmet). Int. J. Pharm. **1984**. *21*, 331-340.) The mean small intestinal

transit time is about 3 to 4 hours (Shargel, L.; Yu, A. *Applied biopharmaceutics and pharmacokinetics*. 4th Ed, ed.; Mehalik, C.L.; McGraw-Hill Companies, Inc.: New York, 1999.; Davis, S.S.; Hardy, J.G.; Taylor, M.J.; Whalley, D.R.; Wilson, C.G. The effect of food on the gastrointestinal transit of pellets and an osmotic device (Osmet). Int. J. Pharm. **1984**. *21*, 331-340.; Davis, S.S.; Khosla, R.; Wilson, C.G.; Washington, N. Gastrointestinal transit of a controlled-release pellet formulation of tiaprofenic acid and the effect of food. Int. J. Pharm. **1987**. *35*, 253-258.; Fischer, W.; Boertz, A.; Davis, S.S.; Khosla, R.; Cawello, W.; Sandrock, K.; Cordes, G. Investigation of the gastrointestinal transit and in vivo drug release of isosorbide-5-nitrate pellets. Pharm. Res. **1987**. *4* (6), 480-485.) and independent of the feeding state. (Davis, S.S.; Hardy, J.G.; Taylor, M.J.; Whalley, D.R.; Wilson, C.G. The effect of food on the gastrointestinal transit of pellets and an osmotic device (Osmet). Int. J. Pharm. **1984**. *21*, 331-340.; Davis, S.S.; Khosla, R.; Wilson, C.G.; Washington, N. Gastrointestinal transit of a controlled-release pellet formulation of tiaprofenic acid and the effect of food. Int. J. Pharm. **1987**. *35*, 253-258. Multiple-unit pellets and non-disintegrating single-unit tablets have similar small intestinal transit time. (Davis, S.S.; Hardy, J.G.; Taylor, M.J.; Whalley, D.R.; Wilson, C.G. The effect of food on the gastrointestinal transit of pellets and an osmotic device (Osmet). Int. J. Pharm. **1984**. *21*, 331-340). Depending on the feeding state, the mean time for the arrival at caecum of pellets ranges from 4 to 8 hours. (Shargel, L.; Yu, A. *Applied biopharmaceutics and pharmacokinetics*. 4th Ed, ed.; Mehalik, C.L.; McGraw-Hill Companies, Inc.: New York, 1999.; Davis, S.S.; Hardy, J.G.; Taylor, M.J.; Whalley, D.R.; Wilson, C.G. The effect of food on the gastrointestinal transit of pellets and an osmotic device (Osmet). Int. J. Pharm. **1984**. *21*, 331-340.; Davis, S.S.; Khosla, R.; Wilson, C.G.; Washington, N. Gastrointestinal transit of a controlled-release pellet formulation of tiaprofenic acid and the effect of food. Int. J. Pharm. **1987**. *35*, 253-258.; Fischer, W.; Boertz, A.; Davis, S.S.; Khosla, R.; Cawello, W.; Sandrock, K.; Cordes, G. Investigation of the gastrointestinal transit and in vivo drug release of isosorbide-5-nitrate pellets. Pharm. Res. **1987**. *4* (6), 480-485.)

Thus, drug release and effect onset time from enteric-coated compositions is highly variable. Drug release and effect onset time depend on a number of factors, including whether: (1) the composition is a relatively large unit dosage composition, such as a single enteric-coated capsule or tablet; (2) whether the composition is a multiplicity of enteric particulates, such as enteric-coated beads or granules; (3) there is food in the stomach at the same time the composition is in the stomach, and how much time elapses before the housekeeper wave transports the composition into the intestine. Then, there is still some additional lag time until the enteric composition actually starts releasing drug. In some

cases, an enteric composition may not release drug for 12 or more hours following administration. The new compositions disclosed herein decrease variability in drug release and onset time by avoiding or minimizing the effect of food to delay drug release by trapping the composition in the stomach. These new compositions still may be trapped in the stomach, but drug release occurs at least partially in the stomach and is not entirely delayed until the composition reaches the intestine.

U.S. Patent No. 5,232,704 teaches that prostoglandins are principally absorbed from the stomach and hence there is a need to prolong the time such drugs are delivered in the stomach fluid. Moreover, *in vivo* studies with buoyant, single-unit dosage forms indicate that a mean gastric residence time ranging between 3 and 4 hours can be obtained with fed subjects (light breakfast).

SUMMARY

Disclosed embodiments of the present invention are directed primarily to drugs that are best absorbed from the upper intestine. But novel enteric compositions that release drug in the stomach also are ideal for drug delivery, such as mistoprostol and other prostaglandins that have a direct action on cells in the stomach or are best absorbed from the stomach. And desirable combinations of drugs, such as, for example, those taught in U.S. Patent No. 5,232,704, incorporated herein by reference in its entirety, also are advantageously prepared with the novel enteric compositions that release drug in the stomach. In one preferred embodiment, a drug that has a direct action on cells in the stomach or is best absorbed from the stomach, or any other therapeutic agent that is preferably released in the stomach, is combined with other active agents, if desired, and formulated as a single-unit, enteric-coated dosage form, such as a tablet or a capsule that releases drug in gastric fluid. This dosage form preferably is administered before, during, or after a meal such that food is present in the stomach at the same time as the dosage form. The combination of food and a traditional, enteric-coated, single-unit dosage form, especially when the dosage form is a relatively large size, such as commonly used intermediate or large tablets and capsules, is well known to prolong retention of the dosage form in the stomach, often for as long as 12 hours. Because the novel enteric coating compositions release drug in gastric fluid the result is prolonged release of the drug or drugs in the stomach. Multiparticulate leaky enteric compositions also are beneficial to deliver drugs best released in the stomach, especially in a preferred embodiment of dosing at a time proximate to food administration such that food is present with the composition in the stomach.

There is no known method or composition other than as now disclosed herein for use of multiple-unit dosage forms, such as pellets or beads, to improve delivery of drugs that have a window of absorption in the jejunum and/or duodenum.

Thus, it is counterintuitive to deliberately provide a coating that results in prolonged drug input of a therapeutic agent for the purpose of increasing the amount of drug to be absorbed into the body.

It has now been discovered that what has heretofore been considered to be an unacceptable enteric coating composition or inadequate amount of enteric coating material, such as a partial or thin, leaky enteric coat on tablets, capsules or multiparticulates, such as beads or granules, is unexpectedly useful, and also effective to provide an increase in drug delivery for many drugs including those which have an absorption window, i.e., are generally best absorbed from the upper small intestine. Put another way, what have typically been considered non-useful enteric coatings prior to this disclosure are now discovered to be unexpectedly useful to deliver therapeutically active agents.

In one embodiment, an enteric-coated, drug dosage form is deliberately prepared such that the enteric coating composition is "leaky." A leaky enteric coat allows exposure of the active ingredients to the acid of the stomach and also allows release of a portion of drug from the enteric coat into the stomach fluids. Further, upon passage from the stomach into the upper small intestine the enteric coating material dissolves rapidly such that remaining drug contained within the dosage form is quickly released. Application of this embodiment is particularly useful in formulation of drugs whose bioavailability is often limited due to saturation of absorption processes within the upper small intestine, i.e, an absorption window. Such drugs may be said to have site-specific absorption as discussed above. Further, drug release from the leaky enteric composition generally is too fast to be considered a sustained release (SR) dosage form. But, the result is still a decrease in required frequency of dosing for some absorption window drugs as readily determined by a person of ordinary skill in the art.

In one disclosed embodiment of the present invention, an enteric-coated, drug dosage form is deliberately prepared such that upon contacting gastric fluid, either *in vivo* or *in vitro,* the enteric coat is "leaky" in that the enteric coat allows exposure of the active ingredients to acid of the stomach or the *in vitro* test fluid and also allows release of at least a portion of drug (at least 10%) from the enteric composition into the gastric fluid. Further, upon passage from the stomach into the upper small intestine or transfer into intestinal fluid *in vitro*, the residual, leaky, enteric coating material dissolves or disintegrates rapidly such that remaining drug (if any) contained within that portion of the dosage form transferred into

intestinal fluid is quickly released (at least 60% release of remaining therapeutic in one hour or less upon contacting intestinal fluid).

The enteric material composition may be made leaky by incorporating materials that allow gastric fluid to penetrate into the composition and drug to be released from the composition while the composition is in the stomach. Drug that has been released in the stomach may exert a local effect on the stomach, be absorbed through stomach cells into the blood stream or pass from the stomach into the intestine as drug free of the composition. In a preferred embodiment only a portion of drug in the composition (at least 10%) is released in the stomach and drug still remaining in the composition is rapidly released when the composition passes from the stomach into the intestine.

Particles containing drug, such as beads, granules, and others, are entrapped in a leaky enteric coating to produce an enteric composition that releases drug in gastric fluid. The leaky, enteric-coated particles can be enclosed in a gelatin or other capsule or dosage form that releases the leaky, enteric-coated particles in gastric fluid. In other embodiments, a single-unit dosage form, such as a tablet or capsule, is coated at least partially with a leaky enteric coating. In still other embodiments a matrix tablet or capsule contains enteric compositions such that a portion of drug in the enteric composition (at least 10%) is released in the stomach. Drug still remaining in the composition is rapidly released when the composition passes from the stomach into the intestine.

Embodiments of the disclosed composition may be administered before, during, or soon after a meal such that the food and composition are in the stomach at the same time. Some or all of the composition is retained in the stomach with the food until the food and the composition are emptied, usually by the housekeeper wave. Disclosed embodiments of the composition slowly release drug into gastric fluids for a prolonged period of up to 8 hours or until the drug is all released, or the composition is transported into the intestine and then remaining drug in the composition is rapidly released, preferably in less than one hour in some embodiments. The effect is to extend the time of drug release into the upper intestinal area by up to 10 or more hours, usually up to 7 hours, and more usually up to 4 hours, compared to what occurs with immediate-release dosage forms, and to also provide an earlier release of drug than occurs with known enteric coatings that cause a delay, often of several hours, before drug is released at all. That is, lag time until active ingredient is released from the new enteric compositions is less than two hours, and generally less than one hour, and preferably less than one-half hour when measured *in vitro* or if measured *in vivo*.

Another disclosed embodiment releases drug more rapidly after transfer into the intestine than a typical enteric coating. This is thought to occur because the new composition is already partially disrupted, hydrated, and weakened, which results in more rapid dissolution of the new enteric composition, once transferred into the intestine, compared to known compositions.

Drug-containing particulate may be coated with enteric materials, which are either a leaky composition or are a traditional enteric composition that prevents drug release into gastric fluid, said compositions being further treated to produce a leaky enteric composition by any effective method. Such methods include, but are not limited to, compressing the enteric coated particulate into a dosage form, such as tablets, to break or weaken some of the coating(s) such that the resulting novel dosage form releases at least some of the drug in gastric fluid.

Thus, several embodiments of a pharmaceutical formulation comprising an enteric material are disclosed. The embodiments release at least a portion of an active ingredient upon contacting gastric fluid. The remaining portion of the formulation releases active ingredient upon contacting intestinal fluid

A first embodiment of the pharmaceutical composition comprises at least one active ingredient in a core and an enteric coating on the core. The enteric coating further comprises a gastric fluid channeling agent.

Another embodiment of the pharmaceutical composition is designed to provide programmed release of active ingredient. The composition comprises at least one active ingredient, excluding amoxicillin, substantially homogeneously admixed with at least one enteric material comprising a gastric fluid channeling agent.

Still another embodiment of the pharmaceutical composition provides programmed release of active ingredient. The composition comprises at least one active ingredient substantially homogeneously admixed with at least one enteric material comprising a gastric fluid channeling agent. The gastric fluid channeling agent is added in amounts ranging from greater than zero percent to about 400% of the weight of the enteric material.

Still another embodiment of the pharmaceutical composition for providing programmed release of active ingredient comprises at least one active ingredient, excluding amoxicillin, substantially homogeneously admixed with at least one enteric material. The composition delivers at least a portion of the active ingredient upon contacting gastric fluid followed by substantially complete release of active ingredient upon contacting intestinal fluid.

Still another embodiment of the pharmaceutical composition comprises at least one active ingredient, excluding riboflavin, and at least one leaky enteric coating. The composition releases at least 10 percent of the active ingredient mass upon contacting gastric fluid. The remaining active ingredient is released substantially completely after contacting intestinal fluid.

Still another embodiment of the pharmaceutical composition comprises at least one active ingredient, excluding riboflavin. The composition also includes a leaky enteric coating.

Still another embodiment of the pharmaceutical composition comprises at least one active ingredient, excluding amoxicillin, acetyl salicylic acid, bisacodyl, indometacin, riboflavin or sulfamethoxozole. The composition also includes a leaky enteric coating.

Still another embodiment of the pharmaceutical composition consists essentially of a core comprising at least one active ingredient and a leaky enteric coating.

Still another embodiment of the pharmaceutical composition consists essentially of a core comprising at least one active ingredient and an enteric coating. The enteric coating further comprises a gastric fluid channeling agent.

Still another embodiment of the pharmaceutical composition comprises a sugarbead core having at least one active ingredient on or in the core. The composition further comprises an enteric coating comprising a gastric fluid channeling agent.

These and other embodiments of the disclosed composition also have other features or characteristics, or can be used in combination with other features of the invention. For example, disclosed embodiments of the composition generally release at least 10% by mass of the active ingredient in gastric fluid, more typically at least 25%. Still other embodiments provide an active ingredient release profile where at least 10% active ingredient by mass is released in gastric fluid, more typically at least 25%, followed by at least 75% release of remaining active ingredient in one hour or less, with some embodiments releasing at least 75% of remaining active ingredient in 30 minutes or less, upon contacting intestinal fluid. Active ingredient release upon contacting gastric fluid may be zero order, mixed order or first order, followed by substantially immediate release when remaining composition contacts intestinal fluid.

Certain of the embodiments include a gastric fluid channeling agent. For such embodiments, the gastric fluid channeling agent may be hydrophilic, hydrophobic, or a combination of both hydrophilic and hydrophobic. One example of a hydrophilic gastric fluid channeling agent is hydroxylated compounds, such as a sugar, or combinations of

sugars. Examples of hydrophobic gastric fluid channeling agents include talc, magnesium salts, silicon dioxide, hydrocarbons, and combinations thereof.

Certain of the embodiments include an enteric coat on or substantially about a core. Such compositions typically have an enteric coating thickness of 25 μm or less, and the coat thickness may be 20 μm or less.

Certain of the embodiments are formulated as a solid composition for oral administration.

Disclosed embodiments of the pharmaceutical composition can comprise one or more additional formulations. Typically, such formulations are designed to provide an active ingredient release profile different from the pharmaceutical composition. For example, a second formulation may provide immediate release in gastric fluid. A specific example of such a composition includes amoxicillin or a biologically active salt thereof as one active ingredient, where the active ingredient of the second formulation is clavulanate or a biologically active salt thereof.

Two or more formulations can be placed in a single capsule or tablet for co-administration. Alternatively, disclosed embodiments of the composition may further comprise an admixture or an overcoat of an immediate release dosage form.

Disclosed embodiments of the pharmaceutical composition may comprise a single active ingredient, or may comprise plural active ingredients. Generally, but not necessarily, the active ingredient has a window of absorption. Examples, without limitation, of active agents having a window of absorption include therapeutic nucleic acids or amino acid sequences, nucleic acids or amino acid derivatives, peptidomimetic drugs, antibiotics, therapeutic ions, vitamins, bronchodilators, anti-gout agents, anti-hypertensive agents, diuretic agents, anti-hyperlipidemic agents or ACE inhibitors, drugs intended for local treatment of the gastrointestinal tract, including anti-tumor agents, histamine (H2) blockers, bismuth salts, synthetic prostaglandins or antibiotic agents, drugs that degrade in the colon, for example metoprolol, formulations useful for treating gastrointestinal associated disorders selected from peptic ulcer, nonulcer dyspepsia, Zollinger-Ellison syndrome, gastritis, duodenitis and the associated ulcerative lesions, stomach or duodenum neoplasms, prazosin, ketanserin, guanabenz acetate, captopril, captopril hydrochloride, enalapril, enalapril maleate, lysinopril, hydralazide, methyldopa, methyldopa hydrochloride, levodopa, carbidopa, benserazide, amlodipine, nitrendipine, nifedipine, nicardipine, verapamil, acyclovir, inosine, pranobex, tribavirine, vidarabine, zidovudine, AZT, active ingredients that exert a medicinal action at the gastric level, including aluminum hydroxide, magnesium carbonate, magnesium oxide, sucralphate, sodium carbenoxolone, pirenzepin, loperamide,

cimetidine, ranitidine, famotidine, misoprostol, omeprazol, and combinations thereof. Additional examples of active ingredients can be selected from the group consisting of AIDS adjunct agents, alcohol abuse preparations, Alzheimer's disease management agents, amyotrophic lateral sclerosis active ingredient agents, analgesics, anesthetics, antacids, antiarythmics, antibiotics, anticonvulsants, antidepressants, antidiabetic agents, antiemetics, antidotes, antifibrosis active ingredient agents, antifungals, antihistamines, antihypertensives, anti-infective agents, antimicrobials, antineoplastics, antipsychotics, antiparkinsonian agents, antirheumatic agents, appetite stimulants, appetite suppressants, biological response modifiers, biologicals, blood modifiers, bone metabolism regulators, cardioprotective agents, cardiovascular agents, central nervous system stimulants, cholinesterase inhibitors, contraceptives, cystic fibrosis management agents, deodorants, diagnostics, dietary supplements, diuretics, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction active ingredients, fatty acids, gastrointestinal agents, Gaucher's disease management agents, gout preparations, homeopathic remedys, hormones, hypercalcemia management agents, hypnotics, hypocalcemia management agents, immunomodulators, immunosuppressives, ion exchange resins, levocarnitine deficiency management agents, mast cell stabilizers, migraine preparations, motion sickness products, multiple sclerosis management agents, muscle relaxants, narcotic detoxification agents, narcotics, nucleoside analogs, non-steroidal anti-inflammatory drugs, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, phosphate binders, porphyria agents, psychoactive ingredient agents, radio-opaque agents, psychotropics, sclerosing agents, sedatives, sickle cell anemia management agents, smoking cessation aids, steroids, stimulants, sympatholytics, sympathomimetics, Tourette's syndrome agents, tremor preparations, urinary tract agents, vaginal preparations, vasodilators, vertigo agents, weight loss agents, Wilson's disease management agents, and mixtures thereof.

Still other embodiments of the composition may include an active ingredient selected from the group consisting of abacavir sulfate, abacavir sulfate/ lamivudine/zidovudine, acetazolamide, acyclovir, albendazole, albuterol, aldactone, allopurinol, amoxicillin, amoxicillin/clavulanate potassium, amprenavir, atovaquone, atovaquone and proguanil hydrochloride, atracurium besylate, beclomethasone dipropionate, berlactone betamethasone valerate, bupropion hydrochloride, bupropion hydrochloride, carvedilol, caspofungin acetate, cefazolin, ceftazidime, cefuroxime , chlorambucil, chlorpromazine, cimetidine, cimetidine hydrochloride, cisatracurium besilate, clobetasol propionate, co-trimoxazole, colfosceril palmitate, dextroamphetamie sulfate, digoxin,

enalapril maleate, epoprostenol, esomepraxole magnesium, fluticasone propionate, furosemide, hydrochlorothiazide, hydrochlorothiazide/triamterene, lamivudine, lamotrigine, lithium carbonate, losartan potassium, melphalan, mercaptopurine, mesalazine, mupirocin calcium cream, nabumetone, naratriptan, omeprazole, ondansetron hydrochloride, ovine, oxiconazole nitrate, paroxetine hydrochloride, prochlorperazine, procyclidine hydrochloride, pyrimethamine, ranitidine bismuth citrate, ranitidine hydrochloride, rofecoxib, ropinirole hydrochloride, rosiglitazone maleate, salmeterol xinafoate, salmeterol, fluticasone propionate, sterile ticarcillin disodium / clavulanate potassium, simvastatin, spironolactone, succinylcholine chloride, sumatriptan, thioguanine, tirofiban HCI, topotecan hydrochloride, tranylcypromine sulfate, trifluoperazine hydrochloride, valacyclovir hydrochloride, vinorelbine, zanamivir, zidovudine, zidovudine or lamivudine, or mixtures thereof.

The disclosed pharmaceutical compositions may include an enteric material. Examples, without limitation, of suitable enteric materials include cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), hydroxypropylmethyl cellulose, hydroxypropyl methylcellulose acetate succinate (HPMCAS), cellulose acetate trimellitate, hydroxypropyl methylcellulose succinate, carboxymethyl cellulose, carboxymethyl ethyl cellulose, cellulose acetate phthalate, cellulose acetate succinate, cellulose acetate hexahydrophthalate, cellulose propionate phthalate, cellulose acetate maleate, cellulose acetate butyrate, cellulose acetate propionate, copolymer of methylmethacrylic acid and methyl methacrylate, copolymer of methyl acrylate, methylmethacrylate and methacrylic acid, copolymer of methylvinyl ether and maleic anhydride (Gantrez ES series), ethyl methyacrylate-methylmethacrylate-chlorotrimethylammonium ethyl acrylate copolymer, polyvinyl acetate phthalate, natural resins such as zein, shellac and copal collophorium, commercially available enteric dispersion systems, including for example Eudragit L30D55, Eudragit FS30D, Eudragit L100, Eudragit S100, Kollicoat EMM30D, Estacryl 30D, Coateric, and Aquateric, and combinations of such materials.

Disclosed embodiments of the pharmaceutical compositions may include other ingredients. For example, and without limitation, such other ingredients include bulking agents, disintegrating agents, anti-adherents and glidants, lubricants, and binding agents. These ingredients are known to persons of ordinary skill in the art. Typical bulking agents include, but are not limited to microcrystalline cellulose (e.g., Avicel.RTM., FMC Corp., Emcocel.RTM., Mendell Incl.), mannitol, xylitol, dicalcium phosphate (eg. Emcompress, Mendell Incl.) calcium sulfate (e.g. Compactrol, Mendell Inc.) starches, lactose, sucrose

(Dipac, Amstar, and Nutab, Ingredient Technology), dextrose (Emdex, Mendell, Inc.), sorbitol, cellulose powder (Elcema, Degussa, and Solka Floc, Mendell, Inc.), and combinations thereof. The bulking agent may be present in the composition in any useful amount, which typically ranges from about 5 wt. % to about 90 wt. %, more typically from about 10 wt. % to about 50 wt. %.

Disintegrating agents that may be included in the composition include, but are not limited to, microcrystalline cellulose, starches, crospovidone (e.g., Polyplasdone XL, International Specialty Products.), sodium starch glycolate (Explotab, Mendell Inc.), crosscarmellose sodium (e.g., Ac-Di-Sol, FMC Corp.), and combinations thereof. The disintegrating agent may be present in the composition in any useful amount, which typically is from about 0.5 wt. % to about 30 wt. %, more typically from about 1 wt. % to about 15 wt. %.

Antiadherants and glidants that may be used in the composition include, but are not limited to, talc, corn starch, silicon dioxide, sodium lauryl sulfate, metallic stearates, and combinations thereof. The antiadherant or glidant may be present in the composition in any useful amount, which typically ranges from about 0.2 wt. % to about 15 wt. %, more typically from about 0.5 wt. % to about 5 wt. %.

Lubricants that may be employed in the composition include, but are not limited to, magnesium stearate, calcium stearate, sodium stearate, stearic acid, sodium stearyl fumarate, hydrogenated cotton seed oil (sterotex), talc, and waxes, including but not limited to, beeswax, carnauba wax, cetyl alcohol, glyceryl stearate, glyceryl palmitate, glyceryl behenate, hydrogenated vegetable oils, stearyl alcohol, and combinations thereof. The lubricant may be present in any useful amount, which typically is from about 0.2 wt. % to about 20 wt. %, more typically from about 0.5 wt. % to about 5 wt. %.

Binding agents that may be employed include, but are not limited to, polyvinyl pyrrollidone, starch, methylcellulose, hydroxypropyl methylcellulose, carboxymethyl cellulose, sucrose solution, dextrose solution, acacia, tragacanth, locust bean gum, and combinations thereof. The binding agent may be present in any useful amount, which typically is from about 0.2 wt. % to about 10 wt. %, and more typically from about 0.5 wt. % to about 5 wt. %.

Embodiments of the disclosed composition may increase active ingredient bioavailability at least 20% relative to an immediate release control or a sustained-release formulation control that does not include enteric material. Still other embodiments of the disclosed composition may provide substantially equivalent bioavailability but a reduced active ingredient excretion rate relative to an immediate release control formulation. Still

other embodiments of the disclosed composition may provide prolonged drug concentrations for active ingredients having, and even if not having, an absorption window relative to an immediate release control. Certain disclosed embodiments provide controlled *in vitro* gastric release, followed by pulsatile *in vitro* intestinal release.

The present disclosure also describes a method for treating a subject having a condition treatable by an active ingredient. The method comprises providing one or more embodiments of the pharmaceutical composition disclosed herein comprising an active ingredient suitable for treating the condition. The pharmaceutical composition is administered to the subject. The active ingredient may be substantially homogeneously mixed with the enteric material. Alternatively, the composition may include a leaky enteric coating, such as a coating comprising a gastric fluid channeling agent or a gastric fluid channel.

The composition may be administered to a fed subject or administered substantially simultaneously when the subject eats or drinks. Alternatively, the composition may be administered to a fasted subject.

A method for making embodiments of the disclosed composition also is described. The method comprises providing a bead core comprising an active ingredient. An enteric material is applied to at least a portion of the bead, and generally on or about a substantial portion of the bead, to form a coat. The composition is then made leaky. This can be accomplished in a number of ways including, without limitation, incorporating a gastric fluid channeling agent, applying pressure, removing solvent, washing, soaking, raising or lowering temperature relative to ambient, abrading, ablating, and any combination thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph of mg. of riboflavin absorbed in people versus time in hours illustrating the cumulative amount of drug absorbed versus time deconvolved from biostudy data for IR (immediate release), SGRD, IGRD, and LGRD (small, intermediate, and large gastric retention device formulation) capsules of Example 1.

FIG. 2 is a dissolution curve of % drug release on the Y-axis as a function of time for a traditional enteric composition coated at 5% weight gain onto drug loaded beads versus new leaky enteric compositions that provide release of drug into gastric fluid at a desired programmed rate, followed by rapid release of drug remaining in the composition when the composition is transferred into intestinal fluid as described in Example 2.

FIG. 3 is a percent of drug dissolved curve versus time in hours at pH 1.4 for two hours and then at pH 6.0 that provides an *in vitro* dissolution profile of commercial mixed

immediate release and enteric-coated pellets of amphetamines, and illustrates that immediate release drug (50%) was released immediately, and that enteric coated drug does not release in gastric fluid but does release when transferred into intestinal fluid as discussed in Example 3.

FIG. 4 is a compartmental diagram that illustrates (i) first-order absorption of drug from immediate release pellets and (ii) zero-order gastric emptying rate in the fed condition of enteric-coated pellets into the intestine and first order absorption of the drug after being released from the pellets as discussed in Example 3.

FIG. 5 is a compartmental diagram that illustrates (i) first-order absorption of drug from immediate release pellets and (ii) first-order gastric emptying rate in the fasted condition of enteric-coated pellets into the intestine and first order absorption of the drug after being released from the pellets.

FIG. 6 provides a mean plot of simulated plasma concentrations versus time for amphetamine from mixed immediate release and enteric-coated pellets in fed subjects, where vertical bars represent standard deviations where the observed values are reported commercial mixed pellets data, and the simulated data are quite accurate.

FIG. 7 is a mean plot of simulated plasma concentrations of amphetamine from mixed immediate release and enteric-coated pellets in fasted subjects, where vertical bars represent standard deviations, and observed values are reported from commercial mixed pellets data.

FIG. 8 is a compartmental diagram of pharmacokinetic model for leaky enteric-coated beads in a fasted condition, where X_{PS} is the amount of drug in beads form in the stomach; X_{SS} is the amount of dissolved drug in the stomach; X_{SI} is the amount of dissolved drug in the intestine; X_1 is the amount of drug in plasma/blood; Dose is a leaky enteric-coated dose; k_{em} is a first-order rate of drug input into the intestine corresponding to the first-order gastric emptying of beads in fasted condition; k_r is a first-order release rate of drug from beads within the stomach; k_s is a first-order rate of drug input into the intestine corresponding to the first-order gastric emptying of liquid; k_a is a first-order absorption rate constant of drug; and k_{el} is a first-order elimination rate constant of drug, as discussed in Example 4.

FIG. 9 is a compartmental diagram of pharmacokinetic model for drug absorption and elimination, and bead transport in the fed condition, using leaky enteric-coated beads, where X_{PS} is the amount of drug in beads form in the stomach; X_{SS} is the amount of dissolved drug in the stomach; X_{SI} is the amount of dissolved drug in the intestine; X_1 is the amount of drug in plasma/blood; Dose is a leaky enteric-coated dose; k_0 is a zero-order rate

of drug input into the intestine corresponding to the zero-order gastric emptying of beads in fed condition; k_r is a first-order release rate of drug from beads within the stomach; k_s is a first-order rate of drug input into the intestine corresponding to the first-order gastric emptying of liquid; k_a is a first-order absorption rate constant of drug; and k_{el} is a first-order elimination rate constant of drug, as discussed in Example 4.

FIG. 10 illustrates drug concentration in plasma curves for riboflavin vs time following administration to human subjects of (IR) immediate release compared to new leaky enteric compositions as discussed in Example 5.

FIG. 11 illustrates the cumulative amount of hydrochlorthiazide excreted following administration to humans of IRF (immediate release formulation) or GRF (gastric retention formulation) versus time in hours as discussed in Example 8.

FIG. 12 illustrates the rate of urinary excretion of hydrochlorthiazide versus time following administration to humans of IRF (immediate release formulation) or GRF (gastric retention device formulation) versus time in hours as discussed in Example 8.

FIG. 13 illustrates the average rate of urine production following administration to humans of IRF (immediate release formulation) or GRF (gastric retention device formulation) versus time in hours as discussed in Example 8.

FIG. 14 illustrates percent drug release for hydrochlorthiazide from novel leaky enteric coated compositions when tested in gastric fluid for 2 hours followed by transfer into intestinal fluid.

FIG. 15 illustrates drug concentration in plasma curves for hydrochlorothiazide versus time following administration to human subjects of immediate release (IR) compared to new leaky enteric compositions as described in Example 8.

FIG. 16 illustrates percent drug release for ranitidine HCl from some new leaky enteric coated compositions when tested in gastric fluid for 2 hours followed by transfer into intestinal fluid as described in Example 9.

FIG. 17 illustrates percent drug release for ranitidine from some more new leaky enteric coated compositions when tested in gastric fluid for 2 hours followed by transfer into intestinal fluid as described in Example 9.

FIG. 18 illustrates percent drug release for ranitidine from some more new leaky enteric coated compositions when tested in gastric fluid for 2 hours followed by transfer into intestinal fluid as described in Example 9.

FIG. 19 illustrates drug concentration in plasma curves for ranitidine vs time following administration to human subjects of (IR) immediate release compared to new leaky enteric compositions as described in Example 10.

DETAILED DESCRIPTION

A. Definitions

Active agent means any therapeutic or diagnostic agent now known or hereinafter discovered that can be formulated as described herein. Examples of therapeutics, without limitation, are listed in Urquhart's U.S. Patent No. 4,649,043, which is incorporated herein by reference. Additional examples are listed in the American Druggist, p. 21-24 (February, 1995).

Active ingredients includes active agents, therapeutic or diagnostic agents. *Active ingredients having an absorption window* are known to persons of ordinary skill in the art. For example, U.S. Patent No. 5,780,057, entitled Pharmaceutical Tablet Characterized by a Showing High Volume Increase When Coming into Contact with Biological Fluids, is primarily concerned with active ingredients that exert their action mostly at the gastroduodenal level and in the first portion of the small intestine. U.S. Patent No. 6,685,962, entitled Gastroretentive Controlled Release Pharmaceutical Dosage, also concerns drugs with a window of absorption tract. These United States patents are incorporated herein by reference. Examples of drugs having a window of absorption include, but are not limited to, therapeutic nucleic acids or amino acid sequences, nucleic acids or amino acid derivatives, peptidomimetic drugs, antibiotics, therapeutic ions, vitamins, bronchodilators, anti-gout agents, anti-hypertensive agents, diuretic agents, anti-hyperlipidemic agents or ACE inhibitors. The present dosage formulation also may be particularly suitable for the delivery of drugs intended for local treatment of the gastrointestinal tract. Examples of such drugs include, but are not limited to, anti-tumor agents, histamine (H2) blockers, bismuth salts, synthetic prostaglandins or antibiotic agents. The present dosage formulation also may be suitable for the delivery of drugs that degrade in the colon, for example metoprolol. The present dosage formulations are useful for treating gastrointestinal associated disorders selected from peptic ulcer, nonulcer dyspepsia, Zollinger-Ellison syndrome, gastritis, duodenitis and the associated ulcerative lesions, stomach or duodenum neoplasms. Additional specific examples of active ingredients having an absorption window include, without limitation, prazosin, ketanserin, guanabenz acetate, captopril, captopril hydrochloride, enalapril, enalapril maleate, lysinopril, hydralazide, methyldopa, methyldopa hydrochloride, levodopa, carbidopa, benserazide, amlodipine, nitrendipine, nifedipine, nicardipine, verapamil, acyclovir, inosine, pranobex, tribavirine, vidarabine, zidovudine, AZT, active ingredients that exert a medicinal action at the gastric level, including aluminum hydroxide, magnesium carbonate, magnesium oxide, sucralphate, sodium carbenoxolone, pirenzepin, loperamide, cimetidine, ranitidine,

famotidine, misoprostol, omeprazol, and combinations thereof. Additional examples of therapeutics, including those having a window of absorption, can be found in the FDA Orange Book, which is incorporated herein by reference. An electronic, searchable version of the Orange Book can be found at http://www.fda.gov/cder/ob/default.htm.

Administration to a subject according to the present invention is intended to be substantially oral administration such that at least a portion of the composition is swallowed.

Channeling agents can be used to tailor drug release from the pharmaceutical composition. Channeling agents provide fluid access to the therapeutic in the pharmaceutical composition in a specific media as desired. The channeling agent may form a tortuous channel in an enteric material by erosion or dissolution of a hydrophobic or hydrophilic material, such as a water soluble, gastric fluid soluble and/or intestinal fluid soluble channeling agent. The channeling agent is incorporated into the enteric material during processing of the dosage form and erodes or leaches from the dosage form after administration of the dosage form to the environment of use. Examples of channeling agents include, without limitation, salts such as sodium chloride and potassium chloride; sugars, such as lactose, sucrose, sorbitol, and mannitol; hydroxylated compounds, including polyvinyl alcohols and glycols, such as polyethylene glycol and propylene glycol; cellulose-derived materials, such as hydroxypropyl cellulose, hydroxypropyl methycellulose, methacrylic acid copolymers; and other miscellaneous materials such as croscarmellose sodium, crospovidone sodium starch glycolate, talc, polyvinyl pyrrolidone, gelling agents such as carbopol, and xanthan gum, or mixtures thereof. The channeling agent also may be a drug that is fluid soluble, including water soluble, gastric fluid soluble, and/or intestinal fluid soluble. The channeling agent is included in the dosage form in an amount to allow active ingredients to leak through the enteric material in gastric fluid, with the preferred amounts being selected to achieve the desired result. Such amounts typically range from greater than 0% to about 400% of the total weight of the enteric material. For coatings, such amounts range from greater than 0% to about 100%, and even more typically from about 5% to about 40% of the total weight of the enteric material. For substantially homogeneous admixtures, channeling agent amounts typically range from about 25% to about 350%, and even more typically from about 75% to about 250% of the total weight of the enteric material.

Coating and overcoating are used interchangeably herein and refer to applying at least one coat, and perhaps plural coats, over a core compact, and core compact or core as used herein.

Controlled release includes timed release, sustained release, extended release, pulse release, prolonged release and other such terms which describe a sustained release pattern from dosage forms as is known to a person of ordinary skill in the art and does not include immediate release, delayed release, or programmed release as described herein. It is common, for one example, to identify a formulation as sustained release if dissolution of the active agent during *in vitro* dissolution tests known to those of ordinary skill in the art is slower than dissolution of the same active agent when compared to an immediate release control formulation. The cause of the slower dissolution is utilization of a type of formulation or process that is known by those or ordinary skill in the art to provide sustained release of active agents. In dissolution tests, generally it is preferred for sustained release formulations that it takes longer than 3 hours for 65% dissolution of the active ingredient, more preferred that it takes longer than 4 hours for 75% dissolution of the active ingredient, and even more preferred that it takes longer than 7 hours for 75% dissolution of the active ingredient. In some cases, it may take more than 18 hours for 85% dissolution of the active ingredient. Some types of sustained-release formulations, without limitation, include formulations known as osmotic pump tablets or capsules, hydrophilic or other polymer or wax matrix tablets, beads, or capsules, and diffusional release controlling membrane containing dosage forms.

Core refers to the center portion of a layered or coated drug delivery system. The core portion typically comprises active agent(s), either with or without added excipients, and also includes beads, such as sugar beads or extruded beads, tablets, beads, particles, or capsules impregnated or coated with an active agent.

Diagnostic means, without limitation, a material useful for testing for the presence or absence of a material or disease, and/or a material that enhances tissue or cavity imaging.

Dissolution or release of drug into gastric fluid includes release into gastric fluid of the stomach *in vivo* or during *in vitro* testing. Many such tests are known in the art. One such test, for example, is the United States Pharmacopea (U.S. Pharmacopeia, 23, U.S. Pharmacopeial Convention: Rockville, Maryland, 1994, pp. 1795) test for drug release for enteric-coated dosage forms.

An *effective amount* is an amount of a diagnostic or therapeutic agent that is useful for producing a desired effect.

An *enteric composition* is a delayed release composition that prevents release of active agent in gastric fluid or exposure of active agent to gastric fluid while the enteric composition is in the stomach or in gastric fluid in an *in vitro* dissolution test, and then the active agent is released from the enteric composition or that portion of the enteric

composition that is transferred into the intestine, such as enteric-coated multiparticulates, for example, where some enteric-coated particles are transferred into the intestine while others remain in the stomach, or into an *in vitro* dissolution test in neutral medium (e.g., pH 6.8 to 8.0). Examples of enteric materials include, but are not limited to, cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), hydroxypropylmethyl cellulose, hydroxypropyl methylcellulose acetate succinate (HPMCAS), cellulose acetate trimellitate, hydroxypropyl methylcellulose succinate, carboxymethyl cellulose, carboxymethyl ethyl cellulose, cellulose acetate phthalate, cellulose acetate succinate, cellulose acetate hexahydrophthalate, cellulose propionate phthalate, cellulose acetate maleate, cellulose acetate butyrate, cellulose acetate propionate, copolymer of methylmethacrylic acid and methyl methacrylate, copolymer of methyl acrylate, methylmethacrylate and methacrylic acid, copolymer of methylvinyl ether and maleic anhydride (Gantrez ES series), ethyl methyacrylate-methylmethacrylate-chlorotrimethylammonium ethyl acrylate copolymer, polyvinyl acetate phthalate, natural resins such as zein, shellac and copal collophorium, commercially available enteric dispersion systems, including for example Eudragit L30D55, Eudragit FS30D, Eudragit L100, Eudragit S100, Kollicoat EMM30D, Estacryl 30D, Coateric, and Aquateric, and combinations of such materials.

Gastric fluid as used herein means the endogenous fluid medium of the stomach, including water and secretions, or simulated gastric fluid, or other aqueous fluids of pH less than 5.5 that are useful to measure drug dissolution from an enteric formulation.

Immediate release means 80% or more of the active ingredient is released when in unprotected contact with gastric fluid or intestinal fluid within 30 minutes of exposure to such fluid.

Intestinal fluid is endogenous fluid medium of the intestine, including water and secretions, or simulated intestinal fluid, or other aqueous fluids of pH 5.5 or greater that are useful for measuring drug dissolution from an enteric coated product.

Leaky enteric composition is an enteric composition that has been modified by formulation, process, or method so that the composition does release active ingredient in gastric fluid or when exposed to gastric fluid. Typically, more than about 5%, even more typically 10% or greater, of the active ingredient is released while the enteric composition is in the stomach or in gastric fluid in an *in vitro* dissolution test, and then the active ingredient is released from the composition or that portion of the composition that is transferred into the intestine or into an *in vitro* dissolution test in neutral medium (e.g., pH 6.8 up to 8.0).

Leaky enteric composition includes any composition that comprises a pH-sensitive

pharmaceutical excipient that has relatively low solubility in gastric fluid and relatively higher solubility (is at least 4 times more soluble) in neutral medium (pH 6.8 up to pH 8.0), and the composition allows release in gastric fluid or exposure to gastric fluid of more than about 5% of the active ingredient, and even more typically greater than about 10%, while the enteric composition is in the stomach or in gastric fluid in a *in vitro* dissolution test, and then at least 75% of any active ingredient not released in gastric fluid is released from the composition or portion of the composition that is transferred into the intestine or into an *in vitro* dissolution test in neutral medium (e.g., pH 6.8 up to 8.0).

Other ingredients include, for example, bulking agents, disintegrating agents, anti-adherents and glidants, lubricants, binding agents, flavoring agents, etc., including without limitation: bulking agents, such as microcrystalline cellulose (e.g., Avicel.RTM., FMC Corp., Emcocel.RTM., Mendell Incl.), mannitol, xylitol, dicalcium phosphate (eg. Emcompress, Mendell Incl.) calcium sulfate (e.g. Compactrol, Mendell Inc.) starches, lactose, sucrose (Dipac, Amstar, and Nutab, Ingredient Technology), dextrose (Emdex, Mendell, Inc.), sorbitol, cellulose powder (Elcema, Degussa, and Solka Floc, Mendell, Inc.), and combinations thereof; disintegrating agents, such as microcrystalline cellulose, starches, crospovidone (e.g., Polyplasdone XL, International Specialty Products.), sodium starch glycolate (Explotab, Mendell Inc.), crosscarmellose sodium (e.g., Ac-Di-Sol, FMC Corp.), and combinations thereof; antiadherants and glidants, such as talc, corn starch, silicon dioxide, sodium lauryl sulfate, metallic stearates, and combinations thereof; lubricants, such as magnesium stearate, calcium stearate, sodium stearate, stearic acid, sodium stearyl fumarate, hydrogenated cotton seed oil (sterotex), talc, and waxes, including but not limited to, beeswax, carnauba wax, cetyl alcohol, glyceryl stearate, glyceryl palmitate, glyceryl behenate, hydrogenated vegetable oils, stearyl alcohol, and combinations thereof; and binding agents, such as polyvinyl pyrrollidone, starch, methylcellulose, hydroxypropyl methylcellulose, carboxymethyl cellulose, sucrose solution, dextrose solution, acacia, tragacanth, locust bean gum, and combinations thereof.

Programmed release means release or exposure of active ingredient in gastric fluid at a rate slower than immediate release, that is less than 80% release on exposure to gastric fluid within 30 minutes, followed by release of more than 60% of active agent not yet released or exposed in gastric fluid in less than one hour from the composition or that portion of the composition when it is transferred into intestinal fluid.

Simulated gastric fluid means any fluid that is generally recognized as providing a useful substitute for authentic gastric fluid in experiments designed to assess the chemical, biochemical or dissolution behavior of substances in the stomach. One such simulated

gastric fluid is USP gastric fluid TS, without enzymes, United States Pharmacopeia and National Formulary 24/19 p. 2235 (1999). Thus, it will be understood throughout this disclosure, unless noted otherwise, that "gastric fluid" means any gastric fluid including authentic gastric fluid or simulated gastric fluid.

Simulated intestinal fluid means any fluid that is generally recognized as providing a useful substitute for authentic intestinal fluid in experiments designed to assess the chemical or biochemical or dissolution behavior of substances in the intestines. One such simulated intestinal fluid is USP intestinal fluid TS, without enzymes, United States Pharmacopeia and National Formulary 24/19 (1999). Thus, it will be understood throughout this disclosure that "intestinal fluid" means any intestinal fluid including authentic intestinal fluid or simulated intestinal fluid.

Spheres, millispheres, pellets, granules, beads, multiparticulates, and particulates are terms which are interchangeable when referring to the drug delivery systems of this invention.

Tablet is a term known to persons of ordinary skill in the art, and is used herein to include all such compacted, or molded, or otherwise formed materials without limitation in terms of sizes or shapes, and all methods of preparation. Thus, as one common example, compressed or molded shapes which are known as caplets, are included. Plural pellets can be compacted into tablets, and such tablets may be chewable.

B. Examples

The following examples are provided to illustrate certain features of disclosed embodiments. The scope of the present invention should not be limited to those features illustrated.

EXAMPLE 1

This example shows that if a drug with an absorption window can be delivered into the upper intestine from the stomach via controlled release in gastric fluid, then bioavailability of the drug can be increased by more than 20% and prolonged drug concentrations in the body occur compared to orally administering an immediate release drug formulation as shown in my European Patent Application PCT WO 03/015745 A1.

The drug riboflavin was formulated in a gastric retention formulation to provide controlled drug release in gastric fluid and thereby prolonged drug input from the stomach into the intestine so long as the device was in the stomach and still contained drug, and

administered in biostudies, and compared to administration of immediate release riboflavin as shown in my European Patent Application PCT WO 03/015745 A1.

Relative fractional absorption of riboflavin from different riboflavin containing formulations was evaluated from urinary excretion data. Mean pharmacokinetic parameters for the different treatments are shown in the following table.

Table 1

Pharmacokinetic Parameters of Riboflavin after Oral Administration of 100 mg in Immediate Release or Slow Input from GRD Capsules to Fasted Volunteers.

	Treatments			
	(IR)	(SGRD)	(IGRD)	**(LGRD)**
Recovery from 0-24h (mg)	5.33 ± 1.74	4.09 ± 1.67	9.3 ± 5.27	**17.36± 9.7**
Max. Urinary excretion rate (mg/h)	1.36 ± 0.42	1.14 ± 0.59	2.05 ± 0.99	**2.52 ± 0.98**
Time of max. excretion rate (h)	2.5 ± 0.6	2.33 ± 0.97	3.25 ± 1.1	**5.08± 2.4**
Mean Residence time (h)	4.73 ± 0.83	5.98 ± 1.06	5.27 ± 1.7	**6.99 ±1.18**
Data are mean values ± SE				

IR is immediate release from a commercial product; SGRD is a small gastric retention device/formulation; IGRD is an intermediate size gastric retention device/formulation: LGRD is a large gastric retention device/formulation **(see** European Patent Application PCT WO 03/015745 A1.

Mean drug recovery $_{0\text{-}24h}$ in subjects urine from the LGRD controlled drug release in gastric fluid (17.3mg) was determined to be 3.25 times (and statistically significantly ($P< 0.05$) different relative to the mean) the mean drug recovery $_{0\text{-}24h}$ in subjects urine from the IR capsule (5.33 mg). Statistical comparison of R_{max} and T_{max} parameters also indicated a significant difference ($P<0.05$) between results from slow drug input from the LGRD capsule (2.5 ± 0.98 mg/h and 5.08 ±2.4 hr respectively) and the IR capsule (1.36 ± 0.4mg/h and 2.5 ± 0.63 hr respectively). Improved bioavailability of riboflavin from slow input of drug from the stomach into the intestine resulted because the released drug passed gradually

through the absorption window and more efficient absorption occurred. Formulation of riboflavin into an embodiment of a leaky, enteric-coated bead formulation of the instant invention also results in an increase in bioavailbility when compared to drug bioavailability from an immediate release formulation because of the unique drug release pattern from the leaky, enteric-coated formulation as described elsewhere herein.

FIG. 1 shows the cumulative amount of drug absorbed versus time deconvolved from biostudy data for the IR, SGRD, IGRD, and LGRD capsules. Absorption continued for up to about 15 hours for the slow drug input LGRD capsule formulation before it stopped. This suggests that the LGRD stayed in the stomach and slowly released the drug for about 15 hours. Drug absorption from the slow release SGRD capsule continued only for 3 hours, indicating that the device was emptied from the stomach by the housekeeper wave (due to its small size) as rapidly as the IR dose. Thus, even though this formulation provided sustained drug release in gastric fluid, when the drug was trapped inside a composition that provided sustained drug release in intestinal fluid and that passed by the absorption window before drug was released, then the bioavailability of the drug was decreased. That is why drugs with absorption windows cannot be formulated using traditional means to provide useful prolonged or sustained drug input.

For compositions of embodiments of the new leaky enteric formulations described herein, some of the drug in the leaky enteric formulation is programmed released in the stomach gastric fluid and trickles into the intestine while the dosage form remains in the stomach. This released drug is well absorbed just as is demonstrated in the GRF example during the time the GRF is in the stomach. Then, any drug that remains inside the dosage form is rapidly released, preferably more than 60 % of active agent not yet released or exposed in gastric fluid is released in less than one hour from the composition or that portion of the composition when the new leaky enteric formulation or a portion thereof is transferred into the intestine. Thus, embodiments of the novel leaky enteric formulations disclosed herein avoid the case shown above for the slow release GRF example where bioavailability is reduced relative to an immediate-release formulation if drug is retained inside the slow-release, GRF formulations when the GRF is transferred from the stomach into the intestine, and passes the absorption window. Note that improved bioavailability of riboflavin from the LGRD capsule was more than triple that measured after administration of the IR formulation in this study.

EXAMPLE 2

Spray-Coating Procedures

Nonpareil sugar beads 18-20 mesh (approximately 0.8 mm in diameter) were placed into a coating chamber of a fluid-bed spray coater (Niro-Aeromatic, model STREA-1, Niro-Aeromatic, Ltd.) with a Wurster column insert. The Wurster column was approximately 1 inch away from the bottom screen of the coating chamber. The sugar beads were fluidized for 5 minutes to equilibrate with the coating temperature (40-45°C) before starting the coating process. At the end of each coating step, the coated beads were dried in the coating chamber at 40°C for approximately 10-15 minutes. Model drugs and leaky enteric-coating polymers were sprayed onto sugar beads (batch size 40-200 g) according to the drug being formulated.

All coating solutions or dispersions were continuously delivered through a feeding tube by a peristaltic pump (Rabbit Peristaltic pump, Gilson Electronics, Middleton, WI). Coating solutions or dispersions were kept stirring using a magnetic stirrer to ensure homogeneity of the solution or dispersions. For each coating step, coating conditions were monitored and adjusted to maintain effective coating conditions. After each coating step, beads were sieved to remove agglomerated and fine particles before proceeding to the next steps.

A composition of enteric coating polymer material (Eudragit L30D-55 from Rhome Pharma) in a quantity that prevents more than 5% drug release in gastric fluid for the beads used was prepared with lactose to modify the coating so as to produce a coating material that releases drug in gastric fluid.

Table 2

Leaky, Enteric-Coated Beads Formulations of Riboflavin-5-Phosphate

Formulations	**Composition of Leaky Enteric-Coating Polymer**	Amount of Leaky Enteric-Coating Polymer (% of Drug-Loaded Beads) [b]
RF1	EUD [a]	**5%**
RF2	EUD with 50% lactose	**5%**
RF3	EUD with 65% lactose	**5%**
RF4	**EUD with 83.5% lactose**	**5%**

[a] Eudragit® L30D-55 (EUD). Working titles of coating formulation are used here and in the figures. Final coating formulations given below.

[b] Weight gain of beads coated with the coating material after drying the coated beads.

Table 3

Ingredients of Leaky Enteric-Coating Composition of Riboflavin-5-Phosphate Formulations.

Ingredients	Formulations (% of Total Coating Materials)			
(Solid Composition)	**RF1**	**RF2**	**RF3**	RF4
Eudragit® L30D-55	66.7	50.0	46.5	**42.8**
Talcum	33.3	25.0	23.3	**21.4**
Lactose	-	**25.0**	**30.2**	**35.8**

Compositions and Preparations of Coating Solution/Dispersion for Riboflavin-5-Phosphate

Table 4

Riboflavin loading solution

Riboflavin-5-phosphate	**7.5 g**
PVP K-30	**2.0 g**
Hydroxypropyl cellulose (HPC) EXF	**1.0 g**
Deionized water	**250.0 ml**

Accurately weighed HPC EXF was dispersed in 50 ml of hot deionized water. Cool deionized water was added to the well-dispersed HPC and the solution was stirred until clear. PVP K-30 was then added and well mixed. Finally, riboflavin was added to the solution and stirred until dissolved. Loading solution was kept protected from light throughout this process.

Table 5

Eudragit® L30D-55 dispersion (EUD)

Eudragit® L30D-55	**50.0 g**
Triethyl citrate	**1.5 g**
Talcum	**7.5 g**
Deionized water	**50.0 ml**

Eudragit® L30D-55 was accurately weighed into a beaker. Triethyl citrate was added to Eudragit® suspension and gently mixed. Talcum was dispersed in deionized water.

The talcum dispersion was then added into Eudragit® mixture and gently mixed. This mixture was gently stirred continuously.

Table 6

Eudragit® L30D-55 with 50% lactose dispersion

Eudragit® L30D-55	**50.0 g**
Triethyl citrate	**1.5 g**
Talcum	**7.5 g**
Lactose	**7.5 g**
Deionized water	**125.0 ml**

Accurately weighed lactose was dissolved in 75 ml of deionized water (solution may be warmed to facilitate the dissolution). Talcum was dispersed in the remaining deionized water. Talcum dispersion was added to lactose solution and kept stirring. Eudragit® L30D-55 was accurately weighed into a beaker. Triethyl citrate was added to Eudragit® suspension and gently mixed. The lactose and talcum dispersion was then added into Eudragit® mixture and gently mixed with continuous stirring. The amount of lactose used in studied formulations was calculated as a percentage of Eudragit® polymer solid (Eudragit® polymer suspension contains 30% polymer solid). The volume of deionized water varied as needed to sufficiently dissolve lactose for other lactose formulations (generally, one part of lactose can be dissolved in 10 part of water).

***In Vitro* Dissolution Testing of Studied Formulations**

In vitro drug release profiles of studied formulations were obtained using the United States Pharmacopoeia (USP) XXIII dissolution apparatus I, basket method (VK 7000, Vankel Industries, Inc., Cary, NC). Dissolution was studied at a basket rotation speed of 100 rpm and the dissolution bath temperaturewas maintained at about 37.5°C. Dissolution testing of all formulations was performed in triplicate.

Studied formulations were placed into dissolution baskets, which were then immersed in dissolution vessels containing 600 ml of simulated gastric fluid. Dissolution testing was run in simulated gastric fluid for 2 hours. At the end of the 2-hour period, the dissolution baskets were transferred into phosphate buffer pH 6.0. Dissolution testing was continued in phosphate buffer until studied formulations were completely disintegrated.

Five (5) ml samples were manually collected without medium replacement at 0.17, 0.33, 0.5, 0.75, 1, 2, 2.08, 2.17, 2.25, 2.5, 2.75, 3, 4 and 5 hours. The samples were

centrifuged at 3,000 rpm for 20 minutes. Supernatant was then collected and measured by UV spectrophotometer at 445, 330, and 318 nm for riboflavin, ranitidine, and hydrochlorothiazide, respectively. The amount of drug released was determined using an appropriate standard curve.

Average drug releases and their standard deviations were calculated from three replications in all dissolution experiments. Dissolution profiles are presented in FIG. 2 as percent drug release versus time curves.

FIG. 2 shows % active ingredient (riboflavin) release on the Y-axis and exemplifies performance of new leaky enteric compositions to provide release of drug into gastric fluid at desired programmed rates, followed by rapid release (more than 60% in less than one hour in this case) of drug remaining in the composition when the composition is transferred into intestinal fluid. The traditional enteric composition with no lactose did not release measurable drug in gastric fluid during the first hour and only released 5.3% of active ingredient after two hours in gastric fluid. The 5.3% drug release in gastric fluid in two hours satisfies USP requirements for enteric-coated (delayed release) dosage forms.

A coating also can be made to provide programmed release of active ingredient in gastric fluid by making the coat too thin to effectively prevent drug release in gastric fluid. That is, just as the traditional enteric coating without lactose can be made thicker to prevent drug release in two hours in the dissolution test in gastric fluid, so also can the same coating be provided in a thinner layer to become a leaky enteric coating and provide desired programmed release of active ingredient in gastric fluid. Increasing weight gain of the coating generally results in increasing coating thickness and resistance to active ingredient release in gastric fluid, wherease decreasing weight gain of the coating generally results in decreasing coating thickness and increased active ingredient release in gastric fluid. In some cases, it is preferable to make the coating thicker to obtain more consistent results and a greater ability to program drug release in gastric fluid. In these cases a hydrophilic or hydrophobic additive that promotes drug release in gastric fluid is generally included in the new leaky enteric compositions.

EXAMPLE 3

Pharmacokinetic models have been used to simulate data for drug concentration versus time curves following administration of a 50/50 mixture of immediate release drug and enteric-coated pellets that do not release drug in gastric fluid. A preliminary report indicated the data are quite accurate (Prapoch Watanalumlerd, J. Mark Christensen, and James W. Ayres, Gastrointestinal Transit Effect on Drug Pharmacokinetics from Mixed

Immediate Release and Enteric-coated Amphetamine Beads, Poster presentation at American Association of Pharmaceutical Scientists (AAPS) Annual Meeting, November 10-14, 2002, Toronto, Canada). This example now shows model equations and assumptions, and that pharmacokinetic models used to generate data for drug concentration versus time curves provide very good data when applied to enteric-coated beads mixed with immediate release drug that is not enteric coated. In this case, data for drug concentrations versus time in fed and fasted subjects are taken from a product based on U.S. Patent No. 6, 322,819. The formulation contained 50% of the dose available as immediate release drug and 50% of the dose in enteric coated pellets that did not release any drug until the pellets passed out of the stomach and were in the intestine.

Commercial mixed immediate-release and enteric-coated amphetamine capsules (Adderall XR™) containing 10 mg of immediate-release amphetamine salts and 10 mg of delayed-release (enteric coated) amphetamine salts were used for in vitro dissolution test. Amphetamine dissolution profile was obtained using USP dissolution apparatus II at 37.5 °C and paddle speed 100 rpm. The formulation without capsule shell was run in simulated gastric fluid (pH 1.4) for 2 hours before the dissolution medium was adjusted to pH 6.0 by adding alkaline solution (0.2 M tribasic sodium phosphate solution) and de-ionized water. Samples were assayed for amphetamine concentration using an ultraviolet spectrophotometer at 257 nm.

FIG. 3 confirms that immediate release drug was released immediately, and that enteric-coated drug does not release in gastric fluid but does release when transferred into intestinal fluid.

A. Pharmacokinetic Models

Using knowledge about gastric emptying and GI transit, compartmental diagrams for pharmacokinetics of drugs from mixed immediate release and enteric-coated pellets in the fed and fasted condition are created and shown in FIGs. 4 and 5, respectively. Compartmental diagrams in FIG. 4 represent (i) first-order absorption of drug from immediate release pellets and (ii) zero-order gastric emptying rate in the fed condition of enteric-coated pellets into the intestine, and first order absorption of the drug after being released from the pellets. Compartmental diagrams in FIG. 5 represent (i) first-order absorption of immediate release pellets and (ii) first-order gastric emptying rate in the fasted condition of enteric-coated pellets into the intestine, and first order absorption of the drug after being released from the pellets. These compartmental

diagrams apply to drugs when pharmacokinetics following oral administration can be described by a one-compartment model.

With reference to FIG. 4, a compartmental diagram of pharmacokinetic models for mixed, immediate-release and enteric-coated pellets in fed condition, $\mathbf{X_G}$ is the amount of released drug in the intestine; $\mathbf{X_1}$ is the amount of drug in plasma/blood; $\mathbf{D_{IR}}$ is an immediate release dose; $\mathbf{D_{EC}}$ is an enteric-coated dose; $\mathbf{k_0}$ is a zero-order input of drug corresponding to the zero-order gastric emptying of enteric-coated pellets in fed condition; $\mathbf{k_a}$ is a first-order absorption rate constant of drug; and $\mathbf{k_{el}}$ is a first-order elimination rate constant of drug.

With reference to FIG. 5, a compartmental diagram of pharmacokinetic model for mixed, immediate-release and enteric-coated pellets in fasted condition, $\mathbf{X_G}$ is the amount of released drug in the intestine; $\mathbf{X_1}$ is the amount of drug in plasma/blood; $\mathbf{D_{IR}}$ is an immediate release dose; $\mathbf{D_{EC}}$ is an enteric-coated dose; $\mathbf{k_{em}}$ is a first-order rate of drug input corresponding to the first-order gastric emptying of enteric-coated pellets in fasted condition; $\mathbf{k_a}$ is a first-order absorption rate constant of drug; and $\mathbf{k_{el}}$ is a first-order elimination rate constant of drug.

Pharmacokinetic models describing pharmacokinetics of mixed immediate release and enteric-coated pellets in the fed condition are presented in Equations 1-3.

For fed condition:

When $t \le \tau$,

$$C_t = \frac{k_a D_{IR}}{V(k_a - k_{el})}\left(e^{-k_{el}t} - e^{-k_a t}\right) + \frac{k_0}{V \cdot k_{el}}\left[1 - \frac{k_{el}}{(k_{el} - k_a)}e^{-k_a t} - \frac{k_a}{(k_a - k_{el})}e^{-k_{el}t}\right] \quad \text{Eqn 1}$$

When $t > \tau$,

$$C_t = \frac{k_a D_{IR}}{V(k_a - k_{el})}\left(e^{-k_{el}t} - e^{-k_a t}\right) + \frac{k_0}{V \cdot k_{el}}\left[1 - \frac{k_{el}}{(k_{el} - k_a)}e^{-k_a \tau} - \frac{k_a}{(k_a - k_{el})}e^{-k_{el}\tau}\right]e^{-k_{el}(t-\tau)} + \frac{k_0\left(1 - e^{-k_a \tau}\right)}{V(k_a - k_{el})}\left[e^{-k_{el}(t-\tau)} - e^{-k_a(t-\tau)}\right] \quad \text{Eqn 2}$$

For the fasted condition, pharmacokinetic model describing plasma concentration of a drug from mixed, immediate-release and enteric-coated pellets can be obtained by combining the pharmacokinetic model of oral-controlled, first-order-release dosage form with a typical extravascular pharmocokinetic model for immediate release pellets. This model is presented in Equation 3.

For a fasted condition:

$$C_t = \frac{k_a D_{IR}}{V(k_a - k_{el})}\left(e^{-k_{el}t} - e^{-k_a t}\right) + \frac{k_{em} k_a D_{EC}}{V}\left[\frac{e^{-k_{em}t}}{(k_a - k_{em})(k_{el} - k_{em})} + \frac{e^{-k_a t}}{(k_{em} - k_a)(k_{el} - k_a)} + \frac{e^{-k_{el}t}}{(k_{em} - k_{el})(k_a - k_{el})}\right] \quad \text{Eqn 3}$$

C_t is plasma concentration of the drug at time t. D_{IR} is an immediate release dose. D_{EC} is an enteric-coated dose. k_{em} represents a first-order rate of drug input corresponding to the first-order gastric emptying of enteric-coated pellets in fasted state. k_0 represents a zero-order input of drug corresponding to the zero-order gastric emptying of enteric-coated pellets in fed state. k_a and k_{el} represent a first-order absorption rate constant and a first-order elimination rate constant of drug, respectively. Tau (τ) is gastric emptying time of enteric-coated pellets (i.e. the time of zero-order input). V is an apparent volume of distribution for the blood compartment. These equations may be multiplied by a factor F, which is the fraction of absorbed drug.

Since a gastric emptying lag time is expected and will affect drug release from enteric-coated pellets, the above equations are modified by including another time parameter - lag time of emptying (*lag*), as presented in Equations 4-8.

For fed condition:

When $t \leq lag$,

$$C_t = \frac{k_a D_{IR}}{V(k_a - k_{el})}\left(e^{-k_{el}t} - e^{-k_a t}\right) \quad \text{Eqn 4}$$

When $lag < t \leq \tau + lag$,

$$C_t = \frac{k_a D_{IR}}{V(k_a - k_{el})}\left(e^{-k_{el}t} - e^{-k_a t}\right) + \frac{k_0}{V \cdot k_{el}}\left[1 - \frac{k_{el}}{(k_{el} - k_a)}e^{-k_a(t-lag)} - \frac{k_a}{(k_a - k_{el})}e^{-k_{el}(t-lag)}\right] \quad \text{Eqn 5}$$

When $t > \tau + lag$,

$$C_t = \frac{k_a D_{IR}}{V(k_a - k_{el})}\left(e^{-k_{el}t} - e^{-k_a t}\right) + \frac{k_0}{V \cdot k_{el}}\left[1 - \frac{k_{el}}{(k_{el} - k_a)}e^{-k_a \tau} - \frac{k_a}{(k_a - k_{el})}e^{-k_{el}\tau}\right]e^{-k_{el}(t-lag-\tau)} + \frac{k_0\left(1 - e^{-k_a \tau}\right)}{V(k_a - k_{el})}\left[e^{-k_{el}(t-lag-\tau)} - e^{-k_a(t-lag-\tau)}\right] \quad \text{Eqn 6}$$

For fasted condition:

When $t \leq lag$,

$$C_t = \frac{k_a D_{IR}}{V(k_a - k_{el})}\left(e^{-k_{el}t} - e^{-k_a t}\right) \quad \text{Eqn 7}$$

When $t > lag$,

$$C_t = \frac{k_a D_{IR}}{V(k_a - k_{el})}\left(e^{-k_{el}t} - e^{-k_a t}\right) + \frac{k_{em} k_a D_{EC}}{V}\left[\frac{e^{-k_{em}(t-lag)}}{(k_a - k_{em})(k_{el} - k_{em})} + \frac{e^{-k_a(t-lag)}}{(k_{em} - k_a)(k_{el} - k_a)} + \frac{e^{-k_{el}(t-lag)}}{(k_{em} - k_{el})(k_a - k_{el})}\right] \quad \text{Eqn 8}$$

Model Assumptions

Several assumptions were made for the models presented above, including:

1. Pharmacokinetic of the drug involved is linear in the dosing range of interest. Thus, superposition for determination of plasma drug concentrations can be applied.

2. Enteric-coated portion of formulations is in multiple-unit pellet/granule (multi-particulate) form and does not release drug in gastric fluid.

3. Enteric-coated polymer dissolves instantaneously upon transfer into the intestine.

4. After the pH-dependent polymer on enteric-coated pellets dissolves in the intestine, then drug release is instantaneous.

5. Once being released from formulations, the drug is absorbed from the gastrointestinal tract by a first-order process.

6. Pharmacokinetics of the drug after absorption is well described by a one-compartment open model.

7. The elimination process is a first-order process.

No assumptions are required to be exact, or even correct, so long as the model adequately approximates the processes described. Results below clearly support validity of the assumptions and models.

Monte Carlo Simulations

Pharmacokinetic models above were used in Monte Carlo simulations of plasma concentration-time curves from mixed immediate release and enteric-coated pellets of amphetamine. Five hundred trials for each simulation were performed using Crystal Ball 2000.2 software (Decisioneering, Inc., Denver, CO). The simulated plasma data concentration-time curves of amphetamine are presented as a mean plot (along with its standard deviation). The peak plasma concentration (C_{max}) of the actual data is then compared to C_{max} of simulated data.

Model Parameters

Following oral administration of immediate-release amphetamine, a one-compartment model best describes plasma drug concentrations both in adults and children. Pharmacokinetic parameters of amphetamine used in the simulations were obtained from pharmacokinetic fitting of available plasma concentration data of amphetamine (Sifton, D.W. *Physician Desk Reference*. 57th Ed. Thomson PDR: Montvale, NJ, 2003.) using Kinetica 2000 software, version 3.0 (InnaPhase Corporation, Philadelphia, PA). These parameters are volume of distribution divided by fraction of dose absorbed (V/F), absorption rate constant (k_a), and elimination rate constant (k_{el}). Since pharmacokinetics of d-amphetamine and l-amphetamine are similar, only simulations of d-amphetamine will be

carried out. Pharmacokinetic parameters of d-amphetamine used in the simulations are summarized in Table 7.

Table 7

Pharmacokinetic Parameters of Model Drug Used in Simulations

Drug	Dose [a] (mg)	V/F (L)	k_a (hr^{-1})	k_{el} (hr^{-1})
d-Amphetamine	20 (fed) 30 (fasted)	247.0	0.744	0.067

[a] Dose represents mixed amphetamine salts dose. Twenty milligrams of the mixed amphetamine salts is equivalent to 12.5 mg of total amphetamine base and contain d-amphetamine and l-amphetamine salts in the ratio of 3:1.

Parameters in the models, which represent GI transit effect, are gastric emptying rate constant and lag time of gastric emptying. The gastric emptying rate constant is zero order for the fed condition and first order for the fasted condition.

Variability of Model Parameters

In Monte Carlo simulations, variability of some or all model parameters is included in the simulations. Because effects of gastric emptying on the plasma concentration-time curve are being considered, variability of gastric emptying time and lag time of emptying was included in the simulations. Variability of other model parameters, on the other hand, was not included.

Gastric emptying time, lag time of emptying and their variability (standard deviation) were obtained from the literature. A lognormal distribution was chosen for all time parameters since time cannot be negative. T_{50} is utilized for calculation of a first-order emptying rate constant in the fasted condition. Lag time of emptying in the fasted condition was selected based on phase 1, a period of motor inactivity, of MMC, which lasts approximately 30 to 60 min. Variability for lag time of emptying in the fasted condition was assumed to be 30 percent. Model parameters and their probability distribution used in the simulations are detailed in Table 8.

Table 8

Probability Distribution of Model Parameters

And Their Mean and Standard Deviation

Parameters (unit)	Distribution	Mean ± SD (ref.)
Fed Condition		
Lag time of emptying (hr)	Lognormal	1 ± 0.37 (9)
Gastric emptying time (hr)	Lognormal	5.7 ± 0.9 (5)
Fasted Condition		
Lag time of emptying (hr)	Lognormal	0.75 ± 0.22 (2)
T_{50} (hr) [a]	Lognormal	0.5 ± 0.2 (6)

[a] First-order emptying rate constant is calculated from $0.693/T_{50}$.

Determination of Amphetamine Absorption Profile from Mixed Immediate Release and Enteric-coated Pellets

Deconvolution of available plasma amphetamine concentration profiles (New drug approval package--Adderall XR clinical pharmacology and biopharmaceutics review (Approval date: October 2001). Website of CDER Freedom of Information Office, U.S. Food and Drug Administration. Retrieved April 15, 2002, http://www.fda.gov/cder/foi/nda/2001/21303_Adderall_biopharmr.pdf) from commercial, mixed, immediate-release and enteric-coated pellets was performed using Kinetica 2000 software, version 3.0 (InnaPhase Corporation, Philadelphia, PA), to obtain the absorption profiles of d-amphetamines.

Average predicted peak concentrations data (C_{max}) from the simulations and observed C_{max} data in fed and fasted subjects are presented in Table 9. Simulated plasma concentration-time data curves are shown as mean plots. The average data values of 500 simulated plasma concentrations for each time point from 500 simulations were plotted in the mean plots. Vertical bars in the mean plots represent the standard deviation of 500 simulated concentrations for each time point.

Table 9

Summary of predicted C_{max} data and observed C_{max} data of d-amphetamines

Condition (Dose)	Predicted C_{max} (ng/ml)	Observed C_{max} (ng/ml)	%Difference [a]
Fasted (30 mg)	43.6	40.2	8.4
Fed (20 mg)	26.0	25.3	2.8

[a] %Differences are presented as percentage of the observed C_{max}. The simulated data are quite accurate and close to the observed data.

A mean plot of simulated plasma concentration-time curve of amphetamine from mixed immediate release and enteric-coated pellets in the fed condition are presented in FIG. 6. FIG. 6 shows that the simulated plasma concentration-time curve of amphetamine, after taking into account GI transit time and lag time of emptying in the fed condition, is very close to the reported amphetamine concentrations in plasma following oral administration of commercial mixed pellets in fed subjects. The predicted C_{max} differs from the observed value by only 2.8 percent (**Table 9**). Actual amphetamine concentrations are close to predicted lines. One explanation for the slightly lower concentration of the first two points is that there might be a delayed absorption of amphetamine from immediate-release pellets in the fed condition. In the presence of a meal, the immediate-release drug must dissolve and then find its way through the food to absorption surfaces of the stomach or travel into the intestine to be absorbed. Therefore, a short lag time of absorption of the drug from immediate-release pellets in the fed condition is not surprising.

A mean plot of simulated plasma concentration-time data curve of amphetamine from mixed immediate release and enteric-coated pellets in the fasted condition is presented in FIG. 7. FIG. 7 shows that the simulated plasma concentration-time curve of amphetamine predicts quite well the reported amphetamine concentrations in plasma from commercial mixed pellets in fasted subjects. The predicted C_{max} differs from the observed value by only 8.4 percent (**Table 9**). The model slightly overestimates the peak concentrations of amphetamine between 4 and 6 hours.

Pharmacokinetic models used above incorporated the effect of gastric emptying on plasma concentration-time curve of amphetamine from mixed, immediate-release and enteric-coated pellets. The enteric-coated pellets did not release drug in gastric fluid. Data provided by the simulations give numerical and pharmacokinetic support that the plasma

concentration-time curve data of amphetamine, when administered as mixed, immediate-release and enteric-coated pellets both in fed and fasted condition, do not produce a double-pulsed absorption pattern even though one-half of the drug is released quickly in gastric fluid and the other one-half of the drug is not released until two hours later in the *in vitro* dissolution test (FIG. 3). Unlike drug release in a dissolution chamber, *in vivo* drug release from enteric-coated pellets is influenced by both the GI transit and pH in the GI tract. Prolonged absorption of active ingredient from enteric-coated pellets is a result of GI transit characteristics under fed and fasted conditions, wherein the immediate-release drug is released quickly in the stomach and the enteric-coated drug is not released until the enteric-coated beads are "trickled" into the intestine.

The assumption of the model about instantaneous dissolution of enteric-coated pellets in the intestine seems to be valid, even though the *in vitro* dissolution profile of the commercial formulation showed that the amphetamine release took about 30 to 45 minutes in pH 6.0 medium. This small "sustaining" release in dissolution is insignificant for amphetamine when compared to the much larger variation of the gastric lag time and emptying. Using the assumption of instantaneous dissolution is advantageous in simplifying the model so that it can be applied to other mixed pellet formulations as long as the drug release time is relatively short. This example clearly shows that data generated by the simulations is quite accurate at predicting drug concentrations. In complex physiological systems like the human body, when considering the effects of product formulation, simulation data often vary by 100% or more from actual data, are preferred to be within 60% of actual data, more preferred to be within 40% of actual data, and most preferred to be within 30% of actual data.

EXAMPLE 4

This example shows experimental processes used to provide expected drug concentration versus time profiles for some drugs following administration of leaky enteric compositions. Pharmacokinetic modeling was applied for fed and fasted human subjects using known GI transit parameters to predict plasma drug concentrations following administration of new leaky enteric compositions. Monte Carlo simulation is applied to the models to include the effect of GI transit variability on simulated plasma concentrations of the drug from novel, leaky, enteric-coated pellets. Available pharmacokinetic data in the fed or fasted condition, depending on the drug, are compared to data generated from the simulation models.

Pharmacokinetic Models of Leaky Enteric-Coated Beads

Compartmental diagrams illustrating pharmacokinetics of drugs from leaky enteric-coated beads in the fasted and fed condition are created and shown in Figures 8 and 9, respectively.

Pharmacokinetic model of leaky enteric-coated beads in fasted condition is presented in Equation 8.

$$C_l = \frac{k_a D}{V}\left[\frac{(k_c k_s - k_{em}k_c)e^{-k_c t}}{(k_a - k_c)(k_s - k_c)(k_{el} - k_c)} + \frac{(k_c k_s - k_{em}k_s)e^{-k_s t}}{(k_a - k_s)(k_c - k_s)(k_{el} - k_s)} + \frac{(k_c k_s - k_{em}k_a)e^{-k_a t}}{(k_s - k_a)(k_c - k_a)(k_{el} - k_a)} + \frac{(k_c k_s - k_{em}k_{el})e^{-k_{el} t}}{(k_a - k_{el})(k_s - k_{el})(k_c - k_{el})}\right] \quad \text{Eqn 9}$$

where $k_c = k_{em} + k_r$

For the fed condition, computer programming codes were developed using MATLAB computer language (The MathWorks, Inc., Natick, MA) to delineate the compartmental diagram.

Model Assumptions

Assumptions underlying pharmacokinetic models of leaky enteric-coated beads used in simulations are:

1) Drug pharmacokinetics are linear in the dosing range of interest. Thus, superposition for determination of plasma drug concentrations can be applied.

2) Leaky enteric-coated formulation is in multi-unit pellet/granule (multi-particulate) form.

3) Drug release from leaky, enteric-coated formulation in the stomach is adequately described by assuming a first-order process.

4) Upon transfer into the intestine, drug release from leaky, enteric-coated formulation in the intestine is instantaneous.

5) Once being released from the formulation into the intestine, the drug is absorbed by a first-order process.

6) Pharmacokinetics of the drug in the body are well described by a one-compartment open model.

7) Drug elimination from the body is a first-order process.

8) No assumptions are required to be exact, or even correct, so long as the model adequately approximates the processes described. Example 3 clearly validates that assumptions and models are adequate.

Model Parameters

Pharmacokinetic parameters of riboflavin-5-phosphate, ranitidine hydrochloride, and hydrochlorothiazide used in simulations were obtained by fitting of plasma concentration-time data from the literature (Zempleni, J.; Galloway, J.R.; McCormick, D.B. Pharmacokinetics of orally and intravenously administered riboflavin in healthy humans. American Journal of Clinical Nutrition **1996**. *63*, 54-66.; Abbreviated New Drug Application (ANDA) 074-467 Ranitidine hydrochloride Geneva Pharmaceuticals. Drugs@FDA Website, Retrieved from http://www.accessdata.fda.gov/scripts/cder/drugsatfda/.; Patel, R.B.; Patel, U.R.; Rogge, M.C.; Shah, V.P.; Prasad, V.K.; Selen, A.; Welling, P.G. Bioavailability of hydrochlorothiazide from tablets and suspensions. J. Pharm. Sci. **1984**. *73* (3), 359-361.).

All data fittings were performed on data from immediate-release formulations using WinNonlin software, version 3.2 (Pharsight Corporation, Mountain View, CA). Table 10 summarizes pharmacokinetic parameters of all model drugs used in simulations.

Table 10

Pharmacokinetic Parameters of Model Drugs Used in Simulations

Dose (mg)	**F**	**V (L)**		**k_{el} (hr^{-1})**	k_r (hr^{-1})
Riboflavin-5-phosphate					
60	85%	190.7	3.67	0.32	**0.144, 0.347, 0.693**
Ranitidine hydrochloride					
300	IR[a]	199.6[b]	0.641	0.239	0.144, 0.347, 0.693
Hydrochlorothiazide					
100	**100%**	**105.9**	**0.94**	**0.13**	**0.144, 0.347, 0.693**

[a] Bioavailability of ranitidine from leaky enteric-coated beads was assumed to equal that of IR formulation.

[b] This value represents V/F.

Bioavailability of 60 mg, immediate-release riboflavin was 36.4% (Zempleni,, et. al.). Bioavailability of 60 mg riboflavin from leaky, enteric-coated beads used in simulations was assumed to be 85% based on results shown in Example 1. Bioavailability of leaky, enteric-coated beads of ranitidine hydrochloride was assumed to be equal to that of immediate-release formulation. Bioavailability of 100 mg, immediate-release hydrochlorothiazide was 50.3% (Patel,, et. al.). Bioavailability of 100 mg hydrochlorothiazide from leaky enteric-coated beads was assumed to be 100% in simulations.

GI transit parameters involved in simulations were gastric emptying of beads and gastric emptying of liquid. Gastric emptying of drug beads in fasted and fed condition are first-order and zero-order processes, respectively (Hardy, J.G.; Lamont, G.L.; Evans, D.F.; Haga, A.K.; Gamst, O.N. Evaluation of an enteric-coated naproxen pellet formulation. Aliment. Pharmacol. Ther. **1991**. *5*, 69-75.; Davis, S.S.; Khosla, R.; Wilson, C.G.; Washington, N. Gastrointestinal transit of a controlled-release pellet formulation of tiaprofenic acid and the effect of food. Int. J. Pharm. **1987**. *35*, 253-258.). Gastric emptying of liquid was a first-order process (Collins, P.J.; Horowitz, M.; Cook, D.J.; Harding, P.E.; Shearman, D.J.C. Gastric emptying in normal subjects--a reproducible technique using a single scintillation camera and computer system. Gut **1983**. *24*, 1117-1125) and was assumed to be a similar rate for both fasted and fed simulations. GI transit parameters used in simulations are shown in Table 11.

Table 11

GI Transit Parameters Used in Simulations

k_{em}[a] (ref.)	Gastric emptying time in fed condition (ref.)	t_{50}[b] (ref.)
1.39 hr^{-1} (4)	**5.7 hr (5)**	**0.25 hr (6)**

[a] First-order gastric emptying rate constant of beads in fasted condition

[b] Half-time for gastric emptying of liquid

Computer Simulations

All simulations were performed using MATLAB software, version 6.5 (The MathWorks, Inc., Natick, MA). The simulated plasma concentration-time curves of each

model drug are visually compared to published literature data of immediate-release formulation.

EXAMPLE 5

Example 1 establishes that the bioavailability of riboflavin is dramatically increased when the drug is released slowly in the stomach and trickles into the intestine. Bioavailability is decreased if the drug is trapped inside a composition and passes the absorption window before drug is released. As described in Example 4, FIG. 10 is a curve of drug concentration versus time for riboflavin. Pharmacokinetic data for riboflavin were obtained from Zempleni, *et. al*, **Am J Clin Nutr**.1996; 63: 54-66. Data points from the immediate-release dosage form were obtained in fed subjects and bioavailability was 36.4% for the immediate-release dosage form and set at 85% from the new leaky enteric formulation, based on Example 1 above.

New enteric compositions can produce (see FIG. 10) an onset time to quantifiable plasma concentrations that is approximately equal to that from an immediate-release dosage form while also providing higher drug concentrations in the body and prolonged drug concentrations in the body. Each effect is dramatic and readily seen to be individually important and beneficial even if only one such effect occurs.

FIG. 10 is a curve of drug concentration in plasma versus time for riboflavin following administration to human subjects of IRF (immediate release formulation) active ingredient or as some novel leaky enteric compositions of riboflavin that give programmed release of their active ingredient into gastric fluid at first order rates as shown in the legend, which results in either 25%, 50%, or 75% release of their active ingredient contents over two hours in gastric fluid.

The release rates and first order character are given as only examples of the infinite number of release rates and types that can occur from drug dosage forms of the new invention. Any type or order of release rate or mixed release-rate from the new leaky enteric compositions is acceptable so long as the desired outcome is obtained. The data points for IR riboflavin are from Zempleni, *et al.*, and solid lines are from data generated as described in Example 4. One of ordinary skill in the art will readily recognize that riboflavin is only one example of active agents that can benefit from the new invention. In fact, currently preferred, novel embodiments of formulations according to the present invention typically comprise active agents other than riboflavin.

A person of ordinary skill in the art will readily appreciate that when bioavailbility is increased and drug input occurs over a longer time period as compared to immediate-

relaease formulations, as shown in examples herein, then dosing frequency can be reduced. Further, dosing frequency may be reduced even if bioavailability is not increased when drug input occurs over a longer time period as compared to immediate-relaease formulations. This is true even for drugs that do not have an absorption window. Note, for only one example, that aspirin and other non-steroidal inflammatory agents or other drugs that irritate stomach tissue are often enteric coated to protect the stomach from irritation by the active agent. Such irritation often is associated with undissolved particles of the agent that are exposed to gastric fluid following disintegration of immediate-release dosage forms of non-steroidal anti-inflammatory agents and other irritating drugs in gastric fluid. These drug particles contact the walls and tissue of the stomach and then drug that is dissolved in the diffusion layer surrounding the particles is in a high enough concentration to damage/irritate the stomach tissues. But, the enteric coating comes with a price in that there is a delayed release of the drug and a delayed onset of action that is not desirable for the patient who needs/desires faster relief.

The novel, leaky enteric compositions disclosed herein are well suited to deliver irritating drugs, including non-steroidal, anti-inflammatory agents because they entrap particles of the drug in the composition, thereby protecting the stomach tissues from damage/irritation, but also allowing a portion of the dose of active ingredient to dissolve into gastric fluid. This results in drug being released and available without the lag time associated with traditional enteric-coated (delayed release) dosage forms. In this case, the active ingredients may or may not have an absorption window but still benefit greatly from the instant invention even if the drug is well absorbed throughout the intestinal tract. And, the prolonged drug input into the body compared to immediate-release dosage forms when using the novel, leaky-enteric formulations also makes it possible to reduce dosing frequency as defined by the FDA. These and other active ingredients will be well recognized as even more preferable agents than riboflavin for use in the new leaky enteric compositions.

EXAMPLE 6

This example shows that a low solubility drug with an absorption window can be delivered into the upper intestine from the stomach in a more slowly controlled fashion than occurs with rapid, immediate drug release in the stomach. Not only a desirable pharmacokinetic outcome can be obtained but the pharmacodynamic effect of the drug also can be unexpectedly changed as shown in my European Patent Application PCT WO 03/015745 A1.

Hydrochlorothiazide was used as a model drug that has an "absorption window" in the upper intestine, and formulated into a gastric retention formulation (GRF) to be retained for a prolonged time in the stomach and provide slow, controlled release of drug in the stomach resulting in slow, controlled delivery of drug from the stomach into the intestine. Prior to conducting a bioavailability/bioequivalency study with the GRF, a drug dissolution profile was used to predict the expected *in vivo* absorption profile by convolution. Pharmacokinetic models were generated and validated using observed plasma concentration data from a reference and compared to a model provided in the literature. The best-fit model was selected to assess convolution to simulate plasma concentration profiles. Good correlation between predicted and observed pharmacokinetic outcome confirms reliability of experimental data simulated from mathematical model pharmacokinetic simulation experiments.

Two formulations for hydrochlorthiazide (an immediate release formulation (IR) and a gastric retention device (GRD) containing sustained release formulations (SR)) were administered in the bio-study (bioavailability study). A commercial tablet containing 50 mg of HCTZ was used as an IR control, and spray-coated beads equivalent to 50 mg of HCTZ were formulated for slow drug release (SR) and included in the GRF. Bioavailability and pharmacodynamics of HCTZ from a GRD were compared to those from an IR.

Monitoring concentrations of hydrochlorthiazide in the urine of healthy adult volunteers allowed comparison of the relative bioavailability of hydrochlorthiazide from the GRD formulation and from a conventional tablet. Participation involved at least two days for each treatment with at least 72-hours washout period between doses. An IR was given once and the GRD was repeated twice to test the reproducibility of the new dosage form. A 50-mg dose was chosen for the study because it was in the range of the recommended dose from the PDR (Physician's Desk References) and it produced concentrations high enough to make HPLC analysis efficient. Six subjects participated in the study, 4 healthy males and 2 healthy females. They were not allowed any food or drink containing caffeine, nor alcohol or other medications. Smokers and vegetarians were not included. Subjects fasted overnight and at least 2 hours following dosing. They voided their bladder before receiving a single dose of hydrochlorthiazide in each study and took the dose with 12 ounces of water. After dosing, subjects received a set of containers in which to collect their urine and a time sheet on which to record the time of urination. Subjects collected all urine within a 24-hour period after oral administration of the formulations. Urine samples were collected during the period 0-1, 1-2, 2-3, 3-4, 4-6, 6-8, 8-10, 10-12, 12-24, 24-36 and 36-48 hours. Urine samples were refrigerated until delivered to the researcher. The volume of urine collected

was measured in order to calculate total amount of drug recovered. A modified method for HPLC (High performance Liquid Chromatography) assay of Papadoyannis *et al.*, (Papadoyannis IN, Samanidou VF, Georga KA, Georgarakis E (1998) High pressure liquid chromatographic determination of hydrochlorothiazide (HCT) in pharmaceutical preparation and human serum after solid phase extraction, J. Liq. Chrom. & Rel. Technol., 21(11): 1671-1683.) was used to analyze small portions of urine samples for the drug content.

Pharmacokinetic parameters and urine output data following administration of either immediate release drug or slow drug input into the upper small intestine from a GRD containing hydrochlorothiazide were then obtained. Average pharmacokinetic parameters for each treatment under fasting conditions are provided in the following Table 12. FIG. 11 shows cumulative amount of drug excreted versus time. Elimination half-life ($t_{1/2}$) was approximately 7 hours. The values of A_{0-36} were compared for statistical analysis because it was not possible to obtain the value at 48 hours for an IR from one subject due to the short half-life.

Mean A_{0-36h} from IR (33.3mg, 66.6%) was found to be significantly different ($P< 0.05$) relative to that from GRD (37 mg, 75.4%) in fasting conditions, although the difference is less than 10%. A difference of less than 20% is generally considered to be insignificant from FDA BA/BE guidance. From FIG. 11[and Table 12, mean values for total drug absorbed and collected in the urine were equivalent, (A_{0-48}) were 38.12 mg (76.2%) and 38.95mg (77.9%) for IR and GRD in fasting conditions, respectively. A_{0-48} was based on assuming 50% of absorbed dose appears intact in the urine. Thus; the GRD resulted in essentially the same amount of drug being absorbed as from an IR up to 48 hours in fasting subjects. However, the effects on urinary excretion were surprisingly quite different.

Table 12

Mean pharmacokinetic parameters of hydrochlorothiazide from 6 subjects in fasting condition.

	Treatments	
	IR	GRD
Total urinary recovery (0-48h) (mg)	38.1 ± 9.6	39.0 ± 5.2
Maximum urinary excretion rate (mg/h)	4.8 ± 1.7	2.5 ± 0.5
Time for maximum urinary excretion rate (h)	2.5	5
Total average uring output (ml in 48 hours)	6,068	7,467
Cummulative average water intake in 48 hours (ml)	6, 013	7, 380

FIG. 12 shows that, as expected, a higher maximum excretion rate of drug (Rmax) occurred at an earlier time (t_{max}) from the immediate release (IR) capsule than that from the new formulation (GRD) (4.84 mg/hr at 2.5hr vs 2.5mg/hr at 5hr).

This example demonstrates that programmed release in gastric fluid give no change in F for hydrochlorthiazide (if the GRD stays in the stomach long enough) but drug efficacy is increased. Leaky enteric compositions also provide programmed release in gastric fluid and the same type of improved efficacy is expected.

The rate of urine production was similar for both IR and GRD up to about 6-8 hours post-dosing (Fig. 13). This is quite unexpected since the initial amount of drug absorbed and drug concentrations in the body are less from the programmed drug release into gastric fluid compared to the commercial IR capsule. And, diuresis started decreasing for the IR capsule after 6-8 hours, whereas a relatively higher amount of diuresis was maintained for GRD for a longer time period.

The initial equal amount of diuresis from slow drug input into gastric fluid is surprising since less drug is absorbed initially from the GRD (Rmax 4.8 (μg/ml) at t_{max}, 2.5 hours and 2.5 (μg/ml) at t_{max}, 5 hours in fasting condition for IR and GRD, respectively) which now teaches that less drug input can be equally effective, which is not common for drugs. In fact, if less amount of drug is input, less effect is expected but the opposite effect occurred with this new GRD and the diuretic.

Drug effect on urine production from the GRD continued until approximately 15 hours (see Fig.13).

Table 12 shows that increasing body fluid excretion in healthy, normal subjects stimulated water-intake. Total amount of urine production was higher from the same dose in a GRD compared to IR, which can be attributed to prolonged drug input from GRD followed by a feedback increased amount of water-intake to compensate for the unexpected increased drug effect.

This overall increased effect is also surprising (in addition to the initial greater effect with a smaller drug input discussed above) since it is well known that in order to increase diuretic effect it is necessary to increase the drug dose. In fact, most drug response curves are log-linear, which means that usually an increase in effect is less (smaller percentage) than the increase in dose after an initial response threshold is crossed. But, in this case, the bioavailability of drug under fasting conditions was essentially equal, but the diuretic effect was increased 27% as shown in Table 12 above.

Results from this bioavailability study of hydrochlorthiazide establishes not only that the device was retained long enough to release all or most drug in the stomach, but also

that the dosage form provided drug release into gastric fluid that resulted in slow drug input into the absorption window area to prolong drug effect. The desirable outcomes occur because the dosage form allows the drug to be released in gastric fluid in a manner that provides slow and prolonged, or "trickle," drug input into the upper small intestine. This dosage form can improve patient care by, amongst other things, (1) avoiding high drug peak concentrations that may induce undesirable side effects (see side effects information below), (2) increasing drug effect per dose administered and/or (3) achieving prolonged drug effect.

Side effects reported from the drug hydrochlorothiazide administered to human subjects as outlined above were:

- Three out of 7 subjects reported side effects from an IR dosage form between 4-6 hours post-dosing.
- Adverse reactions reported were severe or moderate headache, dehydration, and fatigue.
- One subject did not continue in the study due to severe headache, dehydration, and fatigue.
- No adverse reactions were reported from the same dose of hydrochlorthiazide when drug released in gastric fluid as described above.

This example shows that slow drug input, which is produced following administration of leaky, enteric-coated dosage forms as described elsewhere herein, is unexpectedly beneficial in increasing drug effect, particularly for therapeutics having an absorption window. Greater advantages are expected for drugs that have a lower bioavailability from immediate release dosage forms due to regional absorption limitations, e.g., as shown for riboflavin. Disclosed embodiments of the present invention effectively decrease drug peak concentrations by 20% or more, decrease drug side effects by 10% or more, prolong drug concentrations in the body sufficiently to allow a decrease in frequency of dosing, increase drug bioavailability by 10% or more, and improve patient compliance relative to known, immediate-release formulation technology. Not all of these beneficial effects occur for every drug but each effect may occur depending on the active agent involved, and only one such beneficial effect is sufficient reason to use the new compositions disclosed herein.

Prolonging drug concentrations for drugs with an absorption window using multiparticulate bead or granule formulation, capsules, or tablets other than floating (relatively non-effective) dosage forms or gastroretentive devices, while maintaining acceptable bioavailability has been considered impossible because known, sustained-release formulations pass the site of absorption before all the drug is released. The novel, leaky

enteric compositions disclosed herein release drug slowly while in the stomach and then release all or most of the remainder of the drug in the upper small intestine before the composition passes the absorption window. This allows prolonged drug absorption and is beneficial even if bioavailability is reduced.

EXAMPLE 7

Hydrochlorthiazide, which is known to have an absorption window in the intestinal tract and has limited absorption related to limitations on dissolution (Dressman JB, Fleisher D, Amidon GL., *Physicochemical model for dose-dependent drug absorption*, **J Pharm Sci** 1984; 73(9): 1274-9.) was prepared as a leaky enteric composition according to the present invention. Such dosage form was prepared by spray-layering drug on nonpareil sugar beads and then applying an enteric coating formulated to allow drug to be released in gastric fluid at programmed rates. Enteric coating typically would prevent drug release in gastric fluid. But hydroxyproply methylcellulose (HPMC) was used in this example, which allowed drug leakage into gastric fluid and then provided rapid release of remaining drug from the formulation when exposed to intestinal fluid

The formulations were prepared and applied on sugar beads as outlined in Example 2.

Table 13

Leaky Enteric-Coated Beads Formulations of Hydrochlorothiazide

Formulations	**Composition of Leaky Enteric-Coating Polymer**	Amount of Leaky Enteric-Coating Polymer (% of Drug-Loaded Beads) [c]
HCTZ1	EUD [a] with 20% HPMC [b]	**7.5%**
HCTZ2	EUD with 5% HPMC	**5%**
HCTZ3	EUD with 5% HPMC	**7.5%**
HCTZ4	**EUD with 5% HPMC**	**10%**

[a] Eudragit® L30D-55 (EUD). Working titles of coating formulation. Final coating formulation given below.

[b] Hydroxypropyl methylcellulose (HPMC)

[c] Weight gain of beads coated with the coating material after drying the coated beads.

Table 14

Compositions of Leaky Enteric-Coating of Hydrochlorothiazide Formulations

Ingredients (Solid Composition)	Formulations (% of Total Coating Materials)			
	HCTZ1	**HCTZ 2**	**HCTZ 3**	**HCTZ 4**
Eudragit® L30D-55	58.8	64.5	64.5	**64.5**
Talcum	29.4	32.3	32.3	**32.3**
HPMC E5	**11.8**	**3.2**	**3.2**	**3.2**

Table 15

Hydrochlorothiazide loading solution

Ingredient	Amount
Hydrochlorothiazide	**5.0 g**
PVP K-30	**3.0 g**
Deionized water	**30.0 ml**
95% Ethanol	**500.0 ml**

Accurately weighed hydrochlorothiazide was dissolved in 500 ml of ethanol (solution may be warmed to facilitate the dissolution). PVP K-30 was dispersed in 30 ml of deionized water before being added to hydrochlorothiazide solution and well mixed.

Table 16

Eudragit® L30D-55 with 5% HPMC dispersion

Ingredient	Amount
Eudragit® L30D-55	**33.3 g**
Triethyl citrate	**1.0 g**
Talcum	**5.0 g**
HPMC E5	**0.5** [a]
Deionized water	**115.0**

Accurately weighed HPMC E5 was dispersed in approximately 15 ml of hot deionized water. Fifteen (15) ml of cool deionized water were added to the well-dispersed HPMC and the solution was stirred until clear. Talcum was dispersed in the remaining deionized water. Talcum dispersion was added to HPMC solution and kept stirring. Eudragit® L30D-55 was

accurately weighed into a beaker. Triethyl citrate was added to Eudragit® suspension and gently mixed. The HPMC and talcum dispersion was then added into Eudragit® mixture and gently mixed. This mixture was kept gently stirring. The amount of HPMC used in studied formulations was calculated as a percentage of Eudragit® polymer solid (Eudragit® polymer suspension contains 30% polymer solids.)

Dissolution results are shown in the following FIG. 14, which provides percent drug release over time for hydrochlorothiazide as a leaky, enteric coated dosage formulation.

FIG. 14 clearly shows the leaky enteric composition released therapeutic agent into gastric fluid at a programmed rate depending on the new composition used, and then rapidly released the remainder of the therapeutic agent after transfer into intestinal fluid. It is generally preferred that at least 10%, and in more preferred embodiments that at least 20% therapeutic agent, is released in gastric fluid. It is generally preferred that 75% or more therapeutic agent not released in the gastric fluid be released in one hour or less following transfer into intestinal fluid for therapeutic agents with a window of absorption in the duodenum. It is a more preferred embodiment that 75% or more of therapeutic agent not released in the gastric fluid be released in one-half hour or less following transfer into intestinal fluid for therapeutic agents with a window of absorption in the duodenum.

EXAMPLE 8

This Example 8, in combination with Example 6, provides pharmacokinetic effects on a drug with an absorption window in the upper portion of the intestine when formulated as a leaky enteric formulation with programmed drug release in gastric fluid compared to an immediate release dosage form of the drug. For data points and lines in FIG. 15, pharmacokinetic data for hydrochlorthiazide were obtained from Patel, *et. al*, J. Pharm. Sci., Bioavailability of hydrochlorothiazide from tablets and suspensions, 1984, 73(3),359-361. Data points from the immediate-release dosage form reflect administration to fasted subjects and bioavailability set at 50.3% for the immediate-release dosage form and set at 100% from the new, leaky enteric formulation. Drug formulated into a new, leaky enteric composition is delivered more slowly and in a more prolonged manner into the intestine than occurs from an immediate release dosage form as taught herein. Bioavailability may not increase as much as shown in FIG. 15 for hydrochlorthiazide or other drugs, but the resulting change in drug concentration profile in the body is beneficial as taught previously. Increased bioavailability from the new enteric composition is an additional benefit when it occurs. Since data points in FIG. 15 represent fasting subjects receiving an immediate-release dosage form of hydrochlothiazide it is expected that the bioavailability will be

increased in the presence of food and also may be increased from the leaky enteric composition that provides programmed initial drug release in the stomach and then rapid release when transferred into the upper small intestine. Data in FIG. 15 allow presentation of the maximum possible increase in bioavailability for hydrochlorthiazide.

Parameters for stomach transit times in both the fed and fasted conditions are presented in Example 3. Drug release patterns from the new, leaky enteric formulation are approximated as first-order release profiles with k vales of 0.144 hr^{-1}, 0.347 hr^{-1}, or 0.693 hr^{-1} as shown in FIG. 15.

These data for hydrochlorthiazide in FIG. 15 are generated as described in Example 4. While the drug was released in a first-order fashion from the new compositions as described earlier and shown by the rate constants in FIG. 15, the present invention anticipates all types of drug-release mechanisims that provide programmed release in gastric fluid. It can be seen, for example, that a first order release mechanism releases 25% of the active ingredient in gastric fluid in two hours when the rate constant for release is 0.144hr^{-1} Likewise, drug release in gastric fluid is either 50% or 75% in two hours when the first-order release rate of active ingredient in gastric fluid is 0.347 $^{-1}$ or 0.693 $^{-1}$, respectively. It generally is preferred that the leaky enteric compositions release between 10% or more and 90% of the active ingredient in gastric fluid in two hours, independent of release mechanism, and more preferred that the leaky enteric compositions release between 20% or more and 90% of the active ingredient in gastric fluid in two hours, independent of release mechanism, and even more preferred that the leaky enteric compositions release between 10% or more and 35% of the active ingredient in gastric fluid in two hours, independent of release mechanism.

FIG. 15 shows higher drug concentrations in plasma for this drug with an absorption window as expected due to higher bioavailbility, and very substantial extension of drug concentrations in the body versus time compared to the known formulation of hydrochlorthiazide, even in fasted patients. Drug concentrations versus time are even more extended in fed patients. Leaky enteric composition data do not show the usually undesirable but required delay in drug absorption known to occur with traditional enteric coatings, which leads enteric compositions known prior to the present invention to be classified as delayed-release drug products by the FDA. Even if bioavailability is not increased, the leaky enteric composition still releases drug in gastric fluid, thus necessarily avoiding the type of delay that occurs when drug is not released until the composition has completely left the stomach and gastric fluid. Generally, adding a portion of immediate-release drug formulation to the enteric composition is not required since the leaky enteric

release formulation already quickly provides drug concentrations in the body. But, if desired, the enteric composition can also comprise some immediate release drug. For example, in the beads of this example some immediate release drug can be over-coated or spray-layered on top of the enteric composition for even more rapid dissolution or burst effect of some drug, or included in uncoated form. In some cases, the drug may be incorporated directly into the enteric coating material, which would allow more rapid release of some drug. This would not, of course, satisfy the usual requirements for an enteric composition in that the drug incorporated into the coat now will be released into gastric fluid rather than being protected from gastric fluid, thereby meeting a key objective of the current invention.

This example 8, in combination with other examples, illustrates a novel enteric composition formulation with unexpected properties for a drug with a window of absorption that results in sustained drug input into the body without substantial delay or lag time for drug absorption, and increased drug efficacy for the same drug dose compared to traditional, immediate-release formulations of the drug. Example 6 illustrates that there are substantial, improved pharmacodynamics and reduced side effect benefits that result from providing more prolonged input of this absorption window drug using the disclosed formulations of the present invention. These effects occur even if bioavailability from the new dosage form is equivalent to bioavailability from the IR formulation. The combination of desirable effects was previously thought mutually exclusive given the known physiological absorption window and drug characteristics. The unique outcomes are made possible by the embodiments of the new composition disclosed herein that provides drug input in a programmed fashion due to programmed drug release in gastric fluid while the formulation is retained in the stomach, followed by rapid release of any remaining drug in the formulation when the formulation enters the intestine.

EXAMPLE 9

Ranititdine is well absorbed if introduced as an immediate-release formulation into the stomach or into the upper small intestine, but is poorly absorbed if introduced into the colon. Advantages and difficulties of formulating ranititdine as a traditional, sustained-release formulation are discussed in U.S. Patent No. 5,407,687.

The general process for making and preparing the enteric composition of ranitidine that releases drug in gastric fluid was according to Example 2. Specifics for ranitidine are given below.

Table 17

Leaky Enteric-Coated Beads Formulations of Ranitidine Hydrochloride

Formulations	**Composition of Leaky Enteric-Coating Polymer**	Amount of Leaky Enteric-Coating Polymer (% of Drug-Loaded Beads) [b]
RTD1	EUD [a] with 33% lactose	**7.5%**
RTD2	EUD with 33% lactose	**10%**
RTD3	EUD with 33% lactose	**12.5%**
RTD4	EUD with 33% lactose	**15%**
RTD5	EUD with 50% lactose	**10%**
RTD6	EUD with 50% lactose	**12.5%**
RTD7	**EUD with 50% lactose**	**15%**

[a] Eudragit® L30D-55 (EUD)

[b] Amount of leaky enteric-coating polymer is presented as an amount of Eudragit® L30D-55 polymer solid (in leaky enteric-coat layer) coated onto drug-loaded beads. Eudragit® L30D-55 suspension contains 30% polymer solid.

Table 18

Compositions of Leaky, Enteric-Coated Layer of Ranitidine Hydrochloride Formulations

Ingredients (Solid Composition)	Formulations (% of Total Coating Materials)						
	RTD1	**RTD2**	**RTD3**	**RTD4**	**RTD5**	**RTD6**	**RTD7**
Eudragit® L30D-55	54.5	54.5	54.5	54.5	50.0	50.0	**50.0**
Talcum	27.3	27.3	27.3	27.3	25.0	25.0	**25.0**
Lactose	**18.2**	**18.2**	**18.2**	**18.2**	**25.0**	**25.0**	**25.0**

Table 19

Ranitidine Loading Solution

Ingredient	Amount
Ranitidine hydrochloride [a]	**7.5 g**
PVP K-30	**2.0 g**
Hydroxypropyl cellulose (HPC) EXF	**1.0 g**
Deionized water	**60.0 ml**

Accurately weighed HPC EXF was dispersed in 30 ml of hot deionized water. Cool deionized water was added to the well-dispersed HPC and the solution was stirred until clear. PVP K-30 was then added and well mixed. Finally, ranitidine was added to the solution and stirred until dissolved.

Table 20

Eudragit® L30D-55 with 33% lactose dispersion

Eudragit® L30D-55	50.0	g
Triethyl citrate	1.5	g
Talcum	7.5	g
Lactose	5.0 [a]	g
Deionized water	100.0 [b]	ml

Accurately weighed lactose was dissolved in 50 ml of deionized water (solution may be warmed to facilitate the dissolution). Talcum was dispersed in the remaining deionized water. Talcum dispersion was added to lactose solution and kept stirring. Eudragit® L30D-55 was accurately weighed into a beaker. Triethyl citrate was added to Eudragit® suspension and gently mixed. The lactose and talcum dispersion was then added into Eudragit® mixture and gently mixed with continuous stirring. The amount of lactose used in studied formulations was calculated as percentage of Eudragit® polymer solid (Eudragit® polymer suspension contains 30% polymer solid). The volume of deionized water varied as needed to sufficiently dissolve lactose (generally, one part of lactose can be comfortably dissolved in 10 part of water).

FIGs. 16-18 illustrate drug release from some embodiments of the present composition in dissolution testing. FIGs. 16-18 in combination with other figures herein show that formulation of the presently disclosed, novel, leaky enteric compositions can be

easily controlled by one of ordinary skill in the art to obtain a variety of useful drug dissolution patterns in gastric fluid ranging from zero-order through mixed-order and first-order dissolution kinetics. Then, drug remaining in the composition when it leaves the gastric fluid is quickly released after exposure of the composition to intestinal fluid. In many cases this release from the composition after exposure to intestinal fluid is more rapid than occurs with known, effective enteric compositions. This likely is because the new compositions are "weakened" by the inherent structure that results from the combination of the composition formulation and exposure to gastric fluid.

EXAMPLE 10

This example shows prolonged drug concentrations using embodiments of the novel drug dosage formulations disclosed herein with equivalent bioavailability to ranitidine, another drug with an absorption window. IR data points are in fasted patients from the FDA website (Drugs@FDA, ANDA#074-467 Geneva Pharmaceuticals) for the drug product Zantac (ranitidine).

These data for ranitidine in FIG. 19 are generated as described in Example 4. While the drug was released in a first-order fashion from the new compositions as described earlier and shown by the rate constants in the FIG. 15 footnote, this invention anticipates all types of drug release mechanisims that provide programmed release in gastric fluid. It can be seen, for example, that a first-order release mechanism releases 25% of the active ingredient in gastric fluid in two hours when the rate constant for release is 0.144 hr^{-1} Likewise, the drug release in gastric fluid is either 50% or 75% in two hours when the first-order release rate of active ingredient in gastric fluid is 0.347 hr^{-1} or 0.693 hr^{-1}, respectively.

Data from FIG. 19 are for equal bioavailability from all formulations. It is known that average stomach emptying rates vary from study to study and individual to individual and have been reported to vary from at least as much as $k_{em} = 1.4\ hr^{-1}$ to $k_{em} = 0.5\ hr^{-1}$. Table 11 shows that k_{em} was assumed to be 1.38 hr^{-1} for other drug concentration vs. time data for fasting subjects but for the data in FIG. 19, $k_{em} = 0.5\ hr^{-1}$ was used. FIG. 19 shows slower and more prolonged drug input from leaky enteric compositions with more sustained drug concentrations in the body than from an immediate-release formulation for ranitidine in both fasted (when $k_{em} = 0.5\ hr^{-1}$) and fed states. When $k_{em} = 1.4\ hr^{-1}$ in the fasted state for the leaky enteric coated compositions of FIG. 19, then the drug concentrations vs. time curves are almost identical for all three Kr values, and are quite close to the curve for the IR dosage form. Thus, it can be seen that for some individuals, depending on stomach emptying rate, the new leaky enteric compositions will be more beneficial than for others. It

is also anticipated that additional ingredients that decrease k_{em} (such as oils or fats or drugs as non-limiting examples) will be useful ingredients in the leaky enteric compositions. Further, some drugs with an absorption window also undergo first-pass metabolism as do some non-absorption window drugs. Thus, providing a slower input from the new leaky enteric compositions may result in either increased bioavailability, decreased bioavailability, or no change in bioavailability depending on what effects dominate for the specific drug. Even in the case of decreased bioavailability the leaky enteric compositions are beneficial because of other changes in the drug concentration versus time delivery profile, such as decreased maximum drug concentration in the plasma or sustaining drug input over time when compared to immediate release compositions.

Drug peak concentrations, as expected and generally desirable, are lower when drug input is slower and more sustained, compared to more rapid and less sustained drug input. U.S. Patent No. 5,407,687 teaches the need for, but the difficulties associated with preparing, a sustained-release formulation to produce more prolonged drug input compositions with more sustained drug concentrations in the body than from an immediate-release formulation for ranitidine.

The solution provided by U.S. Patent No. 5,407,687 is to produce a laminated, bi-layer tablet containing the drug in a fixed ratio of drug between one immediate-release drug layer and a second, sustained-release drug layer. The fixed ratio, in view of the peculiar properties of ranitidine, is required to obtain sustained drug concentrations in the body (not obtained by known systems).

That is, these (known) systems do not allow for the balance that must be made between the amount of drug immediately released and the amount of time over which the remaining drug in the sustained release (SR) portion is released. For example, if too much ranitidine is present in the immediate release (IR) portion, the result is essentially the same as that obtained with the commercially available tablets, i.e. an immediate release formulation. Conversely, if too little ranitidine is present in the immediate release portion, the resulting formulation exhibits poor bioavailability.

These "peculiar properties" result because ranitidine has site specific absorption, and is known to produce a double-peak in some concentration versus time curves. The double peak is not readily apparent in the fasting data in human subjects shown above and is not present in the new formulations data that did not include the possibility of multiple

windows of absorption, absorption at different rates from different sites, or biliary recycling, all of which have been proposed and challenged in the literature.

While the equipment to make bi-layer tablets is well known in the art the process is not without substantial problems. Tablets often delaminate and production times and complexities are extended due to the multiple steps and multiple formulations involved. These problems are avoided by disclosed embodiments of the present invention, which has the distinct added advantage of not requiring multiple formulations or combinations in fixed amounts of IR and SR drug. While IR drug can be added to embodiments of the compositions of the present invention, this is not required because the leaky enteric composition can be formulated to either begin drug release immediately or after a short lag-time following consumption by a patient. And, the problem of poor bioavailability that occurs in SR formulations that entrap drug too long is avoided because drug is rapidly released upon entering the intestine with disclosed embodiments of the compositions of the present invention. For some drugs like ranitidine, that are well absorbed when introduced either into the duodenum or jejunum, release from the leaky enteric composition is formulated to provide programmed release in gastric fluid followed by a release pattern that is sustained over two to four hours, or even longer, in intestinal fluid, much like the sustained release of bilayer tablet of U.S. Patent 5,407,687 provides sustained release in intestinal fluid. Or, embodiments of the leaky, enteric-coated drug formulations may be combined with sustained-release formulations that provide drug over a release period of up to 8 hours in intestinal fluid. Distinct advantages of the instant invention are that both bilayer tablets and fixed ratio of IR drug to sustained input amounts of drug can be avoided.

Applying superposition principle to data in FIG. 19 illustrates that if the dose is increased, such as by doubling, for one example, the differences in drug concentration peak values and values at prolonged times, such as 6, 8, 10, or 12 hours, for example, between the IR formulation and the new compositions will increase. This is because drug absorption is not sustained from the IR composition but is sustained from the new compositions. Thus, the frequency of dosing can be reduced, which is highly desirable but not known with traditional enteric compositions.

In one preferred embodiment, leaky enteric compositions are provided as compressed tablets. In this case particulates, such as beads or granules, are coated with enteric composition that may or may not release drug in gastric fluid if administered without compaction, but which do release drug in gastric fluid when administered as compacted tablets. This is because the compaction forces can convert non-leaky enteric compositions into leaky enteric compositions. The enteric composition particles may be mixed with usual

tabletting excipients for compaction, or in a more preferred embodiment the enteric composition particles are coated or "layered" with tabletting excipients that are beneficial in promoting tablet disintegration in gastric fluid and tablet compaction. Other known excipients also are anticipated, such as lubricants, colors, flavors, surfactants, and all other types of appropriate excipients for making pharmaceutical formulations. These excipients and their uses are well known in the art.

Traditional, enteric-coated particulates, such as beads, granules or powders, which do not release drug in gastric fluid can be treated by chemical, physical, or mechanical methods to convert the composition into a leaky enteric composition. A few examples of treatments possible includes use of solvents, such as porogenic solvents that provide fluid ingress pores upon removal from the formulation, thermal methods, including heat-freeze cycle(s), granulation equipment, and application of pressure, such as with roller and other mills or tablet machines. Compositions that do release drug in gastric fluid can be filled into capsules for oral administration or compacted into tablets. Chewable tables are anticipated wherein mechanical forces that convert some or all of a non-leaky enteric composition into a leaky enteric composition includes the chewing process.

EXAMPLE 11

U.S. Patent No. 6,399,086 teaches that β-lactam antibiotics have a specific absorption site in the small intestine. The '086 patent also teaches that there is a need for a dosage form that provides a burst effect by releasing about 50% of the drug within 3 to 4 hours of administration, and release of the remainder of the drug at a controlled rate. Such dosage form may comprise a β-lactamase inhibitor. AUC or bioavailability of the β-lactam antibiotic was significantly lower for the sustained release formulation, probably because the drug was trapped in the sustained-release matrix when passing the absorption window. In fact, U.S. Patent No. 6,399,086 states that:

> In principle, extending the residence time of the antibiotic drug in the GI tract by the sustained release formulation may increase, in theory, the GI adverse effects associated with amoxicillin therapy. Obviously, such phenomenon of increased risk of side effects is a limitation for the development of amoxicillin controlled-release formulations. However, in the formulations of the present invention, the unabsorbed portion of the dose that had a prolonged transit time in the GI tract is captured within the matrix formulation and is not available to interact with the intestine epithelia and/or flora, thus eliminating the danger of exposing the patient treated with the formulations of the present invention to said adverse side effects.

Thus, the drug is likely to cause less undesirable gastrointestinal side effects because it is trapped inside the dosage form and not available. And, if the drug is released after passing the absorption window then it is not only not available for the patient but it is then available to be released lower in the intestinal tract to cause undesirable gastrointestinal side effects. This decrease in bioavailability and potential increase in side effects is highly undesirable.

PCT WO 94/27557 discloses thermal infusion wax matrix formulations of amoxicillin and clavulanate, reports to provide prolonged release of both compounds, and teaches the difficulty and need of formulation techniques to provide prolonged input for both drugs. Only 19% of the amoxicillin is released in 6 hours from the prolonged release formulation. Thus, bioavailability is expected to be very low, as reported in U.S. Patent No. 6,399,086, since the drug will be entrapped in the wax matrix when passing the absorption window. Although the clavulanate is released faster, it too can be trapped in the wax matrix and pass the absorption window in those cases when the tablet is taken on an empty stomach only a short time before arrival of the house-keeper wave.

Thus there remains a need for a composition that will provide sustained input of β-lactam antibiotics without entrapping the drug such that the bioavailability is significantly reduced, and without increasing the potential for making gastrointestinal side effects worse than occurs with immediate-release dosage forms of these drugs. An increase in bioavailability relative to immediate release dosage forms is not required to obtain useful benefits in patient care. A change in drug input pattern that extends useful drug concentrations in the body relative to immediate-release dosage forms can reduce dosing frequency, and can improve patient care even if frequency of dosing is not reduced. New leaky enteric compositions disclosed herein are particularly useful for the types of therapeutic agents disclosed in U. S. Patent No. 6,399,086 and PCT WO 94/27557.

For one example, leaky enteric compositions are particularly suited to deliver combinations of β-lactam antibiotics or other combinations of drugs where the effect is synergistic and influenced by the pharmacodynamic/pharmacokinetic effects of one or both drugs. Using amoxicillin and clavulanic acid as examples, clavulanate has only a small antibiotic effect compared to the antibiotic effect of amoxicillin. But, the clavulanate greatly increases the effect of the amoxicillin by inhibiting an enzyme that degrades the amoxicillin. Without the clavulanate the "time above MIC" for amoxicillin, which correlates with antibiotic effect, is decreased due to enzymatic degradation of the amoxicillin. Thus it is desirable for clavulanate to be present in the body at the same time as the amoxicillin. And, based on understanding that some time is needed for the clavulanate

to interact with the enzyme, it is suggested that the most preferred case is when some clavulanate is present at least a short time of 15 minutes or even more before the amoxicillin molecules are present to have an even greater effect.

Both amoxicillin and clavulanate are known to produce adverse gastrointestinal disorders. It is thus preferable that both molecules be absorbed as high in the intestinal tract as possible in order to minimize drug travel distance in the intestines and thereby minimize or prevent drug molecules from exerting their undesirable effects. And, the absorption window for these drugs is in the upper small intestine. Thus, as discussed elsewhere herein, the novel, leaky enteric compositions are ideally suited for delivery of these drugs.

Drug combinations can be separately prepared as individual leaky enteric compositions with individual release rates in gastric fluids, and then combined in any desired ratios. One drug may be released more quickly than the other and therefore be present at a desired site, interacting with an enzyme for one example, before the other drug arrives. Some or none of each drug may be available as IR drug. By way of further illustration, clavulanate is now prepared as any desired salt or as the free molecule in a leaky, enteric-coated bead or other particulate formulation with a controlled dissolution of 80% over 5 hours in gastric fluid. Some IR clavulanate may also be present as part of the 80% or in addition to the 80% to "jump start" drug absorption if desired. Amoxicillin is now prepared separately from the clavulanate as any desired salt or as the free molecule in a different, multiparticulate, leaky enteric-coated bead formulation with a slower overall controlled dissolution of 80% over 7 hours in gastric fluid. Some IR amoxicillin also may be present as part of the 70% or in addition to the 70% to "jump start" drug absorption if desired. In this case there is no additional IR form of drug present. The separately prepared amoxicillin and clavulanate beads are combined in the desired ratio and placed in a gelatin or other capsule and administered to a subject in need of such treatment. Release of the drugs is in a programmed fashion while the beads are in the stomach in gastric fluid and then release of any remaining drug(s) is rapid once the beads are transported into the intestinal fluid, thereby insuring that drug is not entrapped in the composition and unavailable when passing the absorption window. At the same time this embodiment prolonges drug input and drug concentrations in the body compared to immediate-release drug formulations, and demonstrates more rapid absorption of clavulanate than amoxicillin. It is readily understood from the disclosure that this is only one example of combinations of drugs, formulations possible, drug release patterns, and flexibility available to one of ordinary skill in the art that makes it readily possible to provide any ratio of drug combinations and release rates in gastric fluid over any desirable times for any different

drug combinations, as desired. And, of course it is clear that drug combinations also can be formulated together in a single, multiparticulate, such as a bead or granule when desired. Preparation of separate bead or granule compositions is not required but is presented as an example of the flexibility of the invention.

Disclosed embodiments of the present invention have been described with reference to particular features of working or prophetic embodiments. The scope of the invention is not limited to these particular features.

I CLAIM:

1. A pharmaceutical composition comprising at least one active ingredient in a core and an enteric coating on the core, the enteric coating further comprising a gastric fluid channeling agent.

2. The composition according to claim 1 where at least 10% by mass of the active ingredient is released in gastric fluid.

3. The composition according to claim 1 where the active ingredient has a window of absorption.

4. The composition according to claim 3 where the active ingredient is selected from the group consisting of therapeutic nucleic acids or amino acid sequences, nucleic acids or amino acid derivatives, peptidomimetic drugs, antibiotics, therapeutic ions, vitamins, bronchodilators, anti-gout agents, anti-hypertensive agents, diuretic agents, anti-hyperlipidemic agents or ACE inhibitors, drugs intended for local treatment of the gastrointestinal tract, including anti-tumor agents, histamine (H2) blockers, bismuth salts, synthetic prostaglandins or antibiotic agents, drugs that degrade in the colon, for example metoprolol, formulations useful for treating gastrointestinal associated disorders selected from peptic ulcer, nonulcer dyspepsia, Zollinger-Ellison syndrome, gastritis, duodenitis and the associated ulcerative lesions, stomach or duodenum neoplasms, prazosin, ketanserin, guanabenz acetate, captopril, captopril hydrochloride, enalapril, enalapril maleate, lysinopril, hydralazide, methyldopa, methyldopa hydrochloride, levodopa, carbidopa, benserazide, amlodipine, nitrendipine, nifedipine, nicardipine, verapamil, acyclovir, inosine, pranobex, tribavirine, vidarabine, zidovudine, AZT, active ingredients that exert a medicinal action at the gastric level, including aluminum hydroxide, magnesium carbonate, magnesium oxide, sucralphate, sodium carbenoxolone, pirenzepin, loperamide, cimetidine, ranitidine, famotidine, misoprostol, omeprazol, and combinations thereof

5. The composition according to claim 1 providing an active ingredient release profile where at least 10% active ingredient by mass is released in gastric fluid, followed by at least 75% release of remaining active ingredient in one hour or less upon contacting intestinal fluid.

6. The composition according to claim 1 where the active ingredient has a window of absorption, and where at least 10% active ingredient by mass is released in gastric fluid, followed by at least 75% release of remaining active ingredient in 30 minutes or less upon contacting intestinal fluid.

7. The composition according to claim 1 where active ingredient release upon contacting gastric fluid is zero order, mixed order or first order, followed by substantially immediate release when remaining composition contacts intestinal fluid.

8. The composition according to claim 1 where the gastric fluid channeling agent is hydrophilic.

9. The composition according to claim 8 where the gastric fluid channeling agent is a sugar.

10. The composition according to claim 1 where the gastric fluid channeling agent is hydrophobic.

11. The composition of claim 10 where the hydrophobic material is selected from the group consisting of talc, magnesium salts, silicon dioxide, hydrocarbons, and combinations thereof.

12. The composition according to claim 1 where the enteric coating has a thickness of 25 μm or less.

13. The composition according to claim 1 where the enteric coating has a thickness of 20 μm or less.

14. The composition according to claim 1 comprising a solid composition.

15. The composition according to claim 1 formulated for oral administration.

16. The composition according to claim 1 further comprising a second formulation designed to provide an active ingredient release profile different from the pharmaceutical composition.

17. The composition according to claim 16 where the second formulation provides immediate release in gastric fluid.

18. The composition according to claim 16 where the active ingredient is amoxicillin or a biologically active salt thereof.

19. The composition according to claim 18 where the active ingredient of the second formulation is clavulanate or a biologically active salt thereof.

20. The composition according to claim 16 where the two formulations are placed in a single capsule or tablet for co-administration.

21. The composition according to claim 1 where the active ingredient has a window of absorption and the composition provides an active ingredient release profile where at least 10% active ingredient by mass is released in gastric fluid, followed by at least 75% release of remaining active ingredient in one hour or less upon contacting intestinal fluid.

22. The composition according to claim 1 further comprising an admixture or an overcoat of an immediate release dosage form.

23. The composition according to claim 1 comprising an active ingredient selected from the group consisting of AIDS adjunct agents, alcohol abuse preparations, Alzheimer's disease management agents, amyotrophic lateral sclerosis active ingredient agents, analgesics, anesthetics, antacids, antiarythmics, antibiotics, anticonvulsants, antidepressants, antidiabetic agents, antiemetics, antidotes, antifibrosis active ingredient agents, antifungals, antihistamines, antihypertensives, anti-infective agents, antimicrobials, antineoplastics, antipsychotics, antiparkinsonian agents, antirheumatic agents, appetite stimulants, appetite suppressants, biological response modifiers, biologicals, blood modifiers, bone metabolism regulators, cardioprotective agents, cardiovascular agents, central nervous system stimulants, cholinesterase inhibitors, contraceptives, cystic fibrosis management agents, deodorants, diagnostics, dietary supplements, diuretics, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction active ingredients, fatty acids, gastrointestinal agents, Gaucher's disease management agents, gout

preparations, homeopathic remedys, hormones, hypercalcemia management agents, hypnotics, hypocalcemia management agents, immunomodulators, immunosuppressives, ion exchange resins, levocarnitine deficiency management agents, mast cell stabilizers, migraine preparations, motion sickness products, multiple sclerosis management agents, muscle relaxants, narcotic detoxification agents, narcotics, nucleoside analogs, non-steroidal anti-inflammatory drugs, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, phosphate binders, porphyria agents, psychoactive ingredient agents, radio-opaque agents, psychotropics, sclerosing agents, sedatives, sickle cell anemia management agents, smoking cessation aids, steroids, stimulants, sympatholytics, sympathomimetics, Tourette's syndrome agents, tremor preparations, urinary tract agents, vaginal preparations, vasodilators, vertigo agents, weight loss agents, Wilson's disease management agents, and mixtures thereof.

24. The composition according to claim 1 where the active ingredient is selected from the group consisting of abacavir sulfate, abacavir sulfate/ lamivudine/zidovudine, acetazolamide, acyclovir, albendazole, albuterol, aldactone, allopurinol, amoxicillin, amoxicillin/clavulanate potassium, amprenavir, atovaquone, atovaquone and proguanil hydrochloride, atracurium besylate, beclomethasone dipropionate, berlactone betamethasone valerate, bupropion hydrochloride, bupropion hydrochloride, carvedilol, caspofungin acetate, cefazolin, ceftazidime, cefuroxime , chlorambucil, chlorpromazine, cimetidine, cimetidine hydrochloride, cisatracurium besilate, clobetasol propionate, co-trimoxazole, colfosceril palmitate, dextroamphetamie sulfate, digoxin, enalapril maleate, epoprostenol, esomepraxole magnesium, fluticasone propionate, furosemide, hydrochlorothiazide, hydrochlorothiazide/triamterene, lamivudine, lamotrigine, lithium carbonate, losartan potassium, melphalan, mercaptopurine, mesalazine, mupirocin calcium cream, nabumetone, naratriptan, omeprazole, ondansetron hydrochloride, ovine, oxiconazole nitrate, paroxetine hydrochloride, prochlorperazine, procyclidine hydrochloride, pyrimethamine, ranitidine bismuth citrate, ranitidine hydrochloride, rofecoxib, ropinirole hydrochloride, rosiglitazone maleate, salmeterol xinafoate, salmeterol, fluticasone propionate, sterile ticarcillin disodium / clavulanate potassium, simvastatin, spironolactone, succinylcholine chloride, sumatriptan, thioguanine, tirofiban HCI, topotecan hydrochloride, tranylcypromine sulfate, trifluoperazine hydrochloride, valacyclovir hydrochloride, vinorelbine, zanamivir, zidovudine, zidovudine or lamivudine, or mixtures thereof.

25. The composition according to claim 1 further coated by gelatin or placed inside a gelatin capsule or a tablet.

26. The composition according to claim 1 which increases active ingredient bioavailability at least 20% relative to an immediate release control or a sustained-release control that does not include enteric material.

27. The composition according to claim 1 providing substantially equivalent bioavailability but a reduced active ingredient excretion rate relative to an immediate release control formulation.

28. The composition according to claim 1 providing prolonged drug concentrations for an active ingredient or active ingredients having an absorption window relative to an immediate release or a sustained release control.

29. The composition according to claim 1 where the enteric material is selected from the group consisting of cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), hydroxypropylmethyl cellulose, hydroxypropyl methylcellulose acetate succinate (HPMCAS), cellulose acetate trimellitate, hydroxypropyl methylcellulose succinate, carboxymethyl cellulose, carboxymethyl ethyl cellulose, cellulose acetate phthalate, cellulose acetate succinate, cellulose acetate hexahydrophthalate, cellulose propionate phthalate, cellulose acetate maleate, cellulose acetate butyrate, cellulose acetate propionate, copolymer of methylmethacrylic acid and methyl methacrylate, copolymer of methyl acrylate, methylmethacrylate and methacrylic acid, copolymer of methylvinyl ether and maleic anhydride (Gantrez ES series), ethyl methyacrylate-methylmethacrylate-chlorotrimethylammonium ethyl acrylate copolymer, polyvinyl acetate phthalate, zein, shellac, copal collophorium, Eudragit L30D55, Eudragit FS30D, Eudragit L100, Eudragit S100, Kollicoat EMM30D, Estacryl 30D, Coateric, Aquateric, and combinations of such materials.

30. The composition according to claim 1 providing controlled *in vitro* gastric release, followed by pulsatile *in vitro* intestinal release.

31. The composition according to claim 1 comprising plural active ingredients.

32. A pharmaceutical composition that provides programmed release of active ingredient, the composition comprising at least one active ingredient, excluding amoxicillin and bisacodyl, substantially homogeneously admixed with at least one enteric material comprising a gastric fluid channeling agent.

33. The composition according to claim 32 where at least 10% by mass of the active ingredient is released in gastric fluid.

34. The composition according to claim 32 where the active ingredient has a window of absorption.

35. The composition according to claim 34 where the active ingredient is selected from the group consisting of therapeutic nucleic acids or amino acid sequences, nucleic acids or amino acid derivatives, peptidomimetic drugs, antibiotics, therapeutic ions, vitamins, bronchodilators, anti-gout agents, anti-hypertensive agents, diuretic agents, anti-hyperlipidemic agents or ACE inhibitors, drugs intended for local treatment of the gastrointestinal tract, including anti-tumor agents, histamine (H2) blockers, bismuth salts, synthetic prostaglandins or antibiotic agents, drugs that degrade in the colon, for example metoprolol, formulations useful for treating gastrointestinal associated disorders selected from peptic ulcer, nonulcer dyspepsia, Zollinger-Ellison syndrome, gastritis, duodenitis and the associated ulcerative lesions, stomach or duodenum neoplasms, prazosin, ketanserin, guanabenz acetate, captopril, captopril hydrochloride, enalapril, enalapril maleate, lysinopril, hydralazide, methyldopa, methyldopa hydrochloride, levodopa, carbidopa, benserazide, amlodipine, nitrendipine, nifedipine, nicardipine, verapamil, acyclovir, inosine, pranobex, tribavirine, vidarabine, zidovudine, AZT, active ingredients that exert a medicinal action at the gastric level, including aluminum hydroxide, magnesium carbonate, magnesium oxide, sucralphate, sodium carbenoxolone, pirenzepin, loperamide, cimetidine, ranitidine, famotidine, misoprostol, omeprazol, and combinations thereof.

36. The composition according to claim 32 providing an active ingredient release profile where at least 10% active ingredient by mass is released in gastric fluid, followed by at least 75% release of remaining active ingredient in one hour or less upon contacting intestinal fluid.

37. The composition according to claim 32 where the active ingredient has a window of absorption, and where at least 10% active ingredient by mass is released in gastric fluid, followed by at least 75% release of remaining active ingredient in 30 minutes or less upon contacting intestinal fluid.

38. The composition according to claim 32 where active ingredient release upon contacting gastric fluid is zero order, mixed order or first order, followed by substantially immediate release when remaining composition contacts intestinal fluid.

39. The composition according to claim 32 where the gastric fluid channeling agent is hydrophilic.

40. The composition according to claim 39 where the gastric fluid channeling agent is a sugar.

41. The composition according to claim 32 where the gastric fluid channeling agent is hydrophobic.

42. The composition of claim 41 where the hydrophobic material is selected from the group consisting of talc, magnesium salts, silicon dioxide, hydrocarbons, and combinations thereof.

43. The composition according to claim 32 comprising a solid composition.

44. The composition according to claim 32 formulated for oral administration.

45. The composition according to claim 32 further comprising a second formulation designed to provide an active ingredient release profile different from the pharmaceutical composition.

46. The composition according to claim 45 where the second formulation provides substantially immediate release in gastric fluid.

47. The composition according to claim 45 where the active ingredient is amoxicillin or a biologically active salt thereof.

48. The composition according to claim 47 where the active ingredient of the second formulation is clavulanate or a biologically active salt thereof.

49. The composition according to claim 45 where the two formulations are placed in a single capsule or tablet for co-administration.

50. The composition according to claim 32 further comprising an admixture or an overcoat of an immediate release dosage form.

51. The composition according to claim 32 comprising an active ingredient selected from the group consisting of AIDS adjunct agents, alcohol abuse preparations, Alzheimer's disease management agents, amyotrophic lateral sclerosis active ingredient agents, analgesics, anesthetics, antacids, antiarythmics, antibiotics, anticonvulsants, antidepressants, antidiabetic agents, antiemetics, antidotes, antifibrosis active ingredient agents, antifungals, antihistamines, antihypertensives, anti-infective agents, antimicrobials, antineoplastics, antipsychotics, antiparkinsonian agents, antirheumatic agents, appetite stimulants, appetite suppressants, biological response modifiers, biologicals, blood modifiers, bone metabolism regulators, cardioprotective agents, cardiovascular agents, central nervous system stimulants, cholinesterase inhibitors, contraceptives, cystic fibrosis management agents, deodorants, diagnostics, dietary supplements, diuretics, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction active ingredients, fatty acids, gastrointestinal agents, Gaucher's disease management agents, gout preparations, homeopathic remedys, hormones, hypercalcemia management agents, hypnotics, hypocalcemia management agents, immunomodulators, immunosuppressives, ion exchange resins, levocarnitine deficiency management agents, mast cell stabilizers, migraine preparations, motion sickness products, multiple sclerosis management agents, muscle relaxants, narcotic detoxification agents, narcotics, nucleoside analogs, non-steroidal anti-inflammatory drugs, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, phosphate binders, porphyria agents, psychoactive ingredient agents, radio-opaque agents, psychotropics, sclerosing agents, sedatives, sickle cell anemia management agents, smoking cessation aids, steroids, stimulants, sympatholytics, sympathomimetics, Tourette's syndrome agents, tremor preparations, urinary tract agents, vaginal preparations, vasodilators, vertigo agents, weight loss agents, Wilson's disease management agents, and mixtures thereof.

52. The composition according to claim 32 where the active ingredient is selected from the group consisting of abacavir sulfate, abacavir sulfate/ lamivudine/zidovudine, acetazolamide, acyclovir, albendazole, albuterol, aldactone, allopurinol, amprenavir, atovaquone, atovaquone and proguanil hydrochloride, atracurium besylate, beclomethasone dipropionate, berlactone betamethasone valerate, bupropion hydrochloride, bupropion hydrochloride, carvedilol, caspofungin acetate, cefazolin, ceftazidime, cefuroxime , chlorambucil, chlorpromazine, cimetidine, cimetidine hydrochloride, cisatracurium besilate, clobetasol propionate, co-trimoxazole, colfosceril palmitate, dextroamphetamie sulfate, digoxin, enalapril maleate, epoprostenol, esomepraxole magnesium, fluticasone propionate, furosemide, hydrochlorothiazide, hydrochlorothiazide/triamterene, lamivudine, lamotrigine, lithium carbonate, losartan potassium, melphalan, mercaptopurine, mesalazine, mupirocin calcium cream, nabumetone, naratriptan, omeprazole, ondansetron hydrochloride, ovine, oxiconazole nitrate, paroxetine hydrochloride, prochlorperazine, procyclidine hydrochloride, pyrimethamine, ranitidine bismuth citrate, ranitidine hydrochloride, rofecoxib, ropinirole hydrochloride, rosiglitazone maleate, salmeterol xinafoate, salmeterol, fluticasone propionate, sterile ticarcillin disodium / clavulanate potassium, simvastatin, spironolactone, succinylcholine chloride, sumatriptan, thioguanine, tirofiban HCI, topotecan hydrochloride, tranylcypromine sulfate, trifluoperazine hydrochloride, valacyclovir hydrochloride, vinorelbine, zanamivir, zidovudine, zidovudine or lamivudine, or mixtures thereof.

53. The composition according to claim 32 further coated by gelatin or placed inside a gelatin capsule or a tablet.

54. The composition according to claim 32 which increases active ingredient bioavailability at least 20% relative to an immediate release control or a sustained-release control that does not include enteric material.

55. The composition according to claim 32 providing substantially equivalent bioavailability but a reduced active ingredient excretion rate relative to an immediate release control formulation.

56. The composition according to claim 32 providing prolonged drug concentrations for active ingredients having an absorption window relative to an immediate release control or a sustained release control.

57. The composition according to claim 32 where the enteric material is selected from the group consisting of cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), hydroxypropylmethyl cellulose, hydroxypropyl methylcellulose acetate succinate (HPMCAS), cellulose acetate trimellitate, hydroxypropyl methylcellulose succinate, carboxymethyl cellulose, carboxymethyl ethyl cellulose, cellulose acetate phthalate, cellulose acetate succinate, cellulose acetate hexahydrophthalate, cellulose propionate phthalate, cellulose acetate maleate, cellulose acetate butyrate, cellulose acetate propionate, copolymer of methylmethacrylic acid and methyl methacrylate, copolymer of methyl acrylate, methylmethacrylate and methacrylic acid, copolymer of methylvinyl ether and maleic anhydride (Gantrez ES series), ethyl methyacrylate-methylmethacrylate-chlorotrimethylammonium ethyl acrylate copolymer, polyvinyl acetate phthalate, zein, shellac, copal collophorium, Eudragit L30D55, Eudragit FS30D, Eudragit L100, Eudragit S100, Kollicoat EMM30D, Estacryl 30D, Coateric, Aquateric, and combinations of such materials.

58. The composition according to claim 32 providing controlled *in vitro* gastric release, followed by pulsatile *in vitro* intestinal release.

59. The composition according to claim 32 comprising plural active ingredients.

60. A pharmaceutical composition that provides programmed release of active ingredient, the composition comprising at least one active ingredient, excluding bisacodyl, substantially homogeneously admixed with at least one enteric material comprising a gastric fluid channeling agent, the gastric fluid channeling agent being present in a weight ratio from greater than zero percent to about 400% of the weight of the enteric material.

61. The composition according to claim 60 where at least 10% by mass of the active ingredient is released in gastric fluid.

62. The composition according to claim 60 where the active ingredient has a window of absorption.

63. The composition according to claim 62 where the active ingredient is selected from the group consisting of therapeutic nucleic acids or amino acid sequences, nucleic acids or amino acid derivatives, peptidomimetic drugs, antibiotics, therapeutic ions, vitamins, bronchodilators, anti-gout agents, anti-hypertensive agents, diuretic agents, anti-hyperlipidemic agents or ACE inhibitors, drugs intended for local treatment of the gastrointestinal tract, including anti-tumor agents, histamine (H2) blockers, bismuth salts, synthetic prostaglandins or antibiotic agents, drugs that degrade in the colon, for example metoprolol, formulations useful for treating gastrointestinal associated disorders selected from peptic ulcer, nonulcer dyspepsia, Zollinger-Ellison syndrome, gastritis, duodenitis and the associated ulcerative lesions, stomach or duodenum neoplasms, prazosin, ketanserin, guanabenz acetate, captopril, captopril hydrochloride, enalapril, enalapril maleate, lysinopril, hydralazide, methyldopa, methyldopa hydrochloride, levodopa, carbidopa, benserazide, amlodipine, nitrendipine, nifedipine, nicardipine, verapamil, acyclovir, inosine, pranobex, tribavirine, vidarabine, zidovudine, AZT, active ingredients that exert a medicinal action at the gastric level, including aluminum hydroxide, magnesium carbonate, magnesium oxide, sucralphate, sodium carbenoxolone, pirenzepin, loperamide, cimetidine, ranitidine, famotidine, misoprostol, omeprazol, and combinations thereof.

64. The composition according to claim 60 providing an active ingredient release profile where at least 10% active ingredient by mass is released in gastric fluid, followed by at least 75% release of remaining active ingredient in one hour or less upon contacting intestinal fluid.

65. The composition according to claim 60 where the active ingredient has a window of absorption, and where at least 10% active ingredient by mass is released in gastric fluid, followed by at least 75% release of remaining active ingredient in 30 minutes or less upon contacting intestinal fluid.

66. The composition according to claim 60 where active ingredient release upon contacting gastric fluid is zero order, mixed order or first order, followed by substantially immediate release when remaining composition contacts intestinal fluid.

67. The composition according to claim 60 where the gastric fluid channeling agent is hydrophilic.

68. The composition according to claim 67 where the gastric fluid channeling agent is a sugar.

69. The composition according to claim 60 where the gastric fluid channeling agent is hydrophobic.

70. The composition of claim 69 where the hydrophobic material is selected from the group consisting of talc, magnesium salts, silicon dioxide, hydrocarbons, and combinations thereof.

71. The composition according to claim 60 comprising a solid composition.

72. The composition according to claim 60 formulated for oral administration.

73. The composition according to claim 60 further comprising a second formulation designed to provide an active ingredient release profile different from the pharmaceutical composition.

74. The composition according to claim 73 where the second formulation provides immediate release in gastric fluid.

75. The composition according to claim 73 where the active ingredient is amoxicillin or a biologically active salt thereof.

76. The composition according to claim 75 where the active ingredient of the second formulation is clavulanate or a biologically active salt thereof.

77. The composition according to claim 74 where the two formulations are placed in a single capsule or tablet for co-administration.

78. The composition according to claim 60 further comprising an admixture or an overcoat of an immediate release dosage form.

79. The composition according to claim 60 comprising an active ingredient selected from the group consisting of AIDS adjunct agents, alcohol abuse preparations, Alzheimer's disease management agents, amyotrophic lateral sclerosis active ingredient agents, analgesics, anesthetics, antacids, antiarythmics, antibiotics, anticonvulsants, antidepressants, antidiabetic agents, antiemetics, antidotes, antifibrosis active ingredient agents, antifungals, antihistamines, antihypertensives, anti-infective agents, antimicrobials, antineoplastics, antipsychotics, antiparkinsonian agents, antirheumatic agents, appetite stimulants, appetite suppressants, biological response modifiers, biologicals, blood modifiers, bone metabolism regulators, cardioprotective agents, cardiovascular agents, central nervous system stimulants, cholinesterase inhibitors, contraceptives, cystic fibrosis management agents, deodorants, diagnostics, dietary supplements, diuretics, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction active ingredients, fatty acids, gastrointestinal agents, Gaucher's disease management agents, gout preparations, homeopathic remedys, hormones, hypercalcemia management agents, hypnotics, hypocalcemia management agents, immunomodulators, immunosuppressives, ion exchange resins, levocarnitine deficiency management agents, mast cell stabilizers, migraine preparations, motion sickness products, multiple sclerosis management agents, muscle relaxants, narcotic detoxification agents, narcotics, nucleoside analogs, non-steroidal anti-inflammatory drugs, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, phosphate binders, porphyria agents, psychoactive ingredient agents, radio-opaque agents, psychotropics, sclerosing agents, sedatives, sickle cell anemia management agents, smoking cessation aids, steroids, stimulants, sympatholytics, sympathomimetics, Tourette's syndrome agents, tremor preparations, urinary tract agents, vaginal preparations, vasodilators, vertigo agents, weight loss agents, Wilson's disease management agents, and mixtures thereof.

80. The composition according to claim 60 where the active ingredient is selected from the group consisting of abacavir sulfate, abacavir sulfate/ lamivudine/zidovudine, acetazolamide, acyclovir, albendazole, albuterol, aldactone, allopurinol, amoxicillin, amoxicillin/clavulanate potassium, amprenavir, atovaquone, atovaquone and proguanil hydrochloride, atracurium besylate, beclomethasone dipropionate, berlactone betamethasone valerate, bupropion hydrochloride, bupropion hydrochloride, carvedilol, caspofungin acetate, cefazolin, ceftazidime, cefuroxime , chlorambucil, chlorpromazine, cimetidine, cimetidine hydrochloride, cisatracurium besilate, clobetasol

propionate, co-trimoxazole, colfosceril palmitate, dextroamphetamie sulfate, digoxin, enalapril maleate, epoprostenol, esomepraxole magnesium, fluticasone propionate, furosemide, hydrochlorothiazide, hydrochlorothiazide/triamterene, lamivudine, lamotrigine, lithium carbonate, losartan potassium, melphalan, mercaptopurine, mesalazine, mupirocin calcium cream, nabumetone, naratriptan, omeprazole, ondansetron hydrochloride, ovine, oxiconazole nitrate, paroxetine hydrochloride, prochlorperazine, procyclidine hydrochloride, pyrimethamine, ranitidine bismuth citrate, ranitidine hydrochloride, rofecoxib, ropinirole hydrochloride, rosiglitazone maleate, salmeterol xinafoate, salmeterol, fluticasone propionate, sterile ticarcillin disodium / clavulanate potassium, simvastatin, spironolactone, succinylcholine chloride, sumatriptan, thioguanine, tirofiban HCI, topotecan hydrochloride, tranylcypromine sulfate, trifluoperazine hydrochloride, valacyclovir hydrochloride, vinorelbine, zanamivir, zidovudine, zidovudine or lamivudine, or mixtures thereof.

81. The composition according to claim 60 further coated by gelatin or placed inside a gelatin capsule or a tablet.

82. The composition according to claim 60 which increases active ingredient bioavailability at least 20% relative to an immediate release control or a sustained-release control that does not include enteric material.

83. The composition according to claim 60 providing substantially equivalent bioavailability but a reduced active ingredient excretion rate relative to an immediate release control formulation.

84. The composition according to claim 60 providing prolonged drug concentrations for active ingredients having an absorption window relative to an immediate release control or a sustained release control.

85. The composition according to claim 60 where the enteric material is selected from the group consisting of cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), hydroxypropylmethyl cellulose, hydroxypropyl methylcellulose acetate succinate (HPMCAS), cellulose acetate trimellitate, hydroxypropyl methylcellulose succinate, carboxymethyl cellulose, carboxymethyl ethyl cellulose, cellulose acetate phthalate, cellulose acetate succinate, cellulose acetate hexahydrophthalate, cellulose propionate

phthalate, cellulose acetate maleate, cellulose acetate butyrate, cellulose acetate propionate, copolymer of methylmethacrylic acid and methyl methacrylate, copolymer of methyl acrylate, methylmethacrylate and methacrylic acid, copolymer of methylvinyl ether and maleic anhydride (Gantrez ES series), ethyl methyacrylate-methylmethacrylate-chlorotrimethylammonium ethyl acrylate copolymer, polyvinyl acetate phthalate, zein, shellac, copal collophorium, Eudragit L30D55, Eudragit FS30D, Eudragit L100, Eudragit S100, Kollicoat EMM30D, Estacryl 30D, Coateric, Aquateric, and combinations of such materials.

86. The composition according to claim 60 providing controlled *in vitro* gastric release, followed by pulsatile *in vitro* intestinal release.

87. The composition according to claim 60 comprising plural active ingredients.

88. A pharmaceutical composition for providing programmed release of active ingredient, the composition comprising at least one active ingredient, excluding amoxicillin and bisacodyl, substantially homogeneously admixed with at least one enteric material for delivering at least a portion of the active ingredient upon contacting gastric fluid followed by substantially complete release upon contacting intestinal fluid.

89. The composition according to claim 88 where at least 10% by mass of the active ingredient is released in gastric fluid.

90. The composition according to claim 88 where the active ingredient has a window of absorption.

91. The composition according to claim 90 where the active ingredient is selected from the group consisting of therapeutic nucleic acids or amino acid sequences, nucleic acids or amino acid derivatives, peptidomimetic drugs, antibiotics, therapeutic ions, vitamins, bronchodilators, anti-gout agents, anti-hypertensive agents, diuretic agents, anti-hyperlipidemic agents or ACE inhibitors, drugs intended for local treatment of the gastrointestinal tract, including anti-tumor agents, histamine (H2) blockers, bismuth salts, synthetic prostaglandins or antibiotic agents, drugs that degrade in the colon, for example metoprolol, formulations useful for treating gastrointestinal associated disorders selected

from peptic ulcer, nonulcer dyspepsia, Zollinger-Ellison syndrome, gastritis, duodenitis and the associated ulcerative lesions, stomach or duodenum neoplasms, prazosin, ketanserin, guanabenz acetate, captopril, captopril hydrochloride, enalapril, enalapril maleate, lysinopril, hydralazide, methyldopa, methyldopa hydrochloride, levodopa, carbidopa, benserazide, amlodipine, nitrendipine, nifedipine, nicardipine, verapamil, acyclovir, inosine, pranobex, tribavirine, vidarabine, zidovudine, AZT, active ingredients that exert a medicinal action at the gastric level, including aluminum hydroxide, magnesium carbonate, magnesium oxide, sucralphate, sodium carbenoxolone, pirenzepin, loperamide, cimetidine, ranitidine, famotidine, misoprostol, omeprazol, and combinations thereof.

92. The composition according to claim 88 providing an active ingredient release profile where at least 10% active ingredient by mass is released in gastric fluid, followed by at least 75% release of remaining active ingredient in one hour or less upon contacting intestinal fluid.

93. The composition according to claim 88 where the active ingredient has a window of absorption, and where at least 10% active ingredient by mass is released in gastric fluid, followed by at least 75% release of remaining active ingredient in 30 minutes or less upon contacting intestinal fluid.

94. The composition according to claim 88 where active ingredient release upon contacting gastric fluid is zero order, mixed order or first order, followed by substantially immediate release when remaining composition contacts intestinal fluid.

95. The composition according to claim 88 further comprising a hydrophilic gastric fluid channeling agent.

96. The composition according to claim 95 where the gastric fluid channeling agent is a sugar.

97. The composition according to claim 88 further comprising a hydrophobic gastric fluid channeling agent.

98. The composition of claim 97 where the hydrophobic material is selected from the group consisting of talc, magnesium salts, silicon dioxide, hydrocarbons, and combinations thereof.

99. The composition according to claim 88 comprising a solid composition.

100. The composition according to claim 88 formulated for oral administration.

101. The composition according to claim 88 further comprising a second formulation designed to provide an active ingredient release profile different from the pharmaceutical composition.

102. The composition according to claim 101 where the second formulation provides immediate release in gastric fluid.

103. The composition according to claim 101 where the active ingredient is amoxicillin or a biologically active salt thereof.

104. The composition according to claim 103 where the active ingredient of the second formulation is clavulanate or a biologically active salt thereof.

105. The composition according to claim 101 where the two formulations are placed in a single capsule or tablet for co-administration.

106. The composition according to claim 88 further comprising an admixture or an overcoat of an immediate release dosage form.

107. The composition according to claim 88 comprising an active ingredient selected from the group consisting of AIDS adjunct agents, alcohol abuse preparations, Alzheimer's disease management agents, amyotrophic lateral sclerosis active ingredient agents, analgesics, anesthetics, antacids, antiarythmics, antibiotics, anticonvulsants, antidepressants, antidiabetic agents, antiemetics, antidotes, antifibrosis active ingredient agents, antifungals, antihistamines, antihypertensives, anti-infective agents, antimicrobials, antineoplastics, antipsychotics, antiparkinsonian agents, antirheumatic agents, appetite stimulants, appetite suppressants, biological response modifiers, biologicals, blood

modifiers, bone metabolism regulators, cardioprotective agents, cardiovascular agents, central nervous system stimulants, cholinesterase inhibitors, contraceptives, cystic fibrosis management agents, deodorants, diagnostics, dietary supplements, diuretics, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction active ingredients, fatty acids, gastrointestinal agents, Gaucher's disease management agents, gout preparations, homeopathic remedys, hormones, hypercalcemia management agents, hypnotics, hypocalcemia management agents, immunomodulators, immunosuppressives, ion exchange resins, levocarnitine deficiency management agents, mast cell stabilizers, migraine preparations, motion sickness products, multiple sclerosis management agents, muscle relaxants, narcotic detoxification agents, narcotics, nucleoside analogs, non-steroidal anti-inflammatory drugs, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, phosphate binders, porphyria agents, psychoactive ingredient agents, radio-opaque agents, psychotropics, sclerosing agents, sedatives, sickle cell anemia management agents, smoking cessation aids, steroids, stimulants, sympatholytics, sympathomimetics, Tourette's syndrome agents, tremor preparations, urinary tract agents, vaginal preparations, vasodilators, vertigo agents, weight loss agents, Wilson's disease management agents, and mixtures thereof.

108. The composition according to claim 88 where the active ingredient is selected from the group consisting of abacavir sulfate, abacavir sulfate/ lamivudine/zidovudine, acetazolamide, acyclovir, albendazole, albuterol, aldactone, allopurinol, amprenavir, atovaquone, atovaquone and proguanil hydrochloride, atracurium besylate, beclomethasone dipropionate, berlactone betamethasone valerate, bupropion hydrochloride, bupropion hydrochloride, carvedilol, caspofungin acetate, cefazolin, ceftazidime, cefuroxime , chlorambucil, chlorpromazine, cimetidine, cimetidine hydrochloride, cisatracurium besilate, clobetasol propionate, co-trimoxazole, colfosceril palmitate, dextroamphetamie sulfate, digoxin, enalapril maleate, epoprostenol, esomepraxole magnesium, fluticasone propionate, furosemide, hydrochlorothiazide, hydrochlorothiazide/triamterene, lamivudine, lamotrigine, lithium carbonate, losartan potassium, melphalan, mercaptopurine, mesalazine, mupirocin calcium cream, nabumetone, naratriptan, omeprazole, ondansetron hydrochloride, ovine, oxiconazole nitrate, paroxetine hydrochloride, prochlorperazine, procyclidine hydrochloride, pyrimethamine, ranitidine bismuth citrate, ranitidine hydrochloride, rofecoxib, ropinirole hydrochloride, rosiglitazone maleate, salmeterol xinafoate, salmeterol, fluticasone propionate, sterile ticarcillin disodium / clavulanate potassium, simvastatin, spironolactone, succinylcholine chloride, sumatriptan,

thioguanine, tirofiban HCI, topotecan hydrochloride, tranylcypromine sulfate, trifluoperazine hydrochloride, valacyclovir hydrochloride, vinorelbine, zanamivir, zidovudine, zidovudine or lamivudine, or mixtures thereof.

109. The composition according to claim 88 further coated by gelatin or placed inside a gelatin capsule or a tablet.

110. The composition according to claim 88 which increases active ingredient bioavailability at least 20% relative to an immediate release or a sustained release control that does not include enteric material.

111. The composition according to claim 88 providing substantially equivalent bioavailability but a reduced active ingredient excretion rate relative to an immediate release control formulation.

112. The composition according to claim 88 providing prolonged drug concentrations for active ingredients having an absorption window relative to an immediate release or a sustained release control.

113. The composition according to claim 88 where the enteric material is selected from the group consisting of cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), hydroxypropylmethyl cellulose, hydroxypropyl methylcellulose acetate succinate (HPMCAS), cellulose acetate trimellitate, hydroxypropyl methylcellulose succinate, carboxymethyl cellulose, carboxymethyl ethyl cellulose, cellulose acetate phthalate, cellulose acetate succinate, cellulose acetate hexahydrophthalate, cellulose propionate phthalate, cellulose acetate maleate, cellulose acetate butyrate, cellulose acetate propionate, copolymer of methylmethacrylic acid and methyl methacrylate, copolymer of methyl acrylate, methylmethacrylate and methacrylic acid, copolymer of methylvinyl ether and maleic anhydride (Gantrez ES series), ethyl methyacrylate-methylmethacrylate-chlorotrimethylammonium ethyl acrylate copolymer, polyvinyl acetate phthalate, zein, shellac, copal collophorium, Eudragit L30D55, Eudragit FS30D, Eudragit L100, Eudragit S100, Kollicoat EMM30D, Estacryl 30D, Coateric, Aquateric, and combinations of such materials.

114. The composition according to claim 88 providing controlled *in vitro* gastric release, followed by pulsatile *in vitro* intestinal release.

115. The composition according to claim 88 comprising plural active ingredients.

116. A pharmaceutical composition comprising at least one active ingredient, excluding riboflavin and bisacodyl, and at least one leaky enteric coating, the composition releasing at least 10 percent of the active ingredient mass upon contacting gastric fluid, the remaining active ingredient being released substantially completely after contacting intestinal fluid.

117. The composition according to claim 116 where the active ingredient has a window of absorption.

118. The composition according to claim 117 where the active ingredient is selected from the group consisting of therapeutic nucleic acids or amino acid sequences, nucleic acids or amino acid derivatives, peptidomimetic drugs, antibiotics, therapeutic ions, vitamins, bronchodilators, anti-gout agents, anti-hypertensive agents, diuretic agents, anti-hyperlipidemic agents or ACE inhibitors, drugs intended for local treatment of the gastrointestinal tract, including anti-tumor agents, histamine (H2) blockers, bismuth salts, synthetic prostaglandins or antibiotic agents, drugs that degrade in the colon, for example metoprolol, formulations useful for treating gastrointestinal associated disorders selected from peptic ulcer, nonulcer dyspepsia, Zollinger-Ellison syndrome, gastritis, duodenitis and the associated ulcerative lesions, stomach or duodenum neoplasms, prazosin, ketanserin, guanabenz acetate, captopril, captopril hydrochloride, enalapril, enalapril maleate, lysinopril, hydralazide, methyldopa, methyldopa hydrochloride, levodopa, carbidopa, benserazide, amlodipine, nitrendipine, nifedipine, nicardipine, verapamil, acyclovir, inosine, pranobex, tribavirine, vidarabine, zidovudine, AZT, active ingredients that exert a medicinal action at the gastric level, including aluminum hydroxide, magnesium carbonate, magnesium oxide, sucralphate, sodium carbenoxolone, pirenzepin, loperamide, cimetidine, ranitidine, famotidine, misoprostol, omeprazol, and combinations thereof.

119. The composition according to claim 116 providing an active ingredient release profile where at least 10% active ingredient by mass is released in gastric fluid,

followed by at least 75% release of remaining active ingredient in one hour or less upon contacting intestinal fluid.

120. The composition according to claim 116 where the active ingredient has a window of absorption, and where at least 10% active ingredient by mass is released in gastric fluid, followed by at least 75% release of remaining active ingredient in 30 minutes or less upon contacting intestinal fluid.

121. The composition according to claim 116 where active ingredient release upon contacting gastric fluid is zero order, mixed order or first order, followed by substantially immediate release when remaining composition contacts intestinal fluid.

122. The composition according to claim 116 where the enteric material includes a hydrophilic gastric fluid channeling agent.

123. The composition according to claim 122 where the gastric fluid channeling agent is a sugar.

124. The composition according to claim 116 where the enteric material includes a hydrophobic gastric fluid channeling agent.

125. The composition of claim 124 where the hydrophobic material is selected from the group consisting of talc, magnesium salts, silicon dioxide, hydrocarbons, and combinations thereof.

126. The composition according to claim 116 where the enteric coating has a thickness of 25 μm or less.

127. The composition according to claim 116 where the enteric coating has a thickness of 20 μm or less.

128. The composition according to claim 116 comprising a solid composition.

129. The composition according to claim 116 formulated for oral administration.

130. The composition according to claim 116 further comprising a second formulation designed to provide an active ingredient release profile different from the pharmaceutical composition.

131. The composition according to claim 116 where the second formulation provides immediate release in gastric fluid.

132. The composition according to claim 130 where the active ingredient is amoxicillin or a biologically active salt thereof.

133. The composition according to claim 132 where the active ingredient of the second formulation is clavulanate or a biologically active salt thereof.

134. The composition according to claim 130 where the two formulations are placed in a single capsule or tablet for co-administration.

135. The composition according to claim 116 further comprising an admixture or an overcoat of an immediate release dosage form.

136. The composition according to claim 116 comprising an active ingredient selected from the group consisting of AIDS adjunct agents, alcohol abuse preparations, Alzheimer's disease management agents, amyotrophic lateral sclerosis active ingredient agents, analgesics, anesthetics, antacids, antiarythmics, antibiotics, anticonvulsants, antidepressants, antidiabetic agents, antiemetics, antidotes, antifibrosis active ingredient agents, antifungals, antihistamines, antihypertensives, anti-infective agents, antimicrobials, antineoplastics, antipsychotics, antiparkinsonian agents, antirheumatic agents, appetite stimulants, appetite suppressants, biological response modifiers, biologicals, blood modifiers, bone metabolism regulators, cardioprotective agents, cardiovascular agents, central nervous system stimulants, cholinesterase inhibitors, contraceptives, cystic fibrosis management agents, deodorants, diagnostics, dietary supplements, diuretics, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction active ingredients, fatty acids, gastrointestinal agents, Gaucher's disease management agents, gout preparations, homeopathic remedys, hormones, hypercalcemia management agents, hypnotics, hypocalcemia management agents, immunomodulators, immunosuppressives, ion exchange resins, levocarnitine deficiency management agents, mast cell stabilizers, migraine

preparations, motion sickness products, multiple sclerosis management agents, muscle relaxants, narcotic detoxification agents, narcotics, nucleoside analogs, non-steroidal anti-inflammatory drugs, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, phosphate binders, porphyria agents, psychoactive ingredient agents, radio-opaque agents, psychotropics, sclerosing agents, sedatives, sickle cell anemia management agents, smoking cessation aids, steroids, stimulants, sympatholytics, sympathomimetics, Tourette's syndrome agents, tremor preparations, urinary tract agents, vaginal preparations, vasodilators, vertigo agents, weight loss agents, Wilson's disease management agents, and mixtures thereof.

137. The composition according to claim 116 where the active ingredient is selected from the group consisting of abacavir sulfate, abacavir sulfate/ lamivudine/zidovudine, acetazolamide, acyclovir, albendazole, albuterol, aldactone, allopurinol, amoxicillin, amoxicillin/clavulanate potassium, amprenavir, atovaquone, atovaquone and proguanil hydrochloride, atracurium besylate, beclomethasone dipropionate, berlactone betamethasone valerate, bupropion hydrochloride, bupropion hydrochloride, carvedilol, caspofungin acetate, cefazolin, ceftazidime, cefuroxime , chlorambucil, chlorpromazine, cimetidine, cimetidine hydrochloride, cisatracurium besilate, clobetasol propionate, co-trimoxazole, colfosceril palmitate, dextroamphetamie sulfate, digoxin, enalapril maleate, epoprostenol, esomepraxole magnesium, fluticasone propionate, furosemide, hydrochlorothiazide, hydrochlorothiazide/triamterene, lamivudine, lamotrigine, lithium carbonate, losartan potassium, melphalan, mercaptopurine, mesalazine, mupirocin calcium cream, nabumetone, naratriptan, omeprazole, ondansetron hydrochloride, ovine, oxiconazole nitrate, paroxetine hydrochloride, prochlorperazine, procyclidine hydrochloride, pyrimethamine, ranitidine bismuth citrate, ranitidine hydrochloride, rofecoxib, ropinirole hydrochloride, rosiglitazone maleate, salmeterol xinafoate, salmeterol, fluticasone propionate, sterile ticarcillin disodium / clavulanate potassium, simvastatin, spironolactone, succinylcholine chloride, sumatriptan, thioguanine, tirofiban HCI, topotecan hydrochloride, tranylcypromine sulfate, trifluoperazine hydrochloride, valacyclovir hydrochloride, vinorelbine, zanamivir, zidovudine, zidovudine or lamivudine, or mixtures thereof.

138. The composition according to claim 116 further coated by gelatin or placed inside a gelatin capsule or a tablet.

139. The composition according to claim 116 which increases active ingredient bioavailability at least 20% relative to an immediate release or sustained release control that does not include enteric material.

140. The composition according to claim 116 providing substantially equivalent bioavailability but a reduced active ingredient excretion rate relative to an immediate release formulation.

141. The composition according to claim 116 providing prolonged drug concentrations for active ingredients having an absorption window relative to an immediate release or a sustained release control.

142. The composition according to claim 116 where the enteric material is selected from the group consisting of cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), hydroxypropylmethyl cellulose, hydroxypropyl methylcellulose acetate succinate (HPMCAS), cellulose acetate trimellitate, hydroxypropyl methylcellulose succinate, carboxymethyl cellulose, carboxymethyl ethyl cellulose, cellulose acetate phthalate, cellulose acetate succinate, cellulose acetate hexahydrophthalate, cellulose propionate phthalate, cellulose acetate maleate, cellulose acetate butyrate, cellulose acetate propionate, copolymer of methylmethacrylic acid and methyl methacrylate, copolymer of methyl acrylate, methylmethacrylate and methacrylic acid, copolymer of methylvinyl ether and maleic anhydride (Gantrez ES series), ethyl methyacrylate-methylmethacrylate-chlorotrimethylammonium ethyl acrylate copolymer, polyvinyl acetate phthalate, zein, shellac, copal collophorium, Eudragit L30D55, Eudragit FS30D, Eudragit L100, Eudragit S100, Kollicoat EMM30D, Estacryl 30D, Coateric, Aquateric, and combinations of such materials.

143. The composition according to claim 116 providing controlled *in vitro* gastric release, followed by pulsatile *in vitro* intestinal release.

144. The composition according to claim 116 comprising plural active ingredients.

145. A pharmaceutical composition comprising at least one active ingredient, excluding riboflavin and bisacodyl, and having a leaky enteric coating.

146. The composition according to claim 145 where at least 10% by mass of the active ingredient is released in gastric fluid.

147. The composition according to claim 145 where the active ingredient has a window of absorption.

148. The composition according to claim 147 where the active ingredient is selected from the group consisting of therapeutic nucleic acids or amino acid sequences, nucleic acids or amino acid derivatives, peptidomimetic drugs, antibiotics, therapeutic ions, vitamins, bronchodilators, anti-gout agents, anti-hypertensive agents, diuretic agents, anti-hyperlipidemic agents or ACE inhibitors, drugs intended for local treatment of the gastrointestinal tract, including anti-tumor agents, histamine (H2) blockers, bismuth salts, synthetic prostaglandins or antibiotic agents, drugs that degrade in the colon, for example metoprolol, formulations useful for treating gastrointestinal associated disorders selected from peptic ulcer, nonulcer dyspepsia, Zollinger-Ellison syndrome, gastritis, duodenitis and the associated ulcerative lesions, stomach or duodenum neoplasms, prazosin, ketanserin, guanabenz acetate, captopril, captopril hydrochloride, enalapril, enalapril maleate, lysinopril, hydralazide, methyldopa, methyldopa hydrochloride, levodopa, carbidopa, benserazide, amlodipine, nitrendipine, nifedipine, nicardipine, verapamil, acyclovir, inosine, pranobex, tribavirine, vidarabine, zidovudine, AZT, active ingredients that exert a medicinal action at the gastric level, including aluminum hydroxide, magnesium carbonate, magnesium oxide, sucralphate, sodium carbenoxolone, pirenzepin, loperamide, cimetidine, ranitidine, famotidine, misoprostol, omeprazol, and combinations thereof.

149. The composition according to claim 145 providing an active ingredient release profile where at least 10% active ingredient by mass is released in gastric fluid, followed by at least 75% release of remaining active ingredient in one hour or less upon contacting intestinal fluid.

150. The composition according to claim 145 where the active ingredient has a window of absorption, and where at least 10% active ingredient by mass is released in

gastric fluid, followed by at least 75% release of remaining active ingredient in 30 minutes or less upon contacting intestinal fluid.

151. The composition according to claim 145 where active ingredient release upon contacting gastric fluid is zero order, mixed order or first order, followed by substantially immediate release when remaining composition contacts intestinal fluid.

152. The composition according to claim 145 where the enteric coating includes a hydrophilic gastric fluid channeling agent.

153. The composition according to claim 152 where the gastric fluid channeling agent is a sugar.

154. The composition according to claim 145 where the enteric material includes a hydrophobic gastric fluid channeling agent.

155. The composition of claim 154 where the hydrophobic material is selected from the group consisting of talc, magnesium salts, silicon dioxide, hydrocarbons, and combinations thereof.

156. The composition according to claim 145 where the enteric coating has a thickness of 25 μm or less.

157. The composition according to claim 145 where the enteric coating has a thickness of 20 μm or less.

158. The composition according to claim 145 comprising a solid composition.

159. The composition according to claim 145 formulated for oral administration.

160. The composition according to claim 145 further comprising a second formulation designed to provide an active ingredient release profile different from the pharmaceutical composition.

161. The composition according to claim 160 where the second formulation provides immediate release in gastric fluid.

162. The composition according to claim 161 where the active ingredient is clavulanate or a biologically active salt thereof.

163. The composition according to claim 162 where the active ingredient of the second formulation is amoxicillin or a biologically active salt thereof.

164. The composition according to claim 160 where the two formulations are placed in a single capsule or tablet for co-administration.

165. The composition according to claim 145 further comprising an admixture or an overcoat of an immediate release dosage form.

166. The composition according to claim 145 comprising an active ingredient selected from the group consisting of AIDS adjunct agents, alcohol abuse preparations, Alzheimer's disease management agents, amyotrophic lateral sclerosis active ingredient agents, analgesics, anesthetics, antacids, antiarythmics, antibiotics, anticonvulsants, antidepressants, antidiabetic agents, antiemetics, antidotes, antifibrosis active ingredient agents, antifungals, antihistamines, antihypertensives, anti-infective agents, antimicrobials, antineoplastics, antipsychotics, antiparkinsonian agents, antirheumatic agents, appetite stimulants, appetite suppressants, biological response modifiers, biologicals, blood modifiers, bone metabolism regulators, cardioprotective agents, cardiovascular agents, central nervous system stimulants, cholinesterase inhibitors, contraceptives, cystic fibrosis management agents, deodorants, diagnostics, dietary supplements, diuretics, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction active ingredients, fatty acids, gastrointestinal agents, Gaucher's disease management agents, gout preparations, homeopathic remedys, hormones, hypercalcemia management agents, hypnotics, hypocalcemia management agents, immunomodulators, immunosuppressives, ion exchange resins, levocarnitine deficiency management agents, mast cell stabilizers, migraine preparations, motion sickness products, multiple sclerosis management agents, muscle relaxants, narcotic detoxification agents, narcotics, nucleoside analogs, non-steroidal anti-inflammatory drugs, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, phosphate binders, porphyria agents,

psychoactive ingredient agents, radio-opaque agents, psychotropics, sclerosing agents, sedatives, sickle cell anemia management agents, smoking cessation aids, steroids, stimulants, sympatholytics, sympathomimetics, Tourette's syndrome agents, tremor preparations, urinary tract agents, vaginal preparations, vasodilators, vertigo agents, weight loss agents, Wilson's disease management agents, and mixtures thereof.

167. The composition according to claim 145 where the active ingredient is selected from the group consisting of abacavir sulfate, abacavir sulfate/ lamivudine/zidovudine, acetazolamide, acyclovir, albendazole, albuterol, aldactone, allopurinol, amoxicillin, amoxicillin/clavulanate potassium, amprenavir, atovaquone, atovaquone and proguanil hydrochloride, atracurium besylate, beclomethasone dipropionate, berlactone betamethasone valerate, bupropion hydrochloride, bupropion hydrochloride, carvedilol, caspofungin acetate, cefazolin, ceftazidime, cefuroxime , chlorambucil, chlorpromazine, cimetidine, cimetidine hydrochloride, cisatracurium besilate, clobetasol propionate, co-trimoxazole, colfosceril palmitate, dextroamphetamie sulfate, digoxin, enalapril maleate, epoprostenol, esomepraxole magnesium, fluticasone propionate, furosemide, hydrochlorothiazide, hydrochlorothiazide/triamterene, lamivudine, lamotrigine, lithium carbonate, losartan potassium, melphalan, mercaptopurine, mesalazine, mupirocin calcium cream, nabumetone, naratriptan, omeprazole, ondansetron hydrochloride, ovine, oxiconazole nitrate, paroxetine hydrochloride, prochlorperazine, procyclidine hydrochloride, pyrimethamine, ranitidine bismuth citrate, ranitidine hydrochloride, rofecoxib, ropinirole hydrochloride, rosiglitazone maleate, salmeterol xinafoate, salmeterol, fluticasone propionate, sterile ticarcillin disodium / clavulanate potassium, simvastatin, spironolactone, succinylcholine chloride, sumatriptan, thioguanine, tirofiban HCI, topotecan hydrochloride, tranylcypromine sulfate, trifluoperazine hydrochloride, valacyclovir hydrochloride, vinorelbine, zanamivir, zidovudine, zidovudine or lamivudine, or mixtures thereof.

168. The composition according to claim 145 further coated by gelatin or placed inside a gelatin capsule or a tablet.

169. The composition according to claim 145 which increases active ingredient bioavailability at least 20% relative to an immediate release ora sustained release control that does not include enteric material.

170. The composition according to claim 145 providing substantially equivalent bioavailability but a reduced active ingredient excretion rate relative to an immediate release formulation.

171. The composition according to claim 145 providing prolonged drug concentrations for active ingredients having an absorption window relative to an immediate release or a sustained release control.

172. The composition according to claim 145 where the enteric material is selected from the group consisting of cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), hydroxypropylmethyl cellulose, hydroxypropyl methylcellulose acetate succinate (HPMCAS), cellulose acetate trimellitate, hydroxypropyl methylcellulose succinate, carboxymethyl cellulose, carboxymethyl ethyl cellulose, cellulose acetate phthalate, cellulose acetate succinate, cellulose acetate hexahydrophthalate, cellulose propionate phthalate, cellulose acetate maleate, cellulose acetate butyrate, cellulose acetate propionate, copolymer of methylmethacrylic acid and methyl methacrylate, copolymer of methyl acrylate, methylmethacrylate and methacrylic acid, copolymer of methylvinyl ether and maleic anhydride (Gantrez ES series), ethyl methyacrylate-methylmethacrylate-chlorotrimethylammonium ethyl acrylate copolymer, polyvinyl acetate phthalate, zein, shellac, copal collophorium, Eudragit L30D55, Eudragit FS30D, Eudragit L100, Eudragit S100, Kollicoat EMM30D, Estacryl 30D, Coateric, Aquateric, and combinations of such materials.

173. The composition according to claim 145 providing controlled *in vitro* gastric release, followed by pulsatile *in vitro* intestinal release.

174. The composition according to claim 145 comprising plural active ingredients.

175. A pharmaceutical composition consisting essentially of a core comprising at least one active ingredient and a leaky enteric coating.

176. The composition according to claim 175 where at least 10% by mass of the active ingredient is released in gastric fluid.

177. The composition according to claim 175 where the active ingredient has a window of absorption.

178. The composition according to claim 177 where the active ingredient is selected from the group consisting of therapeutic nucleic acids or amino acid sequences, nucleic acids or amino acid derivatives, peptidomimetic drugs, antibiotics, therapeutic ions, vitamins, bronchodilators, anti-gout agents, anti-hypertensive agents, diuretic agents, anti-hyperlipidemic agents or ACE inhibitors, drugs intended for local treatment of the gastrointestinal tract, including anti-tumor agents, histamine (H2) blockers, bismuth salts, synthetic prostaglandins or antibiotic agents, drugs that degrade in the colon, for example metoprolol, formulations useful for treating gastrointestinal associated disorders selected from peptic ulcer, nonulcer dyspepsia, Zollinger-Ellison syndrome, gastritis, duodenitis and the associated ulcerative lesions, stomach or duodenum neoplasms, prazosin, ketanserin, guanabenz acetate, captopril, captopril hydrochloride, enalapril, enalapril maleate, lysinopril, hydralazide, methyldopa, methyldopa hydrochloride, levodopa, carbidopa, benserazide, amlodipine, nitrendipine, nifedipine, nicardipine, verapamil, acyclovir, inosine, pranobex, tribavirine, vidarabine, zidovudine, AZT, active ingredients that exert a medicinal action at the gastric level, including aluminum hydroxide, magnesium carbonate, magnesium oxide, sucralphate, sodium carbenoxolone, pirenzepin, loperamide, cimetidine, ranitidine, famotidine, misoprostol, omeprazol, and combinations thereof.

179. The composition according to claim 175 providing an active ingredient release profile where at least 10% active ingredient by mass is released in gastric fluid, followed by at least 75% release of remaining active ingredient in one hour or less upon contacting intestinal fluid.

180. The composition according to claim 175 where the active ingredient has a window of absorption, and where at least 10% active ingredient by mass is released in gastric fluid, followed by at least 75% release of remaining active ingredient in 30 minutes or less upon contacting intestinal fluid.

181. The composition according to claim 175 where active ingredient release upon contacting gastric fluid is zero order, mixed order or first order, followed by substantially immediate release when remaining composition contacts intestinal fluid.

182. The composition according to claim 175 where the leaky enteric coating includes a hydrophilic gastric fluid channeling agent.

183. The composition according to claim 182 where the gastric fluid channeling agent is a sugar.

184. The composition according to claim 175 where the leaky enteric coating includes a hydrophobic gastric fluid channeling agent.

185. The composition of claim 184 where the hydrophobic material is selected from the group consisting of talc, magnesium salts, silicon dioxide, hydrocarbons, and combinations thereof.

186. The composition according to claim 175 where the enteric coating has a thickness of 25 μm or less.

187. The composition according to claim 175 where the enteric coating has a thickness of 20 μm or less.

188. The composition according to claim 175 comprising a solid composition.

189. The composition according to claim 175 formulated for oral administration.

190. The composition according to claim 175 further comprising a second formulation designed to provide an active ingredient release profile different from the pharmaceutical composition.

191. The composition according to claim 190 where the second formulation provides immediate release in gastric fluid.

192. The composition according to claim 191 where the active ingredient is clavulanate or a biologically active salt thereof.

193. The composition according to claim 192 where the active ingredient of the second formulation is amoxicillin or a biologically active salt thereof.

194. The composition according to claim 190 where the two formulations are placed in a single capsule or tablet for co-administration.

195. The composition according to claim 175 further comprising an admixture of an immediate release dosage form.

196. The composition according to claim 175 comprising an active ingredient selected from the group consisting of AIDS adjunct agents, alcohol abuse preparations, Alzheimer's disease management agents, amyotrophic lateral sclerosis active ingredient agents, analgesics, anesthetics, antacids, antiarythmics, antibiotics, anticonvulsants, antidepressants, antidiabetic agents, antiemetics, antidotes, antifibrosis active ingredient agents, antifungals, antihistamines, antihypertensives, anti-infective agents, antimicrobials, antineoplastics, antipsychotics, antiparkinsonian agents, antirheumatic agents, appetite stimulants, appetite suppressants, biological response modifiers, biologicals, blood modifiers, bone metabolism regulators, cardioprotective agents, cardiovascular agents, central nervous system stimulants, cholinesterase inhibitors, contraceptives, cystic fibrosis management agents, deodorants, diagnostics, dietary supplements, diuretics, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction active ingredients, fatty acids, gastrointestinal agents, Gaucher's disease management agents, gout preparations, homeopathic remedys, hormones, hypercalcemia management agents, hypnotics, hypocalcemia management agents, immunomodulators, immunosuppressives, ion exchange resins, levocarnitine deficiency management agents, mast cell stabilizers, migraine preparations, motion sickness products, multiple sclerosis management agents, muscle relaxants, narcotic detoxification agents, narcotics, nucleoside analogs, non-steroidal anti-inflammatory drugs, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, phosphate binders, porphyria agents, psychoactive ingredient agents, radio-opaque agents, psychotropics, sclerosing agents, sedatives, sickle cell anemia management agents, smoking cessation aids, steroids, stimulants, sympatholytics, sympathomimetics, Tourette's syndrome agents, tremor preparations, urinary tract agents, vaginal preparations, vasodilators, vertigo agents, weight loss agents, Wilson's disease management agents, and mixtures thereof.

197. The composition according to claim 175 where the active ingredient is selected from the group consisting of abacavir sulfate, abacavir sulfate/ lamivudine/zidovudine, acetazolamide, acyclovir, albendazole, albuterol, aldactone, allopurinol, amoxicillin, amoxicillin/clavulanate potassium, amprenavir, atovaquone, atovaquone and proguanil hydrochloride, atracurium besylate, beclomethasone dipropionate, berlactone betamethasone valerate, bupropion hydrochloride, bupropion hydrochloride, carvedilol, caspofungin acetate, cefazolin, ceftazidime, cefuroxime , chlorambucil, chlorpromazine, cimetidine, cimetidine hydrochloride, cisatracurium besilate, clobetasol propionate, co-trimoxazole, colfosceril palmitate, dextroamphetamie sulfate, digoxin, enalapril maleate, epoprostenol, esomepraxole magnesium, fluticasone propionate, furosemide, hydrochlorothiazide, hydrochlorothiazide/triamterene, lamivudine, lamotrigine, lithium carbonate, losartan potassium, melphalan, mercaptopurine, mesalazine, mupirocin calcium cream, nabumetone, naratriptan, omeprazole, ondansetron hydrochloride, ovine, oxiconazole nitrate, paroxetine hydrochloride, prochlorperazine, procyclidine hydrochloride, pyrimethamine, ranitidine bismuth citrate, ranitidine hydrochloride, rofecoxib, ropinirole hydrochloride, rosiglitazone maleate, salmeterol xinafoate, salmeterol, fluticasone propionate, sterile ticarcillin disodium / clavulanate potassium, simvastatin, spironolactone, succinylcholine chloride, sumatriptan, thioguanine, tirofiban HCI, topotecan hydrochloride, tranylcypromine sulfate, trifluoperazine hydrochloride, valacyclovir hydrochloride, vinorelbine, zanamivir, zidovudine, zidovudine or lamivudine, or mixtures thereof.

198. The composition according to claim 175 placed inside a gelatin capsule or a tablet.

199. The composition according to claim 175 which increases active ingredient bioavailability at least 20% relative to an immediate release control or a sustained release control that does not include enteric material.

200. The composition according to claim 175 providing substantially equivalent bioavailability but a reduced active ingredient excretion rate relative to an immediate release control formulation.

201. The composition according to claim 175 providing prolonged drug concentrations for active ingredients having an absorption window relative to an immediate release control or a sustained release control.

202. The composition according to claim 175 where the enteric material is selected from the group consisting of cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), hydroxypropylmethyl cellulose, hydroxypropyl methylcellulose acetate succinate (HPMCAS), cellulose acetate trimellitate, hydroxypropyl methylcellulose succinate, carboxymethyl cellulose, carboxymethyl ethyl cellulose, cellulose acetate phthalate, cellulose acetate succinate, cellulose acetate hexahydrophthalate, cellulose propionate phthalate, cellulose acetate maleate, cellulose acetate butyrate, cellulose acetate propionate, copolymer of methylmethacrylic acid and methyl methacrylate, copolymer of methyl acrylate, methylmethacrylate and methacrylic acid, copolymer of methylvinyl ether and maleic anhydride (Gantrez ES series), ethyl methyacrylate-methylmethacrylate-chlorotrimethylammonium ethyl acrylate copolymer, polyvinyl acetate phthalate, zein, shellac, copal collophorium, Eudragit L30D55, Eudragit FS30D, Eudragit L100, Eudragit S100, Kollicoat EMM30D, Estacryl 30D, Coateric, Aquateric, and combinations of such materials.

203. The composition according to claim 175 providing controlled *in vitro* gastric release, followed by pulsatile *in vitro* intestinal release.

204. The composition according to claim 175 comprising plural active ingredients.

205. A pharmaceutical composition consisting essentially of a core comprising at least one active ingredient and an enteric coating comprising a gastric fluid channeling agent.

206. The composition according to claim 205 where at least 10% by mass of the active ingredient is released in gastric fluid.

207. The composition according to claim 205 where the active ingredient has a window of absorption.

208. The composition according to claim 207 where the active ingredient is selected from the group consisting of therapeutic nucleic acids or amino acid sequences,

nucleic acids or amino acid derivatives, peptidomimetic drugs, antibiotics, therapeutic ions, vitamins, bronchodilators, anti-gout agents, anti-hypertensive agents, diuretic agents, anti-hyperlipidemic agents or ACE inhibitors, drugs intended for local treatment of the gastrointestinal tract, including anti-tumor agents, histamine (H2) blockers, bismuth salts, synthetic prostaglandins or antibiotic agents, drugs that degrade in the colon, for example metoprolol, formulations useful for treating gastrointestinal associated disorders selected from peptic ulcer, nonulcer dyspepsia, Zollinger-Ellison syndrome, gastritis, duodenitis and the associated ulcerative lesions, stomach or duodenum neoplasms, prazosin, ketanserin, guanabenz acetate, captopril, captopril hydrochloride, enalapril, enalapril maleate, lysinopril, hydralazide, methyldopa, methyldopa hydrochloride, levodopa, carbidopa, benserazide, amlodipine, nitrendipine, nifedipine, nicardipine, verapamil, acyclovir, inosine, pranobex, tribavirine, vidarabine, zidovudine, AZT, active ingredients that exert a medicinal action at the gastric level, including aluminum hydroxide, magnesium carbonate, magnesium oxide, sucralphate, sodium carbenoxolone, pirenzepin, loperamide, cimetidine, ranitidine, famotidine, misoprostol, omeprazol, and combinations thereof.

209. The composition according to claim 205 providing an active ingredient release profile where at least 10% active ingredient by mass is released in gastric fluid, followed by at least 75% release of remaining active ingredient in one hour or less upon contacting intestinal fluid.

210. The composition according to claim 205 where the active ingredient has a window of absorption, and where at least 10% active ingredient by mass is released in gastric fluid, followed by at least 75% release of remaining active ingredient in 30 minutes or less upon contacting intestinal fluid.

211. The composition according to claim 205 where active ingredient release upon contacting gastric fluid is zero order, mixed order or first order, followed by substantially immediate release when remaining composition contacts intestinal fluid.

212. The composition according to claim 205 where the gastric fluid channeling agent is hydrophilic.

213. The composition according to claim 212 where the gastric fluid channeling agent is a sugar.

214. The composition according to claim 205 where the gastric fluid channeling agent is hydrophobic.

215. The composition of claim 214 where the hydrophobic material is selected from the group consisting of talc, magnesium salts, silicon dioxide, hydrocarbons, and combinations thereof.

216. The composition according to claim 205 where the enteric coating has a thickness of 25 μm or less.

217. The composition according to claim 205 where the enteric coating has a thickness of 20 μm or less.

218. The composition according to claim 205 comprising a solid composition.

219. The composition according to claim 205 formulated for oral administration.

220. The composition according to claim 205 further comprising a second formulation designed to provide an active ingredient release profile different from the pharmaceutical composition.

221. The composition according to claim 220 where the second formulation provides immediate release in gastric fluid.

222. The composition according to claim 220 where the active ingredient is amoxicillin or a biologically active salt thereof.

223. The composition according to claim 222 where the active ingredient of the second formulation is clavulanate or a biologically active salt thereof.

224. The composition according to claim 220 where the two formulations are placed in a single capsule or tablet for co-administration.

225. The composition according to claim 205 further comprising an admixture of an immediate release dosage form.

226. The composition according to claim 205 comprising an active ingredient selected from the group consisting of AIDS adjunct agents, alcohol abuse preparations, Alzheimer's disease management agents, amyotrophic lateral sclerosis active ingredient agents, analgesics, anesthetics, antacids, antiarythmics, antibiotics, anticonvulsants, antidepressants, antidiabetic agents, antiemetics, antidotes, antifibrosis active ingredient agents, antifungals, antihistamines, antihypertensives, anti-infective agents, antimicrobials, antineoplastics, antipsychotics, antiparkinsonian agents, antirheumatic agents, appetite stimulants, appetite suppressants, biological response modifiers, biologicals, blood modifiers, bone metabolism regulators, cardioprotective agents, cardiovascular agents, central nervous system stimulants, cholinesterase inhibitors, contraceptives, cystic fibrosis management agents, deodorants, diagnostics, dietary supplements, diuretics, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction active ingredients, fatty acids, gastrointestinal agents, Gaucher's disease management agents, gout preparations, homeopathic remedys, hormones, hypercalcemia management agents, hypnotics, hypocalcemia management agents, immunomodulators, immunosuppressives, ion exchange resins, levocarnitine deficiency management agents, mast cell stabilizers, migraine preparations, motion sickness products, multiple sclerosis management agents, muscle relaxants, narcotic detoxification agents, narcotics, nucleoside analogs, non-steroidal anti-inflammatory drugs, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, phosphate binders, porphyria agents, psychoactive ingredient agents, radio-opaque agents, psychotropics, sclerosing agents, sedatives, sickle cell anemia management agents, smoking cessation aids, steroids, stimulants, sympatholytics, sympathomimetics, Tourette's syndrome agents, tremor preparations, urinary tract agents, vaginal preparations, vasodilators, vertigo agents, weight loss agents, Wilson's disease management agents, and mixtures thereof.

227. The composition according to claim 205 where the active ingredient is selected from the group consisting of abacavir sulfate, abacavir sulfate/ lamivudine/zidovudine, acetazolamide, acyclovir, albendazole, albuterol, aldactone, allopurinol, amoxicillin, amoxicillin/clavulanate potassium, amprenavir, atovaquone, atovaquone and proguanil hydrochloride, atracurium besylate, beclomethasone dipropionate, berlactone betamethasone valerate, bupropion hydrochloride, bupropion hydrochloride,

carvedilol, caspofungin acetate, cefazolin, ceftazidime, cefuroxime , chlorambucil, chlorpromazine, cimetidine, cimetidine hydrochloride, cisatracurium besilate, clobetasol propionate, co-trimoxazole, colfosceril palmitate, dextroamphetamie sulfate, digoxin, enalapril maleate, epoprostenol, esomepraxole magnesium, fluticasone propionate, furosemide, hydrochlorothiazide, hydrochlorothiazide/triamterene, lamivudine, lamotrigine, lithium carbonate, losartan potassium, melphalan, mercaptopurine, mesalazine, mupirocin calcium cream, nabumetone, naratriptan, omeprazole, ondansetron hydrochloride, ovine, oxiconazole nitrate, paroxetine hydrochloride, prochlorperazine, procyclidine hydrochloride, pyrimethamine, ranitidine bismuth citrate, ranitidine hydrochloride, rofecoxib, ropinirole hydrochloride, rosiglitazone maleate, salmeterol xinafoate, salmeterol, fluticasone propionate, sterile ticarcillin disodium / clavulanate potassium, simvastatin, spironolactone, succinylcholine chloride, sumatriptan, thioguanine, tirofiban HCI, topotecan hydrochloride, tranylcypromine sulfate, trifluoperazine hydrochloride, valacyclovir hydrochloride, vinorelbine, zanamivir, zidovudine, zidovudine or lamivudine, or mixtures thereof.

228. The composition according to claim 205 placed inside a gelatin capsule or a tablet.

229. The composition according to claim 205 which increases active ingredient bioavailability at least 20% relative to an immediate release control or a sustained release control that does not include enteric material.

230. The composition according to claim 205 providing substantially equivalent bioavailability but a reduced active ingredient excretion rate relative to an immediate release control formulation.

231. The composition according to claim 205 providing prolonged drug concentrations for active ingredients having an absorption window relative to an immediate release or a sustained release control.

232. The composition according to claim 205 where the enteric coating is selected from the group consisting of cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, carboxymethylethylcellulose, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, cellulose acetate

phthalate, poly(methacrylic acid-ethylacrylate), poly(methacrylic acid-methyl methacrylate), Eudagrit L, Eudragit S, and mixtures of enteric materials.

233. The composition according to claim 205 providing controlled *in vitro* gastric release, followed by pulsatile *in vitro* intestinal release.

234. The composition according to claim 205 comprising plural active ingredients.

235. A pharmaceutical composition, comprising:
a sugarbead core;
at least one active ingredient on or in the core; and
an enteric coating comprising a gastric fluid channeling agent.

236. The composition according to claim 235 where at least 10% by mass of the active ingredient is released in gastric fluid.

237. The composition according to claim 235 where the active ingredient has a window of absorption.

238. The composition according to claim 237 where the active ingredient is selected from the group consisting of therapeutic nucleic acids or amino acid sequences, nucleic acids or amino acid derivatives, peptidomimetic drugs, antibiotics, therapeutic ions, vitamins, bronchodilators, anti-gout agents, anti-hypertensive agents, diuretic agents, anti-hyperlipidemic agents or ACE inhibitors, drugs intended for local treatment of the gastrointestinal tract, including anti-tumor agents, histamine (H2) blockers, bismuth salts, synthetic prostaglandins or antibiotic agents, drugs that degrade in the colon, for example metoprolol, formulations useful for treating gastrointestinal associated disorders selected from peptic ulcer, nonulcer dyspepsia, Zollinger-Ellison syndrome, gastritis, duodenitis and the associated ulcerative lesions, stomach or duodenum neoplasms, prazosin, ketanserin, guanabenz acetate, captopril, captopril hydrochloride, enalapril, enalapril maleate, lysinopril, hydralazide, methyldopa, methyldopa hydrochloride, levodopa, carbidopa, benserazide, amlodipine, nitrendipine, nifedipine, nicardipine, verapamil, acyclovir, inosine, pranobex, tribavirine, vidarabine, zidovudine, AZT, active ingredients that exert a medicinal action at the gastric level, including aluminum hydroxide, magnesium carbonate,

magnesium oxide, sucralphate, sodium carbenoxolone, pirenzepin, loperamide, cimetidine, ranitidine, famotidine, misoprostol, omeprazol, and combinations thereof.

239. The composition according to claim 235 providing an active ingredient release profile where at least 10% active ingredient by mass is released in gastric fluid, followed by at least 75% release of remaining active ingredient in one hour or less upon contacting intestinal fluid.

240. The composition according to claim 235 where the active ingredient has a window of absorption, and where at least 10% active ingredient by mass is released in gastric fluid, followed by at least 75% release of remaining active ingredient in 30 minutes or less upon contacting intestinal fluid.

241. The composition according to claim 235 where active ingredient release upon contacting gastric fluid is zero order, mixed order or first order, followed by substantially immediate release when remaining composition contacts intestinal fluid.

242. The composition according to claim 235 where the gastric fluid channeling agent is hydrophilic.

243. The composition according to claim 242 where the gastric fluid channeling agent is a sugar.

244. The composition according to claim 235 where the gastric fluid channeling agent is hydrophobic.

245. The composition of claim 244 where the hydrophobic material is selected from the group consisting of talc, magnesium salts, silicon dioxide, hydrocarbons, and combinations thereof.

246. The composition according to claim 235 where the enteric coating has a thickness of 25 μm or less.

247. The composition according to claim 235 where the enteric coating has a thickness of 20 μm or less.

248. The composition according to claim 235 comprising a solid composition.

249. The composition according to claim 235 formulated for oral administration.

250. The composition according to claim 235 further comprising a second formulation designed to provide an active ingredient release profile different from the pharmaceutical composition.

251. The composition according to claim 250 where the second formulation provides immediate release in gastric fluid.

252. The composition according to claim 250 where the active ingredient is amoxicillin or a biologically active salt thereof.

253. The composition according to claim 252 where the active ingredient of the second formulation is clavulanate or a biologically active salt thereof.

254. The composition according to claim 250 where the two formulations are placed in a single capsule or a tablet for co-administration.

255. The composition according to claim 235 further comprising an admixture or an overcoat of an immediate release dosage form.

256. The composition according to claim 235 comprising an active ingredient selected from the group consisting of AIDS adjunct agents, alcohol abuse preparations, Alzheimer's disease management agents, amyotrophic lateral sclerosis active ingredient agents, analgesics, anesthetics, antacids, antiarythmics, antibiotics, anticonvulsants, antidepressants, antidiabetic agents, antiemetics, antidotes, antifibrosis active ingredient agents, antifungals, antihistamines, antihypertensives, anti-infective agents, antimicrobials, antineoplastics, antipsychotics, antiparkinsonian agents, antirheumatic agents, appetite stimulants, appetite suppressants, biological response modifiers, biologicals, blood modifiers, bone metabolism regulators, cardioprotective agents, cardiovascular agents, central nervous system stimulants, cholinesterase inhibitors, contraceptives, cystic fibrosis management agents, deodorants, diagnostics, dietary supplements, diuretics, dopamine

receptor agonists, endometriosis management agents, enzymes, erectile dysfunction active ingredients, fatty acids, gastrointestinal agents, Gaucher's disease management agents, gout preparations, homeopathic remedys, hormones, hypercalcemia management agents, hypnotics, hypocalcemia management agents, immunomodulators, immunosuppressives, ion exchange resins, levocarnitine deficiency management agents, mast cell stabilizers, migraine preparations, motion sickness products, multiple sclerosis management agents, muscle relaxants, narcotic detoxification agents, narcotics, nucleoside analogs, non-steroidal anti-inflammatory drugs, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, phosphate binders, porphyria agents, psychoactive ingredient agents, radio-opaque agents, psychotropics, sclerosing agents, sedatives, sickle cell anemia management agents, smoking cessation aids, steroids, stimulants, sympatholytics, sympathomimetics, Tourette's syndrome agents, tremor preparations, urinary tract agents, vaginal preparations, vasodilators, vertigo agents, weight loss agents, Wilson's disease management agents, and mixtures thereof.

257. The composition according to claim 235 where the active ingredient is selected from the group consisting of abacavir sulfate, abacavir sulfate/ lamivudine/zidovudine, acetazolamide, acyclovir, albendazole, albuterol, aldactone, allopurinol, amoxicillin, amoxicillin/clavulanate potassium, amprenavir, atovaquone, atovaquone and proguanil hydrochloride, atracurium besylate, beclomethasone dipropionate, berlactone betamethasone valerate, bupropion hydrochloride, bupropion hydrochloride, carvedilol, caspofungin acetate, cefazolin, ceftazidime, cefuroxime , chlorambucil, chlorpromazine, cimetidine, cimetidine hydrochloride, cisatracurium besilate, clobetasol propionate, co-trimoxazole, colfosceril palmitate, dextroamphetamie sulfate, digoxin, enalapril maleate, epoprostenol, esomepraxole magnesium, fluticasone propionate, furosemide, hydrochlorothiazide, hydrochlorothiazide/triamterene, lamivudine, lamotrigine, lithium carbonate, losartan potassium, melphalan, mercaptopurine, mesalazine, mupirocin calcium cream, nabumetone, naratriptan, omeprazole, ondansetron hydrochloride, ovine, oxiconazole nitrate, paroxetine hydrochloride, prochlorperazine, procyclidine hydrochloride, pyrimethamine, ranitidine bismuth citrate, ranitidine hydrochloride, rofecoxib, ropinirole hydrochloride, rosiglitazone maleate, salmeterol xinafoate, salmeterol, fluticasone propionate, sterile ticarcillin disodium / clavulanate potassium, simvastatin, spironolactone, succinylcholine chloride, sumatriptan, thioguanine, tirofiban HCI, topotecan hydrochloride, tranylcypromine sulfate, trifluoperazine hydrochloride, valacyclovir hydrochloride, vinorelbine, zanamivir, zidovudine, zidovudine or lamivudine, or mixtures thereof.

258. The composition according to claim 235 further coated by gelatin or placed inside a gelatin capsule or a tablet.

259. The composition according to claim 235 which increases active ingredient bioavailability at least 20% relative to an immediate release or a sustained release control that does not include enteric material.

260. The composition according to claim 235 providing substantially equivalent bioavailability but a reduced active ingredient excretion rate relative to an immediate release control formulation.

261. The composition according to claim 235 providing prolonged drug concentrations for active ingredients having an absorption window relative to an immediate release or a sustained release control.

262. The composition according to claim 235 where the enteric coating is selected from the group consisting of cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, carboxymethylethylcellulose, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, cellulose acetate phthalate, poly(methacrylic acid-ethylacrylate), poly(methacrylic acid-methyl methacrylate), Eudagrit L, Eudragit S, and mixtures of enteric materials.

263. The composition according to claim 235 providing controlled *in vitro* gastric release, followed by pulsatile *in vitro* intestinal release.

264. The composition according to claim 235 comprising plural active ingredients.

265. A method for treating a subject having a condition treatable by an active ingredient, comprising:

providing a pharmaceutical composition comprising an active ingredient suitable for treating the condition and a leaky enteric material; and

treating the subject by administering the pharmaceutical composition to the subject.

266. The method according to claim 265 where the active ingredient is substantially homogeneously mixed with the enteric material.

267. The method according to claim 265 where the composition includes a leaky enteric coating.

268. The method according to claim 267 where the enteric coating has a layer thickness of 25 microns or less.

269. The method according to claim 267 where the leaky enteric coating includes a gastric fluid channeling agent.

270. The method according to claim 265 comprising administering to a fed subject or administering substantially simultaneously when the subject eats or drinks.

271. The method according to claim 265 comprising administering to a fasted subject.

272. The method according to claim 265 where at least 10% by mass of the active ingredient is released in gastric fluid.

273. The method according to claim 265 where the active ingredient has a window of absorption.

274. The method according to claim 273 where the active ingredient is selected from the group consisting of therapeutic nucleic acids or amino acid sequences, nucleic acids or amino acid derivatives, peptidomimetic drugs, antibiotics, therapeutic ions, vitamins, bronchodilators, anti-gout agents, anti-hypertensive agents, diuretic agents, anti-hyperlipidemic agents or ACE inhibitors, drugs intended for local treatment of the gastrointestinal tract, including anti-tumor agents, histamine (H2) blockers, bismuth salts, synthetic prostaglandins or antibiotic agents, drugs that degrade in the colon, for example metoprolol, formulations useful for treating gastrointestinal associated disorders selected from peptic ulcer, nonulcer dyspepsia, Zollinger-Ellison syndrome, gastritis, duodenitis and the associated ulcerative lesions, stomach or duodenum neoplasms, prazosin, ketanserin, guanabenz acetate, captopril, captopril hydrochloride, enalapril, enalapril maleate,

lysinopril, hydralazide, methyldopa, methyldopa hydrochloride, levodopa, carbidopa, benserazide, amlodipine, nitrendipine, nifedipine, nicardipine, verapamil, acyclovir, inosine, pranobex, tribavirine, vidarabine, zidovudine, AZT, active ingredients that exert a medicinal action at the gastric level, including aluminum hydroxide, magnesium carbonate, magnesium oxide, sucralphate, sodium carbenoxolone, pirenzepin, loperamide, cimetidine, ranitidine, famotidine, misoprostol, omeprazol, and combinations thereof.

275. The method according to claim 265 where the pharmaceutical composition provides an active ingredient release profile where at least 10% active ingredient by mass is released in gastric fluid, followed by at least 75% release of remaining active ingredient in one hour or less upon contacting intestinal fluid.

276. The method according to claim 265 where the active ingredient has a window of absorption, and where at least 10% active ingredient by mass is released in gastric fluid, followed by at least 75% release of remaining active ingredient in 30 minutes or less upon contacting intestinal fluid.

277. The method according to claim 265 where active ingredient release upon contacting gastric fluid is zero order, mixed order or first order, followed by substantially immediate release when remaining composition contacts intestinal fluid.

278. The method according to claim 265 where the leaky enteric material includes a hydrophilic gastric fluid channeling agent.

279. The method according to claim 278 where the gastric fluid channeling agent is a sugar.

280. The method according to claim 265 where the leaky enteric material includes a hydrophobic gastric fluid channeling agent.

281. The method of claim 280 where the hydrophobic material is selected from the group consisting of talc, magnesium salts, silicon dioxide, hydrocarbons, and combinations thereof.

282. The method according to claim 267 where the enteric coating has a thickness of 25 μm or less.

283. The method according to claim 267 where the enteric coating has a thickness of 20 μm or less.

284. The method according to claim 265 comprising a solid composition.

285. The method according to claim 265 comprising treating the subject by oral administration.

286. The method according to claim 265 where the pharmaceutical composition further comprises a second formulation designed to provide an active ingredient release profile different from the pharmaceutical composition.

287. The method according to claim 286 where the second formulation provides immediate release in gastric fluid.

288. The method according to claim 286 where the active ingredient is amoxicillin or a biologically active salt thereof.

289. The method according to claim 288 where the active ingredient of the second formulation is clavulanate or a biologically active salt thereof.

290. The method according to claim 286 where the pharmaceutical composition and the second formulation are placed in a single capsule or tablet for co-administration.

291. The method according to claim 265 where the pharmaceutical composition further comprises an admixture or an overcoat of an immediate release dosage form.

292. The method according to claim 265 where the pharmaceutical composition comprises an active ingredient selected from the group consisting of AIDS adjunct agents, alcohol abuse preparations, Alzheimer's disease management agents, amyotrophic lateral sclerosis active ingredient agents, analgesics, anesthetics, antacids, antiarythmics, antibiotics, anticonvulsants, antidepressants, antidiabetic agents, antiemetics, antidotes,

antifibrosis active ingredient agents, antifungals, antihistamines, antihypertensives, anti-infective agents, antimicrobials, antineoplastics, antipsychotics, antiparkinsonian agents, antirheumatic agents, appetite stimulants, appetite suppressants, biological response modifiers, biologicals, blood modifiers, bone metabolism regulators, cardioprotective agents, cardiovascular agents, central nervous system stimulants, cholinesterase inhibitors, contraceptives, cystic fibrosis management agents, deodorants, diagnostics, dietary supplements, diuretics, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction active ingredients, fatty acids, gastrointestinal agents, Gaucher's disease management agents, gout preparations, homeopathic remedys, hormones, hypercalcemia management agents, hypnotics, hypocalcemia management agents, immunomodulators, immunosuppressives, ion exchange resins, levocarnitine deficiency management agents, mast cell stabilizers, migraine preparations, motion sickness products, multiple sclerosis management agents, muscle relaxants, narcotic detoxification agents, narcotics, nucleoside analogs, non-steroidal anti-inflammatory drugs, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, phosphate binders, porphyria agents, psychoactive ingredient agents, radio-opaque agents, psychotropics, sclerosing agents, sedatives, sickle cell anemia management agents, smoking cessation aids, steroids, stimulants, sympatholytics, sympathomimetics, Tourette's syndrome agents, tremor preparations, urinary tract agents, vaginal preparations, vasodilators, vertigo agents, weight loss agents, Wilson's disease management agents, and mixtures thereof.

293. The method according to claim 265 where the pharmaceutical composition comprises an active ingredient selected from the group consisting of abacavir sulfate, abacavir sulfate/ lamivudine/zidovudine, acetazolamide, acyclovir, albendazole, albuterol, aldactone, allopurinol, amoxicillin, amoxicillin/clavulanate potassium, amprenavir, atovaquone, atovaquone and proguanil hydrochloride, atracurium besylate, beclomethasone dipropionate, berlactone betamethasone valerate, bupropion hydrochloride, bupropion hydrochloride, carvedilol, caspofungin acetate, cefazolin, ceftazidime, cefuroxime , chlorambucil, chlorpromazine, cimetidine, cimetidine hydrochloride, cisatracurium besilate, clobetasol propionate, co-trimoxazole, colfosceril palmitate, dextroamphetamie sulfate, digoxin, enalapril maleate, epoprostenol, esomepraxole magnesium, fluticasone propionate, furosemide, hydrochlorothiazide, hydrochlorothiazide/triamterene, lamivudine, lamotrigine, lithium carbonate, losartan potassium, melphalan, mercaptopurine, mesalazine, mupirocin calcium cream, nabumetone, naratriptan, omeprazole, ondansetron hydrochloride, ovine, oxiconazole nitrate, paroxetine hydrochloride, prochlorperazine, procyclidine hydrochloride,

pyrimethamine, ranitidine bismuth citrate, ranitidine hydrochloride, rofecoxib, ropinirole hydrochloride, rosiglitazone maleate, salmeterol xinafoate, salmeterol, fluticasone propionate, sterile ticarcillin disodium / clavulanate potassium, simvastatin, spironolactone, succinylcholine chloride, sumatriptan, thioguanine, tirofiban HCl, topotecan hydrochloride, tranylcypromine sulfate, trifluoperazine hydrochloride, valacyclovir hydrochloride, vinorelbine, zanamivir, zidovudine, zidovudine or lamivudine, or mixtures thereof.

294. The method according to claim 265 where the pharmaceutical composition is coated by gelatin or placed inside a gelatin capsule or a tablet.

295. The method according to claim 265 where the pharmaceutical composition increases active ingredient bioavailability at least 20% relative to an immediate release or a sustained release control that does not include enteric material.

296. The method according to claim 265 where the pharmaceutical composition provides substantially equivalent bioavailability but a reduced active ingredient excretion rate relative to an immediate release control formulation.

297. The method according to claim 265 where the pharmaceutical composition provides prolonged drug concentrations for active ingredients having an absorption window relative to an immediate release or a sustained release control.

298. The method according to claim 265 where the enteric coating is selected from the group consisting of cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, carboxymethylethylcellulose, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, cellulose acetate phthalate, poly(methacrylic acid-ethylacrylate), poly(methacrylic acid-methyl methacrylate), Eudagrit L, Eudragit S, and mixtures of enteric materials.

299. The method according to claim 265 where the pharmaceutical composition provides controlled *in vitro* gastric release, followed by pulsatile *in vitro* intestinal release.

300. The method according to claim 265 where the pharmaceutical composition comprises plural active ingredients.

301. A method for treating a subject having a condition treatable by an active ingredient, comprising:

providing a composition comprising an active ingredient suitable for treating the condition and an enteric coating having a layer thickness of 25 microns or less; and

treating the subject by administering the composition to the subject.

302. The method according to claim 301 where the enteric coating includes a gastric fluid channeling agent.

303. The method according to claim 301 comprising administering to a fed subject or administering substantially simultaneously while the subject eats or drings.

304. The method according to claim 301 comprising administering to a fasted subject.

305. The method according to claim 301 where at least 10% by mass of the active ingredient is released in gastric fluid.

306. The method according to claim 301 where the active ingredient has a window of absorption.

307. The method according to claim 306 where the active ingredient is selected from the group consisting of therapeutic nucleic acids or amino acid sequences, nucleic acids or amino acid derivatives, peptidomimetic drugs, antibiotics, therapeutic ions, vitamins, bronchodilators, anti-gout agents, anti-hypertensive agents, diuretic agents, anti-hyperlipidemic agents or ACE inhibitors, drugs intended for local treatment of the gastrointestinal tract, including anti-tumor agents, histamine (H2) blockers, bismuth salts, synthetic prostaglandins or antibiotic agents, drugs that degrade in the colon, for example metoprolol, formulations useful for treating gastrointestinal associated disorders selected from peptic ulcer, nonulcer dyspepsia, Zollinger-Ellison syndrome, gastritis, duodenitis and the associated ulcerative lesions, stomach or duodenum neoplasms, prazosin, ketanserin, guanabenz acetate, captopril, captopril hydrochloride, enalapril, enalapril maleate, lysinopril, hydralazide, methyldopa, methyldopa hydrochloride, levodopa, carbidopa, benserazide, amlodipine, nitrendipine, nifedipine, nicardipine, verapamil, acyclovir, inosine, pranobex, tribavirine, vidarabine, zidovudine, AZT, active ingredients that exert a medicinal

action at the gastric level, including aluminum hydroxide, magnesium carbonate, magnesium oxide, sucralphate, sodium carbenoxolone, pirenzepin, loperamide, cimetidine, ranitidine, famotidine, misoprostol, omeprazol, and combinations thereof.

308. The method according to claim 301 providing an active ingredient release profile where at least 10% active ingredient by mass is released in gastric fluid, followed by at least 75% release of remaining active ingredient in one hour or less upon contacting intestinal fluid.

309. The method according to claim 301 where the active ingredient has a window of absorption, and where at least 10% active ingredient by mass is released in gastric fluid, followed by at least 75% release of remaining active ingredient in 30 minutes or less upon contacting intestinal fluid.

310. The method according to claim 301 where active ingredient release upon contacting gastric fluid is zero order, mixed order or first order, followed by substantially immediate release when remaining composition contacts intestinal fluid.

311. The method according to claim 301 where the enteric coating includes a hydrophilic gastric fluid channeling agent.

312. The method according to claim 311 where the gastric fluid channeling agent is a sugar.

313. The method according to claim 301 where the enteric coating includes a hydrophobic gastric fluid channeling agent.

314. The method of claim 313 where the hydrophobic material is selected from the group consisting of talc, magnesium salts, silicon dioxide, hydrocarbons, and combinations thereof.

315. The method according to claim 301 where the enteric coating has a thickness of 20 μm or less.

316. The method according to claim 301 where the pharmaceutical composition comprises a solid composition.

317. The method according to claim 301 comprising treating the subject by oral administration.

318. The method according to claim 301 where the pharmaceutical composition further comprises a second formulation designed to provide an active ingredient release profile different from the pharmaceutical composition.

319. The method according to claim 318 where the second formulation provides immediate release in gastric fluid.

320. The method according to claim 318 where the active ingredient is amoxicillin or a biologically active salt thereof.

321. The method according to claim 320 where the active ingredient of the second formulation is clavulanate or a biologically active salt thereof.

322. The method according to claim 318 where the two formulations are placed in a single capsule or tablet for co-administration.

323. The method according to claim 301 where the pharmaceutical composition further comprises an admixture or an overcoat of an immediate release dosage form.

324. The method according to claim 301 where the pharmaceutical composition comprises an active ingredient selected from the group consisting of AIDS adjunct agents, alcohol abuse preparations, Alzheimer's disease management agents, amyotrophic lateral sclerosis active ingredient agents, analgesics, anesthetics, antacids, antiarythmics, antibiotics, anticonvulsants, antidepressants, antidiabetic agents, antiemetics, antidotes, antifibrosis active ingredient agents, antifungals, antihistamines, antihypertensives, anti-infective agents, antimicrobials, antineoplastics, antipsychotics, antiparkinsonian agents, antirheumatic agents, appetite stimulants, appetite suppressants, biological response modifiers, biologicals, blood modifiers, bone metabolism regulators, cardioprotective agents, cardiovascular agents, central nervous system stimulants, cholinesterase inhibitors,

contraceptives, cystic fibrosis management agents, deodorants, diagnostics, dietary supplements, diuretics, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction active ingredients, fatty acids, gastrointestinal agents, Gaucher's disease management agents, gout preparations, homeopathic remedys, hormones, hypercalcemia management agents, hypnotics, hypocalcemia management agents, immunomodulators, immunosuppressives, ion exchange resins, levocarnitine deficiency management agents, mast cell stabilizers, migraine preparations, motion sickness products, multiple sclerosis management agents, muscle relaxants, narcotic detoxification agents, narcotics, nucleoside analogs, non-steroidal anti-inflammatory drugs, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, phosphate binders, porphyria agents, psychoactive ingredient agents, radio-opaque agents, psychotropics, sclerosing agents, sedatives, sickle cell anemia management agents, smoking cessation aids, steroids, stimulants, sympatholytics, sympathomimetics, Tourette's syndrome agents, tremor preparations, urinary tract agents, vaginal preparations, vasodilators, vertigo agents, weight loss agents, Wilson's disease management agents, and mixtures thereof.

325. The method according to claim 301 where the pharmaceutical composition comprises an active ingredient selected from the group consisting of abacavir sulfate, abacavir sulfate/ lamivudine/zidovudine, acetazolamide, acyclovir, albendazole, albuterol, aldactone, allopurinol, amoxicillin, amoxicillin/clavulanate potassium, amprenavir, atovaquone, atovaquone and proguanil hydrochloride, atracurium besylate, beclomethasone dipropionate, berlactone betamethasone valerate, bupropion hydrochloride, bupropion hydrochloride, carvedilol, caspofungin acetate, cefazolin, ceftazidime, cefuroxime , chlorambucil, chlorpromazine, cimetidine, cimetidine hydrochloride, cisatracurium besilate, clobetasol propionate, co-trimoxazole, colfosceril palmitate, dextroamphetamie sulfate, digoxin, enalapril maleate, epoprostenol, esomepraxole magnesium, fluticasone propionate, furosemide, hydrochlorothiazide, hydrochlorothiazide/triamterene, lamivudine, lamotrigine, lithium carbonate, losartan potassium, melphalan, mercaptopurine, mesalazine, mupirocin calcium cream, nabumetone, naratriptan, omeprazole, ondansetron hydrochloride, ovine, oxiconazole nitrate, paroxetine hydrochloride, prochlorperazine, procyclidine hydrochloride, pyrimethamine, ranitidine bismuth citrate, ranitidine hydrochloride, rofecoxib, ropinirole hydrochloride, rosiglitazone maleate, salmeterol xinafoate, salmeterol, fluticasone propionate, sterile ticarcillin disodium / clavulanate potassium, simvastatin, spironolactone, succinylcholine chloride, sumatriptan, thioguanine, tirofiban HCI, topotecan hydrochloride,

tranylcypromine sulfate, trifluoperazine hydrochloride, valacyclovir hydrochloride, vinorelbine, zanamivir, zidovudine, zidovudine or lamivudine, or mixtures thereof.

326. The method according to claim 301 where the pharmaceutical composition is coated by gelatin or placed inside a gelatin capsule or a tablet.

327. The method according to claim 301 where the pharmaceutical composition increases active ingredient bioavailability at least 20% relative to an immediate release or a sustained release control that does not include enteric material.

328. The method according to claim 301 where the pharmaceutical composition provides substantially equivalent bioavailability but a reduced active ingredient excretion rate relative to an immediate release control formulation.

329. The method according to claim 301 where the pharmaceutical composition provides prolonged drug concentrations for active ingredients having an absorption window relative to an immediate release or a sustained release control.

330. The method according to claim 301 where the enteric coating is selected from the group consisting of cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, carboxymethylethylcellulose, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, cellulose acetate phthalate, poly(methacrylic acid-ethylacrylate), poly(methacrylic acid-methyl methacrylate), Eudagrit L, Eudragit S, and mixtures of enteric materials.

331. The method according to claim 301 where the pharmaceutical composition provides controlled *in vitro* gastric release, followed by pulsatile *in vitro* intestinal release.

332. The method according to claim 301 where the pharmaceutical composition comprises plural active ingredients.

333. A method for treating a subject having a condition treatable by an active ingredient, comprising:

providing a composition comprising at least one active ingredient suitable for treating the condition in or on a core and an enteric coating further comprising a gastric fluid channeling agent; and

treating the subject by administering the composition to the subject.

334. The method according to claim 333 where the enteric coating has a layer thickness of 25 microns or less.

335. The method according to claim 333 comprising administering to a fed subject or administering substantially simultaneously while the subject eats or drinks.

336. The method according to claim 333 comprising administering to a fasted subject.

337. The method according to claim 333 where at least 10% by mass of the active ingredient is released in gastric fluid.

338. The method according to claim 333 where the active ingredient has a window of absorption.

339. The method according to claim 338 where the active ingredient is selected from the group consisting of therapeutic nucleic acids or amino acid sequences, nucleic acids or amino acid derivatives, peptidomimetic drugs, antibiotics, therapeutic ions, vitamins, bronchodilators, anti-gout agents, anti-hypertensive agents, diuretic agents, anti-hyperlipidemic agents or ACE inhibitors, drugs intended for local treatment of the gastrointestinal tract, including anti-tumor agents, histamine (H2) blockers, bismuth salts, synthetic prostaglandins or antibiotic agents, drugs that degrade in the colon, for example metoprolol, formulations useful for treating gastrointestinal associated disorders selected from peptic ulcer, nonulcer dyspepsia, Zollinger-Ellison syndrome, gastritis, duodenitis and the associated ulcerative lesions, stomach or duodenum neoplasms, prazosin, ketanserin, guanabenz acetate, captopril, captopril hydrochloride, enalapril, enalapril maleate, lysinopril, hydralazide, methyldopa, methyldopa hydrochloride, levodopa, carbidopa, benserazide, amlodipine, nitrendipine, nifedipine, nicardipine, verapamil, acyclovir, inosine, pranobex, tribavirine, vidarabine, zidovudine, AZT, active ingredients that exert a medicinal action at the gastric level, including aluminum hydroxide, magnesium carbonate,

magnesium oxide, sucralphate, sodium carbenoxolone, pirenzepin, loperamide, cimetidine, ranitidine, famotidine, misoprostol, omeprazol, and combinations thereof.

340. The method according to claim 333 providing an active ingredient release profile where at least 10% active ingredient by mass is released in gastric fluid, followed by at least 75% release of remaining active ingredient in one hour or less upon contacting intestinal fluid.

341. The method according to claim 333 where the active ingredient has a window of absorption, and where at least 10% active ingredient by mass is released in gastric fluid, followed by at least 75% release of remaining active ingredient in 30 minutes or less upon contacting intestinal fluid.

342. The method according to claim 333 where active ingredient release upon contacting gastric fluid is zero order, mixed order or first order, followed by substantially immediate release when remaining composition contacts intestinal fluid.

343 The method according to claim 333 where the gastric fluid channeling agent is hydrophilic.

344. The method according to claim 343 where the gastric fluid channeling agent is a sugar.

345. The method according to claim 333 where the gastric fluid channeling agent is hydrophobic.

346. The method of claim 345 where the hydrophobic material is selected from the group consisting of talc, magnesium salts, silicon dioxide, hydrocarbons, and combinations thereof.

347. The method according to claim 333 where the enteric coating has a thickness of 20 μm or less.

348. The method according to claim 333 comprising administering the compositions as a solid composition.

349. The method according to claim 333 comprising treating the subject by oral administration.

350. The method according to claim 333 where the pharmaceutical composition further comprises a second formulation designed to provide an active ingredient release profile different from the pharmaceutical composition.

351. The method according to claim 350 where the second formulation provides immediate release in gastric fluid.

352. The method according to claim 350 where the active ingredient is amoxicillin or a biologically active salt thereof.

353. The method according to claim 352 where the active ingredient of the second formulation is clavulanate or a biologically active salt thereof.

354. The method according to claim 350 where the two formulations are placed in a single capsule or tablet for co-administration.

355. The method according to claim 333 where the pharmaceutical composition further comprises an admixture or an overcoat of an immediate release dosage form.

356. The method according to claim 333 where the pharmaceutical composition comprises an active ingredient selected from the group consisting of AIDS adjunct agents, alcohol abuse preparations, Alzheimer's disease management agents, amyotrophic lateral sclerosis active ingredient agents, analgesics, anesthetics, antacids, antiarythmics, antibiotics, anticonvulsants, antidepressants, antidiabetic agents, antiemetics, antidotes, antifibrosis active ingredient agents, antifungals, antihistamines, antihypertensives, anti-infective agents, antimicrobials, antineoplastics, antipsychotics, antiparkinsonian agents, antirheumatic agents, appetite stimulants, appetite suppressants, biological response modifiers, biologicals, blood modifiers, bone metabolism regulators, cardioprotective agents, cardiovascular agents, central nervous system stimulants, cholinesterase inhibitors, contraceptives, cystic fibrosis management agents, deodorants, diagnostics, dietary supplements, diuretics, dopamine receptor agonists, endometriosis management agents,

enzymes, erectile dysfunction active ingredients, fatty acids, gastrointestinal agents, Gaucher's disease management agents, gout preparations, homeopathic remedys, hormones, hypercalcemia management agents, hypnotics, hypocalcemia management agents, immunomodulators, immunosuppressives, ion exchange resins, levocarnitine deficiency management agents, mast cell stabilizers, migraine preparations, motion sickness products, multiple sclerosis management agents, muscle relaxants, narcotic detoxification agents, narcotics, nucleoside analogs, non-steroidal anti-inflammatory drugs, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, phosphate binders, porphyria agents, psychoactive ingredient agents, radio-opaque agents, psychotropics, sclerosing agents, sedatives, sickle cell anemia management agents, smoking cessation aids, steroids, stimulants, sympatholytics, sympathomimetics, Tourette's syndrome agents, tremor preparations, urinary tract agents, vaginal preparations, vasodilators, vertigo agents, weight loss agents, Wilson's disease management agents, and mixtures thereof.

357. The method according to claim 333 where the pharmaceutical composition comprises an active ingredient selected from the group consisting of abacavir sulfate, abacavir sulfate/ lamivudine/zidovudine, acetazolamide, acyclovir, albendazole, albuterol, aldactone, allopurinol, amoxicillin, amoxicillin/clavulanate potassium, amprenavir, atovaquone, atovaquone and proguanil hydrochloride, atracurium besylate, beclomethasone dipropionate, berlactone betamethasone valerate, bupropion hydrochloride, bupropion hydrochloride, carvedilol, caspofungin acetate, cefazolin, ceftazidime, cefuroxime , chlorambucil, chlorpromazine, cimetidine, cimetidine hydrochloride, cisatracurium besilate, clobetasol propionate, co-trimoxazole, colfosceril palmitate, dextroamphetamie sulfate, digoxin, enalapril maleate, epoprostenol, esomepraxole magnesium, fluticasone propionate, furosemide, hydrochlorothiazide, hydrochlorothiazide/triamterene, lamivudine, lamotrigine, lithium carbonate, losartan potassium, melphalan, mercaptopurine, mesalazine, mupirocin calcium cream, nabumetone, naratriptan, omeprazole, ondansetron hydrochloride, ovine, oxiconazole nitrate, paroxetine hydrochloride, prochlorperazine, procyclidine hydrochloride, pyrimethamine, ranitidine bismuth citrate, ranitidine hydrochloride, rofecoxib, ropinirole hydrochloride, rosiglitazone maleate, salmeterol xinafoate, salmeterol, fluticasone propionate, sterile ticarcillin disodium / clavulanate potassium, simvastatin, spironolactone, succinylcholine chloride, sumatriptan, thioguanine, tirofiban HCI, topotecan hydrochloride, tranylcypromine sulfate, trifluoperazine hydrochloride, valacyclovir hydrochloride, vinorelbine, zanamivir, zidovudine, zidovudine or lamivudine, or mixtures thereof.

358. The method according to claim 333 where the pharmaceutical composition is coated by gelatin or placed inside a gelatin capsule or a tablet.

359. The method according to claim 333 where the pharmaceutical composition increases active ingredient bioavailability at least 20% relative to an immediate release or a sustained release control that does not include enteric material.

360. The method according to claim 333 where the pharmaceutical composition provides substantially equivalent bioavailability but a reduced active ingredient excretion rate relative to an immediate release control formulation.

361. The method according to claim 333 where the pharmaceutical composition provides prolonged drug concentrations for active ingredients having an absorption window relative to an immediate or a sustained release release control.

362. The method according to claim 333 where the enteric coating is selected from the group consisting of cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, carboxymethylethylcellulose, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, cellulose acetate phthalate, poly(methacrylic acid-ethylacrylate), poly(methacrylic acid-methyl methacrylate), Eudagrit L, Eudragit S, and mixtures of enteric materials.

363. The method according to claim 333 where the pharmaceutical composition provides controlled *in vitro* gastric release, followed by pulsatile *in vitro* intestinal release.

364. The method according to claim 333 where the pharmaceutical composition comprises plural active ingredients.

365. A method for treating a subject having a condition treatable by an active ingredient, comprising:

providing a pharmaceutical composition that provides programmed active ingredient release, the composition comprising at least one active ingredient substantially homogeneously admixed with at least one enteric material comprising a gastric channeling agent; and

treating the subject by administering the composition to the subject.

366. The method according to claim 365 comprising administering to a fed subject or administering substantially simultaneously while the subject eats or drinks.

367. The method according to claim 365 comprising administering to a fasted subject.

368. The method according to claim 365 where at least 10% by mass of the active ingredient is released in gastric fluid.

369. The method according to claim 365 where the active ingredient has a window of absorption.

370. The method according to claim 369 where the active ingredient is selected from the group consisting of therapeutic nucleic acids or amino acid sequences, nucleic acids or amino acid derivatives, peptidomimetic drugs, antibiotics, therapeutic ions, vitamins, bronchodilators, anti-gout agents, anti-hypertensive agents, diuretic agents, anti-hyperlipidemic agents or ACE inhibitors, drugs intended for local treatment of the gastrointestinal tract, including anti-tumor agents, histamine (H2) blockers, bismuth salts, synthetic prostaglandins or antibiotic agents, drugs that degrade in the colon, for example metoprolol, formulations useful for treating gastrointestinal associated disorders selected from peptic ulcer, nonulcer dyspepsia, Zollinger-Ellison syndrome, gastritis, duodenitis and the associated ulcerative lesions, stomach or duodenum neoplasms, prazosin, ketanserin, guanabenz acetate, captopril, captopril hydrochloride, enalapril, enalapril maleate, lysinopril, hydralazide, methyldopa, methyldopa hydrochloride, levodopa, carbidopa, benserazide, amlodipine, nitrendipine, nifedipine, nicardipine, verapamil, acyclovir, inosine, pranobex, tribavirine, vidarabine, zidovudine, AZT, active ingredients that exert a medicinal action at the gastric level, including aluminum hydroxide, magnesium carbonate, magnesium oxide, sucralphate, sodium carbenoxolone, pirenzepin, loperamide, cimetidine, ranitidine, famotidine, misoprostol, omeprazol, and combinations thereof.

371. The method according to claim 365 providing an active ingredient release profile where at least 10% active ingredient by mass is released in gastric fluid, followed by at least 75% release of remaining active ingredient in one hour or less upon contacting intestinal fluid.

372. The method according to claim 365 where the active ingredient has a window of absorption, and where at least 10% active ingredient by mass is released in gastric fluid, followed by at least 75% release of remaining active ingredient in 30 minutes or less upon contacting intestinal fluid.

373. The method according to claim 365 where active ingredient release upon contacting gastric fluid is zero order, mixed order or first order, followed by substantially immediate release when remaining composition contacts intestinal fluid.

374. The method according to claim 365 where the gastric fluid channeling agent is hydrophilic.

375. The method according to claim 374 where the gastric fluid channeling agent is a sugar.

376. The method according to claim 365 where the gastric fluid channeling agent is hydrophobic.

377. The method of claim 376 where the hydrophobic material is selected from the group consisting of talc, magnesium salts, silicon dioxide, hydrocarbons, and combinations thereof.

378. The method according to claim 365 comprising administering the composition as a solid composition.

379. The method according to claim 365 comprising treating the subject by oral administration.

380. The method according to claim 365 where the pharmaceutical composition further comprises a second formulation designed to provide an active ingredient release profile different from the pharmaceutical composition.

381. The method according to claim 380 where the second formulation provides immediate release in gastric fluid.

382. The method according to claim 380 where the active ingredient is amoxicillin or a biologically active salt thereof.

383. The method according to claim 382 where the active ingredient of the second formulation is clavulanate or a biologically active salt thereof.

384. The method according to claim 380 where the two formulations are placed in a single capsule or tablet for co-administration.

385. The method according to claim 365 where the pharmaceutical composition further comprises an admixture or an overcoat of an immediate release dosage form.

386. The method according to claim 365 where the pharmaceutical composition comprises an active ingredient selected from the group consisting of AIDS adjunct agents, alcohol abuse preparations, Alzheimer's disease management agents, amyotrophic lateral sclerosis active ingredient agents, analgesics, anesthetics, antacids, antiarythmics, antibiotics, anticonvulsants, antidepressants, antidiabetic agents, antiemetics, antidotes, antifibrosis active ingredient agents, antifungals, antihistamines, antihypertensives, anti-infective agents, antimicrobials, antineoplastics, antipsychotics, antiparkinsonian agents, antirheumatic agents, appetite stimulants, appetite suppressants, biological response modifiers, biologicals, blood modifiers, bone metabolism regulators, cardioprotective agents, cardiovascular agents, central nervous system stimulants, cholinesterase inhibitors, contraceptives, cystic fibrosis management agents, deodorants, diagnostics, dietary supplements, diuretics, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction active ingredients, fatty acids, gastrointestinal agents, Gaucher's disease management agents, gout preparations, homeopathic remedys, hormones, hypercalcemia management agents, hypnotics, hypocalcemia management agents, immunomodulators, immunosuppressives, ion exchange resins, levocarnitine deficiency management agents, mast cell stabilizers, migraine preparations, motion sickness products, multiple sclerosis management agents, muscle relaxants, narcotic detoxification agents, narcotics, nucleoside analogs, non-steroidal anti-inflammatory drugs, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, phosphate binders, porphyria agents, psychoactive ingredient agents, radio-opaque agents, psychotropics, sclerosing agents, sedatives, sickle cell anemia management agents, smoking

cessation aids, steroids, stimulants, sympatholytics, sympathomimetics, Tourette's syndrome agents, tremor preparations, urinary tract agents, vaginal preparations, vasodilators, vertigo agents, weight loss agents, Wilson's disease management agents, and mixtures thereof.

387. The method according to claim 365 where the pharmaceutical composition comprises an active ingredient selected from the group consisting of abacavir sulfate, abacavir sulfate/ lamivudine/zidovudine, acetazolamide, acyclovir, albendazole, albuterol, aldactone, allopurinol, amoxicillin, amoxicillin/clavulanate potassium, amprenavir, atovaquone, atovaquone and proguanil hydrochloride, atracurium besylate, beclomethasone dipropionate, berlactone betamethasone valerate, bupropion hydrochloride, bupropion hydrochloride, carvedilol, caspofungin acetate, cefazolin, ceftazidime, cefuroxime , chlorambucil, chlorpromazine, cimetidine, cimetidine hydrochloride, cisatracurium besilate, clobetasol propionate, co-trimoxazole, colfosceril palmitate, dextroamphetamie sulfate, digoxin, enalapril maleate, epoprostenol, esomepraxole magnesium, fluticasone propionate, furosemide, hydrochlorothiazide, hydrochlorothiazide/triamterene, lamivudine, lamotrigine, lithium carbonate, losartan potassium, melphalan, mercaptopurine, mesalazine, mupirocin calcium cream, nabumetone, naratriptan, omeprazole, ondansetron hydrochloride, ovine, oxiconazole nitrate, paroxetine hydrochloride, prochlorperazine, procyclidine hydrochloride, pyrimethamine, ranitidine bismuth citrate, ranitidine hydrochloride, rofecoxib, ropinirole hydrochloride, rosiglitazone maleate, salmeterol xinafoate, salmeterol, fluticasone propionate, sterile ticarcillin disodium / clavulanate potassium, simvastatin, spironolactone, succinylcholine chloride, sumatriptan, thioguanine, tirofiban HCI, topotecan hydrochloride, tranylcypromine sulfate, trifluoperazine hydrochloride, valacyclovir hydrochloride, vinorelbine, zanamivir, zidovudine, zidovudine or lamivudine, or mixtures thereof.

388. The method according to claim 365 where the pharmaceutical composition is coated by gelatin or placed inside a gelatin capsule.

389. The method according to claim 365 where the pharmaceutical composition increases active ingredient bioavailability at least 20% relative to an immediate release or a sustained release control that does not include enteric material.

390. The method according to claim 365 where the pharmaceutical composition provides substantially equivalent bioavailability but a reduced active ingredient excretion rate relative to an immediate release control formulation.

391. The method according to claim 365 where the pharmaceutical composition provides prolonged drug concentrations for active ingredients having an absorption window relative to an immediate release or a sustained release control.

392. The method according to claim 365 where the enteric material is selected from the group consisting of cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), hydroxypropylmethyl cellulose, hydroxypropyl methylcellulose acetate succinate (HPMCAS), cellulose acetate trimellitate, hydroxypropyl methylcellulose succinate, carboxymethyl cellulose, carboxymethyl ethyl cellulose, cellulose acetate phthalate, cellulose acetate succinate, cellulose acetate hexahydrophthalate, cellulose propionate phthalate, cellulose acetate maleate, cellulose acetate butyrate, cellulose acetate propionate, copolymer of methylmethacrylic acid and methyl methacrylate, copolymer of methyl acrylate, methylmethacrylate and methacrylic acid, copolymer of methylvinyl ether and maleic anhydride (Gantrez ES series), ethyl methyacrylate-methylmethacrylate-chlorotrimethylammonium ethyl acrylate copolymer, polyvinyl acetate phthalate, zein, shellac, copal collophorium, Eudragit L30D55, Eudragit FS30D, Eudragit L100, Eudragit S100, Kollicoat EMM30D, Estacryl 30D, Coateric, Aquateric, and combinations of such materials.

393. The method according to claim 365 where the pharmaceutical composition provides controlled *in vitro* gastric release, followed by pulsatile *in vitro* intestinal release.

394. The method according to claim 365 where the pharmaceutical composition comprises plural active ingredients.

395. A method for treating a subject having a condition treatable by an active ingredient, comprising:

providing a pharmaceutical composition that provides programmed active ingredient release, the composition comprising at least one active ingredient suitable for treating the condition substantially homogeneously admixed with at least one enteric material for delivering at least a portion of the active ingredient upon contacting gastric fluid followed by substantially complete release thereafter upon contacting intestinal fluid; and

treating the subject by administering the composition to the subject.

396. The method according to claim 395 comprising administering to a fed subject or administering substantially simultaneously while the subject eats or drinks.

397. The method according to claim 395 comprising administering to a fasted subject.

398. The method according to claim 395 where at least 10% by mass of the active ingredient is released in gastric fluid.

399. The method according to claim 395 where the active ingredient has a window of absorption.

400. The method according to claim 399 where the active ingredient is selected from the group consisting of therapeutic nucleic acids or amino acid sequences, nucleic acids or amino acid derivatives, peptidomimetic drugs, antibiotics, therapeutic ions, vitamins, bronchodilators, anti-gout agents, anti-hypertensive agents, diuretic agents, anti-hyperlipidemic agents or ACE inhibitors, drugs intended for local treatment of the gastrointestinal tract, including anti-tumor agents, histamine (H2) blockers, bismuth salts, synthetic prostaglandins or antibiotic agents, drugs that degrade in the colon, for example metoprolol, formulations useful for treating gastrointestinal associated disorders selected from peptic ulcer, nonulcer dyspepsia, Zollinger-Ellison syndrome, gastritis, duodenitis and the associated ulcerative lesions, stomach or duodenum neoplasms, prazosin, ketanserin, guanabenz acetate, captopril, captopril hydrochloride, enalapril, enalapril maleate, lysinopril, hydralazide, methyldopa, methyldopa hydrochloride, levodopa, carbidopa, benserazide, amlodipine, nitrendipine, nifedipine, nicardipine, verapamil, acyclovir, inosine, pranobex, tribavirine, vidarabine, zidovudine, AZT, active ingredients that exert a medicinal action at the gastric level, including aluminum hydroxide, magnesium carbonate, magnesium oxide, sucralphate, sodium carbenoxolone, pirenzepin, loperamide, cimetidine, ranitidine, famotidine, misoprostol, omeprazol, and combinations thereof.

401. The method according to claim 395 providing an active ingredient release profile where at least 10% active ingredient by mass is released in gastric fluid, followed by at least 75% release of remaining active ingredient in one hour or less upon contacting intestinal fluid.

402. The method according to claim 395 where the active ingredient has a window of absorption, and where at least 10% active ingredient by mass is released in gastric fluid, followed by at least 75% release of remaining active ingredient in 30 minutes or less upon contacting intestinal fluid.

403. The method according to claim 395 where active ingredient release upon contacting gastric fluid is zero order, mixed order or first order, followed by substantially immediate release when remaining composition contacts intestinal fluid.

404. The method according to claim 395 where the enteric material includes a hydrophilic gastric fluid channeling agent.

405. The method according to claim 404 where the gastric fluid channeling agent is a sugar.

406. The method according to claim 395 where the enteric material includes a hydrophobic gastric fluid channeling agent.

407. The method of claim 406 where the hydrophobic material is selected from the group consisting of talc, magnesium salts, silicon dioxide, hydrocarbons, and combinations thereof.

408. The method according to claim 395 comprising a solid composition.

409. The method according to claim 395 comprising treating the subject by oral administration.

410. The method according to claim 395 where the pharmaceutical composition further comprises a second formulation designed to provide an active ingredient release profile different from the pharmaceutical composition.

411. The method according to claim 410 where the second formulation provides immediate release in gastric fluid.

412. The method according to claim 410where the active ingredient is amoxicillin or a biologically active salt thereof.

413. The method according to claim 412 where the active ingredient of the second formulation is clavulanate or a biologically active salt thereof.

414. The method according to claim 410where the two formulations are placed in a single capsule or tablet for co-administration.

415. The method according to claim 395where the pharmaceutical composition further comprises an admixture or an overcoat of an immediate release dosage form.

416. The method according to claim 395where the pharmaceutical composition comprises an active ingredient selected from the group consisting of AIDS adjunct agents, alcohol abuse preparations, Alzheimer's disease management agents, amyotrophic lateral sclerosis active ingredient agents, analgesics, anesthetics, antacids, antiarythmics, antibiotics, anticonvulsants, antidepressants, antidiabetic agents, antiemetics, antidotes, antifibrosis active ingredient agents, antifungals, antihistamines, antihypertensives, anti-infective agents, antimicrobials, antineoplastics, antipsychotics, antiparkinsonian agents, antirheumatic agents, appetite stimulants, appetite suppressants, biological response modifiers, biologicals, blood modifiers, bone metabolism regulators, cardioprotective agents, cardiovascular agents, central nervous system stimulants, cholinesterase inhibitors, contraceptives, cystic fibrosis management agents, deodorants, diagnostics, dietary supplements, diuretics, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction active ingredients, fatty acids, gastrointestinal agents, Gaucher's disease management agents, gout preparations, homeopathic remedys, hormones, hypercalcemia management agents, hypnotics, hypocalcemia management agents, immunomodulators, immunosuppressives, ion exchange resins, levocarnitine deficiency management agents, mast cell stabilizers, migraine preparations, motion sickness products, multiple sclerosis management agents, muscle relaxants, narcotic detoxification agents, narcotics, nucleoside analogs, non-steroidal anti-inflammatory drugs, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, phosphate binders, porphyria agents, psychoactive ingredient agents, radio-opaque agents, psychotropics, sclerosing agents, sedatives, sickle cell anemia management agents, smoking cessation aids, steroids, stimulants, sympatholytics, sympathomimetics, Tourette's syndrome

agents, tremor preparations, urinary tract agents, vaginal preparations, vasodilators, vertigo agents, weight loss agents, Wilson's disease management agents, and mixtures thereof.

417. The method according to claim 395 where the pharmaceutical composition comprises an active ingredient selected from the group consisting of abacavir sulfate, abacavir sulfate/ lamivudine/zidovudine, acetazolamide, acyclovir, albendazole, albuterol, aldactone, allopurinol, amoxicillin, amoxicillin/clavulanate potassium, amprenavir, atovaquone, atovaquone and proguanil hydrochloride, atracurium besylate, beclomethasone dipropionate, berlactone betamethasone valerate, bupropion hydrochloride, bupropion hydrochloride, carvedilol, caspofungin acetate, cefazolin, ceftazidime, cefuroxime , chlorambucil, chlorpromazine, cimetidine, cimetidine hydrochloride, cisatracurium besilate, clobetasol propionate, co-trimoxazole, colfosceril palmitate, dextroamphetamie sulfate, digoxin, enalapril maleate, epoprostenol, esomepraxole magnesium, fluticasone propionate, furosemide, hydrochlorothiazide, hydrochlorothiazide/triamterene, lamivudine, lamotrigine, lithium carbonate, losartan potassium, melphalan, mercaptopurine, mesalazine, mupirocin calcium cream, nabumetone, naratriptan, omeprazole, ondansetron hydrochloride, ovine, oxiconazole nitrate, paroxetine hydrochloride, prochlorperazine, procyclidine hydrochloride, pyrimethamine, ranitidine bismuth citrate, ranitidine hydrochloride, rofecoxib, ropinirole hydrochloride, rosiglitazone maleate, salmeterol xinafoate, salmeterol, fluticasone propionate, sterile ticarcillin disodium / clavulanate potassium, simvastatin, spironolactone, succinylcholine chloride, sumatriptan, thioguanine, tirofiban HCI, topotecan hydrochloride, tranylcypromine sulfate, trifluoperazine hydrochloride, valacyclovir hydrochloride, vinorelbine, zanamivir, zidovudine, zidovudine or lamivudine, or mixtures thereof.

418. The method according to claim 395 where the pharmaceutical composition is coated by gelatin or placed inside a gelatin capsule or a tablet.

419. The method according to claim 395 where the pharmaceutical composition increases active ingredient bioavailability at least 20% relative to an immediate release or a sustained release control that does not include enteric material.

420. The method according to claim 395 where the pharmaceutical composition provides substantially equivalent bioavailability but a reduced active ingredient excretion rate relative to an immediate release control formulation.

421. The method according to claim 395 where the pharmaceutical composition provides prolonged drug concentrations for active ingredients having an absorption window relative to an immediate release or a sustained release control.

422. The method according to claim 395 where the enteric material is selected from the group consisting of cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), hydroxypropylmethyl cellulose, hydroxypropyl methylcellulose acetate succinate (HPMCAS), cellulose acetate trimellitate, hydroxypropyl methylcellulose succinate, carboxymethyl cellulose, carboxymethyl ethyl cellulose, cellulose acetate phthalate, cellulose acetate succinate, cellulose acetate hexahydrophthalate, cellulose propionate phthalate, cellulose acetate maleate, cellulose acetate butyrate, cellulose acetate propionate, copolymer of methylmethacrylic acid and methyl methacrylate, copolymer of methyl acrylate, methylmethacrylate and methacrylic acid, copolymer of methylvinyl ether and maleic anhydride (Gantrez ES series), ethyl methyacrylate-methylmethacrylate-chlorotrimethylammonium ethyl acrylate copolymer, polyvinyl acetate phthalate, zein, shellac, copal collophorium, Eudragit L30D55, Eudragit FS30D, Eudragit L100, Eudragit S100, Kollicoat EMM30D, Estacryl 30D, Coateric, Aquateric, and combinations of such materials.

423. The method according to claim 395 where the pharmaceutical composition provides controlled *in vitro* gastric release, followed by pulsatile *in vitro* intestinal release.

424. The method according to claim 395 where the pharmaceutical composition comprises plural active ingredients.

425. A method for treating a subject having a condition treatable by an active ingredient, comprising:

providing a pharmaceutical composition comprising at least one active ingredient suitable for treating the condition and a leaky enteric coating, the composition releasing at least 10 percent of the active ingredient mass while contacting gastric fluid, the remaining active ingredient being released substantially completely after contacting intestinal fluid; and

treating the subject by administering the composition to the subject.

426. The method according to claim 425 where the leaky enteric coating has a layer thickness of 25 microns or less.

427. The method according to claim 425 where the leaky enteric coating includes a gastric fluid channeling agent.

428. The method according to claim 425 comprising administering to a fed subject or administering substantially simultaneously while the subject eats or drinks.

429. The method according to claim 425 comprising administering to a fasted subject.

430. The method according to claim 425 where the active ingredient has a window of absorption.

431. The method according to claim 430 where the active ingredient is selected from the group consisting of therapeutic nucleic acids or amino acid sequences, nucleic acids or amino acid derivatives, peptidomimetic drugs, antibiotics, therapeutic ions, vitamins, bronchodilators, anti-gout agents, anti-hypertensive agents, diuretic agents, anti-hyperlipidemic agents or ACE inhibitors, drugs intended for local treatment of the gastrointestinal tract, including anti-tumor agents, histamine (H2) blockers, bismuth salts, synthetic prostaglandins or antibiotic agents, drugs that degrade in the colon, for example metoprolol, formulations useful for treating gastrointestinal associated disorders selected from peptic ulcer, nonulcer dyspepsia, Zollinger-Ellison syndrome, gastritis, duodenitis and the associated ulcerative lesions, stomach or duodenum neoplasms, prazosin, ketanserin, guanabenz acetate, captopril, captopril hydrochloride, enalapril, enalapril maleate, lysinopril, hydralazide, methyldopa, methyldopa hydrochloride, levodopa, carbidopa, benserazide, amlodipine, nitrendipine, nifedipine, nicardipine, verapamil, acyclovir, inosine, pranobex, tribavirine, vidarabine, zidovudine, AZT, active ingredients that exert a medicinal action at the gastric level, including aluminum hydroxide, magnesium carbonate, magnesium oxide, sucralphate, sodium carbenoxolone, pirenzepin, loperamide, cimetidine, ranitidine, famotidine, misoprostol, omeprazol, and combinations thereof.

432. The method according to claim 425 providing an active ingredient release profile where at least 10% active ingredient by mass is released in gastric fluid, followed by

at least 75% release of remaining active ingredient in one hour or less upon contacting intestinal fluid.

433. The method according to claim 425 where the active ingredient has a window of absorption, and where at least 10% active ingredient by mass is released in gastric fluid, followed by at least 75% release of remaining active ingredient in 30 minutes or less upon contacting intestinal fluid.

434. The method according to claim 425 where active ingredient release upon contacting gastric fluid is zero order, mixed order or first order, followed by immediate release when remaining composition contacts intestinal fluid.

435. The method according to claim 425 where the leaky enteric material includes a hydrophilic gastric fluid channeling agent.

436. The method according to claim 435 where the gastric fluid channeling agent is a sugar.

437. The method according to claim 425 where the leaky enteric material includes a hydrophobic gastric fluid channeling agent.

438. The method of claim 437 where the hydrophobic material is selected from the group consisting of talc, magnesium salts, silicon dioxide, hydrocarbons, and combinations thereof.

439. The method according to claim 425 where the leaky enteric coating has a thickness of 20 μm or less.

440. The method according to claim 425 comprising a solid composition.

441. The method according to claim 425 comprising treating the subject by oral administration.

442. The method according to claim 425 where the pharmaceutical composition further comprises a second formulation designed to provide an active ingredient release profile different from the pharmaceutical composition.

443. The method according to claim 442 where the second formulation provides immediate release in gastric fluid.

444. The method according to claim 442 where the active ingredient is amoxicillin or a biologically active salt thereof.

445. The method according to claim 444 where the active ingredient of the second formulation is clavulanate or a biologically active salt thereof.

446. The method according to claim 442 where the two formulations are placed in a single capsule or tablet for co-administration.

447. The method according to claim 425 where the pharmaceutical composition further comprises an admixture or an overcoat of an immediate release dosage form.

448. The method according to claim 425 where the pharmaceutical composition comprises an active ingredient selected from the group consisting of AIDS adjunct agents, alcohol abuse preparations, Alzheimer's disease management agents, amyotrophic lateral sclerosis active ingredient agents, analgesics, anesthetics, antacids, antiarythmics, antibiotics, anticonvulsants, antidepressants, antidiabetic agents, antiemetics, antidotes, antifibrosis active ingredient agents, antifungals, antihistamines, antihypertensives, anti-infective agents, antimicrobials, antineoplastics, antipsychotics, antiparkinsonian agents, antirheumatic agents, appetite stimulants, appetite suppressants, biological response modifiers, biologicals, blood modifiers, bone metabolism regulators, cardioprotective agents, cardiovascular agents, central nervous system stimulants, cholinesterase inhibitors, contraceptives, cystic fibrosis management agents, deodorants, diagnostics, dietary supplements, diuretics, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction active ingredients, fatty acids, gastrointestinal agents, Gaucher's disease management agents, gout preparations, homeopathic remedys, hormones, hypercalcemia management agents, hypnotics, hypocalcemia management agents, immunomodulators, immunosuppressives, ion exchange resins, levocarnitine deficiency

management agents, mast cell stabilizers, migraine preparations, motion sickness products, multiple sclerosis management agents, muscle relaxants, narcotic detoxification agents, narcotics, nucleoside analogs, non-steroidal anti-inflammatory drugs, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, phosphate binders, porphyria agents, psychoactive ingredient agents, radio-opaque agents, psychotropics, sclerosing agents, sedatives, sickle cell anemia management agents, smoking cessation aids, steroids, stimulants, sympatholytics, sympathomimetics, Tourette's syndrome agents, tremor preparations, urinary tract agents, vaginal preparations, vasodilators, vertigo agents, weight loss agents, Wilson's disease management agents, and mixtures thereof.

449. The method according to claim 425 where the pharmaceutical composition comprises an active ingredient selected from the group consisting of abacavir sulfate, abacavir sulfate/ lamivudine/zidovudine, acetazolamide, acyclovir, albendazole, albuterol, aldactone, allopurinol, amoxicillin, amoxicillin/clavulanate potassium, amprenavir, atovaquone, atovaquone and proguanil hydrochloride, atracurium besylate, beclomethasone dipropionate, berlactone betamethasone valerate, bupropion hydrochloride, bupropion hydrochloride, carvedilol, caspofungin acetate, cefazolin, ceftazidime, cefuroxime , chlorambucil, chlorpromazine, cimetidine, cimetidine hydrochloride, cisatracurium besilate, clobetasol propionate, co-trimoxazole, colfosceril palmitate, dextroamphetamie sulfate, digoxin, enalapril maleate, epoprostenol, esomepraxole magnesium, fluticasone propionate, furosemide, hydrochlorothiazide, hydrochlorothiazide/triamterene, lamivudine, lamotrigine, lithium carbonate, losartan potassium, melphalan, mercaptopurine, mesalazine, mupirocin calcium cream, nabumetone, naratriptan, omeprazole, ondansetron hydrochloride, ovine, oxiconazole nitrate, paroxetine hydrochloride, prochlorperazine, procyclidine hydrochloride, pyrimethamine, ranitidine bismuth citrate, ranitidine hydrochloride, rofecoxib, ropinirole hydrochloride, rosiglitazone maleate, salmeterol xinafoate, salmeterol, fluticasone propionate, sterile ticarcillin disodium / clavulanate potassium, simvastatin, spironolactone, succinylcholine chloride, sumatriptan, thioguanine, tirofiban HCl, topotecan hydrochloride, tranylcypromine sulfate, trifluoperazine hydrochloride, valacyclovir hydrochloride, vinorelbine, zanamivir, zidovudine, zidovudine or lamivudine, or mixtures thereof.

450. The method according to claim 425 where the pharmaceutical composition is coated by gelatin or placed inside a gelatin capsule or a tablet.

451. The method according to claim 425 where the pharmaceutical composition increases active ingredient bioavailability at least 20% relative to an immediate release or a sustained release control that does not include enteric material.

452. The method according to claim 425 where the pharmaceutical composition provides substantially equivalent bioavailability but a reduced active ingredient excretion rate relative to an immediate release control formulation.

453. The method according to claim 425 where the pharmaceutical composition provides prolonged drug concentrations for active ingredients having an absorption window relative to an immediate release or a sustained release control.

454. The method according to claim 425 where the enteric material is selected from the group consisting of cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), hydroxypropylmethyl cellulose, hydroxypropyl methylcellulose acetate succinate (HPMCAS), cellulose acetate trimellitate, hydroxypropyl methylcellulose succinate, carboxymethyl cellulose, carboxymethyl ethyl cellulose, cellulose acetate phthalate, cellulose acetate succinate, cellulose acetate hexahydrophthalate, cellulose propionate phthalate, cellulose acetate maleate, cellulose acetate butyrate, cellulose acetate propionate, copolymer of methylmethacrylic acid and methyl methacrylate, copolymer of methyl acrylate, methylmethacrylate and methacrylic acid, copolymer of methylvinyl ether and maleic anhydride (Gantrez ES series), ethyl methyacrylate-methylmethacrylate-chlorotrimethylammonium ethyl acrylate copolymer, polyvinyl acetate phthalate, zein, shellac, copal collophorium, Eudragit L30D55, Eudragit FS30D, Eudragit L100, Eudragit S100, Kollicoat EMM30D, Estacryl 30D, Coateric, Aquateric, and combinations of such materials.

455. The method according to claim 425 where the pharmaceutical composition provides controlled *in vitro* gastric release, followed by pulsatile *in vitro* intestinal release.

456. The method according to claim 425 where the pharmaceutical composition comprises plural active ingredients.

457. A method for treating a subject having a condition treatable by an active ingredient, comprising:

providing a pharmaceutical composition comprising at least one active ingredient, excluding riboflavin, suitable for treating the condition and having a leaky enteric coating; and

treating the subject by administering the composition to the subject.

458. The method according to claim 457 where the enteric coating has a layer thickness of 25 microns or less.

459. The method according to claim 457 where the leaky enteric coating includes a gastric fluid channeling agent.

460. The method according to claim 457 comprising administering to a fed subject or administering substantially simultaneously while the subject eats or drinks.

461. The method according to claim 457 comprising administering to a fasted subject.

462. The method according to claim 457 where at least 10% by mass of the active ingredient is released in gastric fluid.

463. The method according to claim 457 where the active ingredient has a window of absorption.

464. The method according to claim 463 where the active ingredient is selected from the group consisting of therapeutic nucleic acids or amino acid sequences, nucleic acids or amino acid derivatives, peptidomimetic drugs, antibiotics, therapeutic ions, vitamins, bronchodilators, anti-gout agents, anti-hypertensive agents, diuretic agents, anti-hyperlipidemic agents or ACE inhibitors, drugs intended for local treatment of the gastrointestinal tract, including anti-tumor agents, histamine (H2) blockers, bismuth salts, synthetic prostaglandins or antibiotic agents, drugs that degrade in the colon, for example metoprolol, formulations useful for treating gastrointestinal associated disorders selected from peptic ulcer, nonulcer dyspepsia, Zollinger-Ellison syndrome, gastritis, duodenitis and the associated ulcerative lesions, stomach or duodenum neoplasms, prazosin, ketanserin,

guanabenz acetate, captopril, captopril hydrochloride, enalapril, enalapril maleate, lysinopril, hydralazide, methyldopa, methyldopa hydrochloride, levodopa, carbidopa, benserazide, amlodipine, nitrendipine, nifedipine, nicardipine, verapamil, acyclovir, inosine, pranobex, tribavirine, vidarabine, zidovudine, AZT, active ingredients that exert a medicinal action at the gastric level, including aluminum hydroxide, magnesium carbonate, magnesium oxide, sucralphate, sodium carbenoxolone, pirenzepin, loperamide, cimetidine, ranitidine, famotidine, misoprostol, omeprazol, and combinations thereof.

465. The method according to claim 457 providing an active ingredient release profile where at least 10% active ingredient by mass is released in gastric fluid, followed by at least 75% release of remaining active ingredient in one hour or less upon contacting intestinal fluid.

466. The method according to claim 457 where the active ingredient has a window of absorption, and where at least 10% active ingredient by mass is released in gastric fluid, followed by at least 75% release of remaining active ingredient in 30 minutes or less upon contacting intestinal fluid.

467. The method according to claim 457 where active ingredient release upon contacting gastric fluid is zero order, mixed order or first order, followed by substantially immediate release when remaining composition contacts intestinal fluid.

468. The method according to claim 457 where the leaky enteric material includes a hydrophilic gastric fluid channeling agent.

469. The method according to claim 468 where the gastric fluid channeling agent is a sugar.

470. The method according to claim 457 where the leaky enteric material includes a hydrophobic gastric fluid channeling agent.

471. The method of claim 470 where the hydrophobic material is selected from the group consisting of talc, magnesium salts, silicon dioxide, hydrocarbons, and combinations thereof.

472. The method according to claim 457 where the enteric coating has a thickness of 20 μm or less.

473. The method according to claim 457 comprising a solid composition.

474. The method according to claim 457 comprising treating the subject by oral administration.

475. The method according to claim 457 where the pharmaceutical composition further comprises a second formulation designed to provide an active ingredient release profile different from the pharmaceutical composition.

476. The method according to claim 475 where the second formulation provides immediate release in gastric fluid.

477. The method according to claim 475 where the active ingredient is amoxicillin or a biologically active salt thereof.

478. The method according to claim 477 where the active ingredient of the second formulation is clavulanate or a biologically active salt thereof.

479. The method according to claim 475 where the two formulations are placed in a single capsule or tablet for co-administration.

480. The method according to claim 457 where the pharmaceutical composition further comprises an admixture or an overcoat of an immediate release dosage form.

481. The method according to claim 457 where the pharmaceutical composition comprises an active ingredient selected from the group consisting of AIDS adjunct agents, alcohol abuse preparations, Alzheimer's disease management agents, amyotrophic lateral sclerosis active ingredient agents, analgesics, anesthetics, antacids, antiarythmics, antibiotics, anticonvulsants, antidepressants, antidiabetic agents, antiemetics, antidotes, antifibrosis active ingredient agents, antifungals, antihistamines, antihypertensives, anti-infective agents, antimicrobials, antineoplastics, antipsychotics, antiparkinsonian agents, antirheumatic agents, appetite stimulants, appetite suppressants, biological response

modifiers, biologicals, blood modifiers, bone metabolism regulators, cardioprotective agents, cardiovascular agents, central nervous system stimulants, cholinesterase inhibitors, contraceptives, cystic fibrosis management agents, deodorants, diagnostics, dietary supplements, diuretics, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction active ingredients, fatty acids, gastrointestinal agents, Gaucher's disease management agents, gout preparations, homeopathic remedys, hormones, hypercalcemia management agents, hypnotics, hypocalcemia management agents, immunomodulators, immunosuppressives, ion exchange resins, levocarnitine deficiency management agents, mast cell stabilizers, migraine preparations, motion sickness products, multiple sclerosis management agents, muscle relaxants, narcotic detoxification agents, narcotics, nucleoside analogs, non-steroidal anti-inflammatory drugs, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, phosphate binders, porphyria agents, psychoactive ingredient agents, radio-opaque agents, psychotropics, sclerosing agents, sedatives, sickle cell anemia management agents, smoking cessation aids, steroids, stimulants, sympatholytics, sympathomimetics, Tourette's syndrome agents, tremor preparations, urinary tract agents, vaginal preparations, vasodilators, vertigo agents, weight loss agents, Wilson's disease management agents, and mixtures thereof.

482. The method according to claim 457 where the pharmaceutical composition comprises an active ingredient selected from the group consisting of abacavir sulfate, abacavir sulfate/ lamivudine/zidovudine, acetazolamide, acyclovir, albendazole, albuterol, aldactone, allopurinol, amoxicillin, amoxicillin/clavulanate potassium, amprenavir, atovaquone, atovaquone and proguanil hydrochloride, atracurium besylate, beclomethasone dipropionate, berlactone betamethasone valerate, bupropion hydrochloride, bupropion hydrochloride, carvedilol, caspofungin acetate, cefazolin, ceftazidime, cefuroxime , chlorambucil, chlorpromazine, cimetidine, cimetidine hydrochloride, cisatracurium besilate, clobetasol propionate, co-trimoxazole, colfosceril palmitate, dextroamphetamie sulfate, digoxin, enalapril maleate, epoprostenol, esomepraxole magnesium, fluticasone propionate, furosemide, hydrochlorothiazide, hydrochlorothiazide/triamterene, lamivudine, lamotrigine, lithium carbonate, losartan potassium, melphalan, mercaptopurine, mesalazine, mupirocin calcium cream, nabumetone, naratriptan, omeprazole, ondansetron hydrochloride, ovine, oxiconazole nitrate, paroxetine hydrochloride, prochlorperazine, procyclidine hydrochloride, pyrimethamine, ranitidine bismuth citrate, ranitidine hydrochloride, rofecoxib, ropinirole hydrochloride, rosiglitazone maleate, salmeterol xinafoate, salmeterol, fluticasone propionate, sterile ticarcillin disodium / clavulanate potassium, simvastatin, spironolactone,

succinylcholine chloride, sumatriptan, thioguanine, tirofiban HCl, topotecan hydrochloride, tranylcypromine sulfate, trifluoperazine hydrochloride, valacyclovir hydrochloride, vinorelbine, zanamivir, zidovudine, zidovudine or lamivudine, or mixtures thereof.

483. The method according to claim 457 where the pharmaceutical composition is coated by gelatin or placed inside a gelatin capsule or a tablet.

484. The method according to claim 457 where the pharmaceutical composition increases active ingredient bioavailability at least 20% relative to an immediate release or a sustained release control that does not include enteric material.

485. The method according to claim 457 where the pharmaceutical composition provides substantially equivalent bioavailability but a reduced active ingredient excretion rate relative to an immediate release control formulation.

486. The method according to claim 457 where the pharmaceutical composition provides prolonged drug concentrations for active ingredients having an absorption window relative to an immediate release or a sustained release control.

487. The method according to claim 457 where the enteric coating is selected from the group consisting of cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, carboxymethylethylcellulose, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, cellulose acetate phthalate, poly(methacrylic acid-ethylacrylate), poly(methacrylic acid-methyl methacrylate), Eudagrit L, Eudragit S, and mixtures of enteric materials.

488. The method according to claim 457 where the pharmaceutical composition provides controlled *in vitro* gastric release, followed by pulsatile *in vitro* intestinal release.

489. The method according to claim 457 where the pharmaceutical composition comprises plural active ingredients.

490. A method for treating a subject having a condition treatable by an active ingredient, comprising:

providing a pharmaceutical composition consisting essentially of a core comprising an active ingredient suitable for treating the condition, and a leaky enteric coating; and

treating the subject by administering the composition to the subject.

491. The method according to claim 490 where the enteric coating has a layer thickness of 25 microns or less.

492. The method according to claim 490 where the leaky enteric coating includes a gastric fluid channeling agent or a gastric fluid channel.

493. The method according to claim 490 comprising administering to a fed subject or administering substantially simultaneously while the subject eats or drinks.

494. The method according to claim 490 comprising administering to a fasted subject.

495. The method according to claim 490 where at least 10% by mass of the active ingredient is released in gastric fluid.

496. The method according to claim 490 where the active ingredient has a window of absorption.

497. The method according to claim 490 where the active ingredient is selected from the group consisting of therapeutic nucleic acids or amino acid sequences, nucleic acids or amino acid derivatives, peptidomimetic drugs, antibiotics, therapeutic ions, vitamins, bronchodilators, anti-gout agents, anti-hypertensive agents, diuretic agents, anti-hyperlipidemic agents or ACE inhibitors, drugs intended for local treatment of the gastrointestinal tract, including anti-tumor agents, histamine (H2) blockers, bismuth salts, synthetic prostaglandins or antibiotic agents, drugs that degrade in the colon, for example metoprolol, formulations useful for treating gastrointestinal associated disorders selected from peptic ulcer, nonulcer dyspepsia, Zollinger-Ellison syndrome, gastritis, duodenitis and the associated ulcerative lesions, stomach or duodenum neoplasms, prazosin, ketanserin, guanabenz acetate, captopril, captopril hydrochloride, enalapril, enalapril maleate, lysinopril, hydralazide, methyldopa, methyldopa hydrochloride, levodopa, carbidopa, benserazide, amlodipine, nitrendipine, nifedipine, nicardipine, verapamil, acyclovir, inosine,

pranobex, tribavirine, vidarabine, zidovudine, AZT, active ingredients that exert a medicinal action at the gastric level, including aluminum hydroxide, magnesium carbonate, magnesium oxide, sucralphate, sodium carbenoxolone, pirenzepin, loperamide, cimetidine, ranitidine, famotidine, misoprostol, omeprazol, and combinations thereof.

498. The method according to claim 490 providing an active ingredient release profile where at least 10% active ingredient by mass is released in gastric fluid, followed by at least 75% release of remaining active ingredient in one hour or less upon contacting intestinal fluid.

499. The method according to claim 490 where the active ingredient has a window of absorption, and where at least 10% active ingredient by mass is released in gastric fluid, followed by at least 75% release of remaining active ingredient in 30 minutes or less upon contacting intestinal fluid.

500. The method according to claim 490 where active ingredient release upon contacting gastric fluid is zero order, mixed order or first order, followed by substantially immediate release when remaining composition contacts intestinal fluid.

501. The method according to claim 490 where the leaky enteric material includes a hydrophilic gastric fluid channeling agent.

502. The method according to claim 501 where the gastric fluid channeling agent is a sugar.

503. The method according to claim 490 where the leaky enteric material includes a hydrophobic gastric fluid channeling agent.

504. The method of claim 503 where the hydrophobic material is selected from the group consisting of talc, magnesium salts, silicon dioxide, hydrocarbons, and combinations thereof.

505. The method according to claim 490 where the enteric coating has a thickness of 20 μm or less.

506. The method according to claim 490 comprising a solid composition.

507. The method according to claim 490 comprising treating the subject by oral administration.

508. The method according to claim 490 where the pharmaceutical composition further comprises a second formulation designed to provide an active ingredient release profile different from the pharmaceutical composition.

509. The method according to claim 508 where the second formulation provides immediate release in gastric fluid.

510. The method according to claim 508 where the active ingredient is amoxicillin or a biologically active salt thereof.

511. The method according to claim 510 where the active ingredient of the second formulation is clavulanate or a biologically active salt thereof.

512. The method according to claim 508 where the two formulations are placed in a single capsule or tablet for co-administration.

513. The method according to claim 495 where the pharmaceutical composition further comprises an admixture of an immediate release dosage form.

514. The method according to claim 490 where the pharmaceutical composition comprises an active ingredient selected from the group consisting of AIDS adjunct agents, alcohol abuse preparations, Alzheimer's disease management agents, amyotrophic lateral sclerosis active ingredient agents, analgesics, anesthetics, antacids, antiarythmics, antibiotics, anticonvulsants, antidepressants, antidiabetic agents, antiemetics, antidotes, antifibrosis active ingredient agents, antifungals, antihistamines, antihypertensives, anti-infective agents, antimicrobials, antineoplastics, antipsychotics, antiparkinsonian agents, antirheumatic agents, appetite stimulants, appetite suppressants, biological response modifiers, biologicals, blood modifiers, bone metabolism regulators, cardioprotective agents, cardiovascular agents, central nervous system stimulants, cholinesterase inhibitors, contraceptives, cystic fibrosis management agents, deodorants, diagnostics, dietary

supplements, diuretics, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction active ingredients, fatty acids, gastrointestinal agents, Gaucher's disease management agents, gout preparations, homeopathic remedys, hormones, hypercalcemia management agents, hypnotics, hypocalcemia management agents, immunomodulators, immunosuppressives, ion exchange resins, levocarnitine deficiency management agents, mast cell stabilizers, migraine preparations, motion sickness products, multiple sclerosis management agents, muscle relaxants, narcotic detoxification agents, narcotics, nucleoside analogs, non-steroidal anti-inflammatory drugs, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, phosphate binders, porphyria agents, psychoactive ingredient agents, radio-opaque agents, psychotropics, sclerosing agents, sedatives, sickle cell anemia management agents, smoking cessation aids, steroids, stimulants, sympatholytics, sympathomimetics, Tourette's syndrome agents, tremor preparations, urinary tract agents, vaginal preparations, vasodilators, vertigo agents, weight loss agents, Wilson's disease management agents, and mixtures thereof.

515. The method according to claim 490 where the pharmaceutical composition comprises an active ingredient selected from the group consisting of abacavir sulfate, abacavir sulfate/ lamivudine/zidovudine, acetazolamide, acyclovir, albendazole, albuterol, aldactone, allopurinol, amoxicillin, amoxicillin/clavulanate potassium, amprenavir, atovaquone, atovaquone and proguanil hydrochloride, atracurium besylate, beclomethasone dipropionate, berlactone betamethasone valerate, bupropion hydrochloride, bupropion hydrochloride, carvedilol, caspofungin acetate, cefazolin, ceftazidime, cefuroxime , chlorambucil, chlorpromazine, cimetidine, cimetidine hydrochloride, cisatracurium besilate, clobetasol propionate, co-trimoxazole, colfosceril palmitate, dextroamphetamie sulfate, digoxin, enalapril maleate, epoprostenol, esomepraxole magnesium, fluticasone propionate, furosemide, hydrochlorothiazide, hydrochlorothiazide/triamterene, lamivudine, lamotrigine, lithium carbonate, losartan potassium, melphalan, mercaptopurine, mesalazine, mupirocin calcium cream, nabumetone, naratriptan, omeprazole, ondansetron hydrochloride, ovine, oxiconazole nitrate, paroxetine hydrochloride, prochlorperazine, procyclidine hydrochloride, pyrimethamine, ranitidine bismuth citrate, ranitidine hydrochloride, rofecoxib, ropinirole hydrochloride, rosiglitazone maleate, salmeterol xinafoate, salmeterol, fluticasone propionate, sterile ticarcillin disodium / clavulanate potassium, simvastatin, spironolactone, succinylcholine chloride, sumatriptan, thioguanine, tirofiban HCl, topotecan hydrochloride, tranylcypromine sulfate, trifluoperazine hydrochloride, valacyclovir hydrochloride, vinorelbine, zanamivir, zidovudine, zidovudine or lamivudine, or mixtures thereof.

516. The method according to claim 490 where the pharmaceutical composition is placed inside a gelatin capsule or a tablet.

517. The method according to claim 490 where the pharmaceutical composition increases active ingredient bioavailability at least 20% relative to an immediate release or a ustained release control that does not include enteric material.

518. The method according to claim 490 where the pharmaceutical composition provides substantially equivalent bioavailability but a reduced active ingredient excretion rate relative to an immediate release control formulation.

519. The method according to claim 490 where the pharmaceutical composition provides prolonged drug concentrations for active ingredients having an absorption window relative to an immediate release or a sustained release control.

520. The method according to claim 490 where the enteric coating is selected from the group consisting of cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, carboxymethylethylcellulose, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, cellulose acetate phthalate, poly(methacrylic acid-ethylacrylate), poly(methacrylic acid-methyl methacrylate), Eudagrit L, Eudragit S, and mixtures of enteric materials.

521. The method according to claim 490 where the pharmaceutical composition provides controlled *in vitro* gastric release, followed by pulsatile *in vitro* intestinal release.

522. The method according to claim 490 where the pharmaceutical composition comprises plural active ingredients.

523. A method for treating a subject having a condition treatable by an active ingredient, comprising:

providing a pharmaceutical composition comprising a sugarbead core, an active ingredient suitable for treating the condition on or in the core, and an enteric coating comprising a gastric channeling agent; and

treating the subject by administering the composition to the subject.

524. The method according to claim 523 where the enteric coating has a layer thickness of 25 microns or less.

525. The method according to claim 523 where the enteric coating has a thickness of 20 μm or less.

526. The method according to claim 523 comprising administering to a fed subject or administering substantially simultaneously while the subject eats or drinks.

527. The method according to claim 523 comprising administering to a fasted subject.

528. The method according to claim 523 where at least 10% by mass of the active ingredient is released in gastric fluid.

529. The method according to claim 523 where the active ingredient has a window of absorption.

530. The method according to claim 529 where the active ingredient is selected from the group consisting of therapeutic nucleic acids or amino acid sequences, nucleic acids or amino acid derivatives, peptidomimetic drugs, antibiotics, therapeutic ions, vitamins, bronchodilators, anti-gout agents, anti-hypertensive agents, diuretic agents, anti-hyperlipidemic agents or ACE inhibitors, drugs intended for local treatment of the gastrointestinal tract, including anti-tumor agents, histamine (H2) blockers, bismuth salts, synthetic prostaglandins or antibiotic agents, drugs that degrade in the colon, for example metoprolol, formulations useful for treating gastrointestinal associated disorders selected from peptic ulcer, nonulcer dyspepsia, Zollinger-Ellison syndrome, gastritis, duodenitis and the associated ulcerative lesions, stomach or duodenum neoplasms, prazosin, ketanserin, guanabenz acetate, captopril, captopril hydrochloride, enalapril, enalapril maleate, lysinopril, hydralazide, methyldopa, methyldopa hydrochloride, levodopa, carbidopa, benserazide, amlodipine, nitrendipine, nifedipine, nicardipine, verapamil, acyclovir, inosine, pranobex, tribavirine, vidarabine, zidovudine, AZT, active ingredients that exert a medicinal action at the gastric level, including aluminum hydroxide, magnesium carbonate,

magnesium oxide, sucralphate, sodium carbenoxolone, pirenzepin, loperamide, cimetidine, ranitidine, famotidine, misoprostol, omeprazol, and combinations thereof.

531. The method according to claim 523 providing an active ingredient release profile where at least 10% active ingredient by mass is released in gastric fluid, followed by at least 75% release of remaining active ingredient in one hour or less upon contacting intestinal fluid.

532. The method according to claim 523 where the active ingredient has a window of absorption, and where at least 10% active ingredient by mass is released in gastric fluid, followed by at least 75% release of remaining active ingredient in 30 minutes or less upon contacting intestinal fluid.

533. The method according to claim 523 where active ingredient release upon contacting gastric fluid is zero order, mixed order or first order, followed by substantially immediate release when remaining composition contacts intestinal fluid.

534. The method according to claim 523 where the gastric fluid channeling agent is hydrophilic.

535. The method according to claim 534 where the gastric fluid channeling agent is a sugar.

536. The method according to claim 523 where the gastric fluid channeling agent is hydrophobic.

537. The method of claim 536 where the hydrophobic material is selected from the group consisting of talc, magnesium salts, silicon dioxide, hydrocarbons, and combinations thereof.

538. The method according to claim 523 comprising administering the composition as a solid composition.

539. The method according to claim 523 comprising treating the subject by oral administration.

540. The method according to claim 523 where the pharmaceutical composition further comprises a second formulation designed to provide an active ingredient release profile different from the pharmaceutical composition.

541. The method according to claim 540 where the second formulation provides immediate release in gastric fluid.

542. The method according to claim 540 where the active ingredient is amoxicillin or a biologically active salt thereof.

543. The method according to claim 542 where the active ingredient of the second formulation is clavulanate or a biologically active salt thereof.

544. The method according to claim 540 where the two formulations are placed in a single capsule or tablet for co-administration.

545. The method according to claim 523 where the pharmaceutical composition further comprises an admixture or an overcoat of an immediate release dosage form.

546. The method according to claim 523 where the pharmaceutical composition comprises an active ingredient selected from the group consisting of AIDS adjunct agents, alcohol abuse preparations, Alzheimer's disease management agents, amyotrophic lateral sclerosis active ingredient agents, analgesics, anesthetics, antacids, antiarythmics, antibiotics, anticonvulsants, antidepressants, antidiabetic agents, antiemetics, antidotes, antifibrosis active ingredient agents, antifungals, antihistamines, antihypertensives, anti-infective agents, antimicrobials, antineoplastics, antipsychotics, antiparkinsonian agents, antirheumatic agents, appetite stimulants, appetite suppressants, biological response modifiers, biologicals, blood modifiers, bone metabolism regulators, cardioprotective agents, cardiovascular agents, central nervous system stimulants, cholinesterase inhibitors, contraceptives, cystic fibrosis management agents, deodorants, diagnostics, dietary supplements, diuretics, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction active ingredients, fatty acids, gastrointestinal agents, Gaucher's disease management agents, gout preparations, homeopathic remedys, hormones, hypercalcemia management agents, hypnotics, hypocalcemia management agents,

immunomodulators, immunosuppressives, ion exchange resins, levocarnitine deficiency management agents, mast cell stabilizers, migraine preparations, motion sickness products, multiple sclerosis management agents, muscle relaxants, narcotic detoxification agents, narcotics, nucleoside analogs, non-steroidal anti-inflammatory drugs, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, phosphate binders, porphyria agents, psychoactive ingredient agents, radio-opaque agents, psychotropics, sclerosing agents, sedatives, sickle cell anemia management agents, smoking cessation aids, steroids, stimulants, sympatholytics, sympathomimetics, Tourette's syndrome agents, tremor preparations, urinary tract agents, vaginal preparations, vasodilators, vertigo agents, weight loss agents, Wilson's disease management agents, and mixtures thereof.

547. The method according to claim 523 where the pharmaceutical composition comprises an active ingredient selected from the group consisting of abacavir sulfate, abacavir sulfate/ lamivudine/zidovudine, acetazolamide, acyclovir, albendazole, albuterol, aldactone, allopurinol, amoxicillin, amoxicillin/clavulanate potassium, amprenavir, atovaquone, atovaquone and proguanil hydrochloride, atracurium besylate, beclomethasone dipropionate, berlactone betamethasone valerate, bupropion hydrochloride, bupropion hydrochloride, carvedilol, caspofungin acetate, cefazolin, ceftazidime, cefuroxime , chlorambucil, chlorpromazine, cimetidine, cimetidine hydrochloride, cisatracurium besilate, clobetasol propionate, co-trimoxazole, colfosceril palmitate, dextroamphetamie sulfate, digoxin, enalapril maleate, epoprostenol, esomepraxole magnesium, fluticasone propionate, furosemide, hydrochlorothiazide, hydrochlorothiazide/triamterene, lamivudine, lamotrigine, lithium carbonate, losartan potassium, melphalan, mercaptopurine, mesalazine, mupirocin calcium cream, nabumetone, naratriptan, omeprazole, ondansetron hydrochloride, ovine, oxiconazole nitrate, paroxetine hydrochloride, prochlorperazine, procyclidine hydrochloride, pyrimethamine, ranitidine bismuth citrate, ranitidine hydrochloride, rofecoxib, ropinirole hydrochloride, rosiglitazone maleate, salmeterol xinafoate, salmeterol, fluticasone propionate, sterile ticarcillin disodium / clavulanate potassium, simvastatin, spironolactone, succinylcholine chloride, sumatriptan, thioguanine, tirofiban HCI, topotecan hydrochloride, tranylcypromine sulfate, trifluoperazine hydrochloride, valacyclovir hydrochloride, vinorelbine, zanamivir, zidovudine, zidovudine or lamivudine, or mixtures thereof.

548. The method according to claim 523 where the pharmaceutical composition is coated by gelatin or placed inside a gelatin capsule or a tablet.

549. The method according to claim 523 where the pharmaceutical composition increases active ingredient bioavailability at least 20% relative to an immediate release or a sustained release control that does not include enteric material.

550. The method according to claim 523 where the pharmaceutical composition provides substantially equivalent bioavailability but a reduced active ingredient excretion rate relative to an immediate release control formulation.

551. The method according to claim 523 where the pharmaceutical composition provides prolonged drug concentrations for active ingredients having an absorption window relative to an immediate release or a sustained release control.

552. The method according to claim 523 where the enteric coating is selected from the group consisting of cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, carboxymethylethylcellulose, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, cellulose acetate phthalate, poly(methacrylic acid-ethylacrylate), poly(methacrylic acid-methyl methacrylate), Eudagrit L, Eudragit S, and mixtures of enteric materials.

553. The method according to claim 523 where the pharmaceutical composition provides controlled *in vitro* gastric release, followed by pulsatile *in vitro* intestinal release.

554. The method according to claim 523 where the pharmaceutical composition comprises plural active ingredients.

555. A method for making a gastrically leaky, enteric-coated pharmaceutical composition, comprising:

providing a core comprising an active ingredient;

applying an enteric coating material to the core; and

making the enteric coating leaky.

556. The method according to claim 555 where making the enteric coating leaky comprises applying pressure, removing solvent, washing, soaking, raising or lowering temperature relative to ambient, abrading, ablating, and combinations thereof.

557. The method according to claim 555 where the enteric coating has a layer thickness of 25 microns or less.

558. The method according to claim 555 where the enteric coating has a thickness of 20 μm or less.

559. The method according to claim 555 where the active ingredient has a window of absorption.

560. The method according to claim 559 where the active ingredient is selected from the group consisting of therapeutic nucleic acids or amino acid sequences, nucleic acids or amino acid derivatives, peptidomimetic drugs, antibiotics, therapeutic ions, vitamins, bronchodilators, anti-gout agents, anti-hypertensive agents, diuretic agents, anti-hyperlipidemic agents or ACE inhibitors, drugs intended for local treatment of the gastrointestinal tract, including anti-tumor agents, histamine (H2) blockers, bismuth salts, synthetic prostaglandins or antibiotic agents, drugs that degrade in the colon, for example metoprolol, formulations useful for treating gastrointestinal associated disorders selected from peptic ulcer, nonulcer dyspepsia, Zollinger-Ellison syndrome, gastritis, duodenitis and the associated ulcerative lesions, stomach or duodenum neoplasms, prazosin, ketanserin, guanabenz acetate, captopril, captopril hydrochloride, enalapril, enalapril maleate, lysinopril, hydralazide, methyldopa, methyldopa hydrochloride, levodopa, carbidopa, benserazide, amlodipine, nitrendipine, nifedipine, nicardipine, verapamil, acyclovir, inosine, pranobex, tribavirine, vidarabine, zidovudine, AZT, active ingredients that exert a medicinal action at the gastric level, including aluminum hydroxide, magnesium carbonate, magnesium oxide, sucralphate, sodium carbenoxolone, pirenzepin, loperamide, cimetidine, ranitidine, famotidine, misoprostol, omeprazol, and combinations thereof.

561. The method according to claim 555 where the enteric material includes a gastric fluid channeling agent.

562. The method according to claim 561 where the gastric fluid channeling agent is hydrophilic.

563. The method according to claim 562 where the gastric fluid channeling agent is a sugar.

564. The method according to claim 561 where the gastric fluid channeling agent is hydrophobic.

565. The method of claim 564 where the hydrophobic material is selected from the group consisting of talc, magnesium salts, silicon dioxide, hydrocarbons, and combinations thereof.

566. The method according to claim 555 where the pharmaceutical composition further comprises a second formulation designed to provide an active ingredient release profile different from the pharmaceutical composition.

567. The method according to claim 566 further comprising placing the two formulations placed in a single capsule or tablet for co-administration.

568. The method according to claim 555 where the pharmaceutical composition further comprises an admixture or an overcoat of an immediate release dosage form.

569. The method according to claim 555 where the pharmaceutical composition comprises an active ingredient selected from the group consisting of AIDS adjunct agents, alcohol abuse preparations, Alzheimer's disease management agents, amyotrophic lateral sclerosis active ingredient agents, analgesics, anesthetics, antacids, antiarythmics, antibiotics, anticonvulsants, antidepressants, antidiabetic agents, antiemetics, antidotes, antifibrosis active ingredient agents, antifungals, antihistamines, antihypertensives, anti-infective agents, antimicrobials, antineoplastics, antipsychotics, antiparkinsonian agents, antirheumatic agents, appetite stimulants, appetite suppressants, biological response modifiers, biologicals, blood modifiers, bone metabolism regulators, cardioprotective agents, cardiovascular agents, central nervous system stimulants, cholinesterase inhibitors, contraceptives, cystic fibrosis management agents, deodorants, diagnostics, dietary supplements, diuretics, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction active ingredients, fatty acids, gastrointestinal agents, Gaucher's disease management agents, gout preparations, homeopathic remedys, hormones, hypercalcemia management agents, hypnotics, hypocalcemia management agents,

immunomodulators, immunosuppressives, ion exchange resins, levocarnitine deficiency management agents, mast cell stabilizers, migraine preparations, motion sickness products, multiple sclerosis management agents, muscle relaxants, narcotic detoxification agents, narcotics, nucleoside analogs, non-steroidal anti-inflammatory drugs, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, phosphate binders, porphyria agents, psychoactive ingredient agents, radio-opaque agents, psychotropics, sclerosing agents, sedatives, sickle cell anemia management agents, smoking cessation aids, steroids, stimulants, sympatholytics, sympathomimetics, Tourette's syndrome agents, tremor preparations, urinary tract agents, vaginal preparations, vasodilators, vertigo agents, weight loss agents, Wilson's disease management agents, and mixtures thereof.

570. The method according to claim 555 where the pharmaceutical composition comprises an active ingredient selected from the group consisting of abacavir sulfate, abacavir sulfate/ lamivudine/zidovudine, acetazolamide, acyclovir, albendazole, albuterol, aldactone, allopurinol, amoxicillin, amoxicillin/clavulanate potassium, amprenavir, atovaquone, atovaquone and proguanil hydrochloride, atracurium besylate, beclomethasone dipropionate, berlactone betamethasone valerate, bupropion hydrochloride, bupropion hydrochloride, carvedilol, caspofungin acetate, cefazolin, ceftazidime, cefuroxime , chlorambucil, chlorpromazine, cimetidine, cimetidine hydrochloride, cisatracurium besilate, clobetasol propionate, co-trimoxazole, colfosceril palmitate, dextroamphetamie sulfate, digoxin, enalapril maleate, epoprostenol, esomepraxole magnesium, fluticasone propionate, furosemide, hydrochlorothiazide, hydrochlorothiazide/triamterene, lamivudine, lamotrigine, lithium carbonate, losartan potassium, melphalan, mercaptopurine, mesalazine, mupirocin calcium cream, nabumetone, naratriptan, omeprazole, ondansetron hydrochloride, ovine, oxiconazole nitrate, paroxetine hydrochloride, prochlorperazine, procyclidine hydrochloride, pyrimethamine, ranitidine bismuth citrate, ranitidine hydrochloride, rofecoxib, ropinirole hydrochloride, rosiglitazone maleate, salmeterol xinafoate, salmeterol, fluticasone propionate, sterile ticarcillin disodium / clavulanate potassium, simvastatin, spironolactone, succinylcholine chloride, sumatriptan, thioguanine, tirofiban HCI, topotecan hydrochloride, tranylcypromine sulfate, trifluoperazine hydrochloride, valacyclovir hydrochloride, vinorelbine, zanamivir, zidovudine, zidovudine or lamivudine, or mixtures thereof.

571. The method according to claim 555 where the pharmaceutical composition is coated by gelatin or placed inside a gelatin capsule or a tablet.

572. The method according to claim 555 where the enteric coating is selected from the group consisting of cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, carboxymethylethylcellulose, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, cellulose acetate phthalate, poly(methacrylic acid-ethylacrylate), poly(methacrylic acid-methyl methacrylate), Eudagrit L, Eudragit S, and mixtures of enteric materials.

573. The method according to claim 555 where the pharmaceutical composition comprises plural active ingredients.

574. A pharmaceutical composition comprising at least one active ingredient in a core and an enteric coating on the core, the enteric coating further comprising a gastric fluid channel.

575. A pharmaceutical composition that provides programmed release of active ingredient, the composition comprising at least one active ingredient, excluding amoxicillin and bisacodyl, substantially homogeneously admixed with at least one enteric material comprising a gastric fluid channel.

576. A pharmaceutical composition consisting essentially of a core comprising at least one active ingredient and an enteric coating comprising a gastric fluid channel.

577. A pharmaceutical composition, comprising:
a sugarbead core;
at least one active ingredient on or in the core; and
an enteric coating comprising a gastric fluid channel.

578. The pharmaceutical composition according to claim 1 excluding amoxicillin, acetyl salicylic acid, bisacodyl, indometacin, riboflavin or sulfametoxozole.

579. The pharmaceutical composition according to claim 116 further excluding amoxicillin, acetyl salicylic acid, indometacin, or sulfametoxozole.

580. The pharmaceutical composition according to claim 175 further excluding amoxicillin, acetyl salicylic acid, indometacin, or sulfametoxozole.

581. The pharmaceutical composition according to claim 205 further excluding amoxicillin, acetyl salicylic acid, bisacodyl, indometacin, riboflavin or sulfametoxozole.

582. The pharmaceutical composition according to claim 235 further excluding amoxicillin, acetyl salicylic acid, bisacodyl, indometacin, riboflavin or sulfametoxozole.

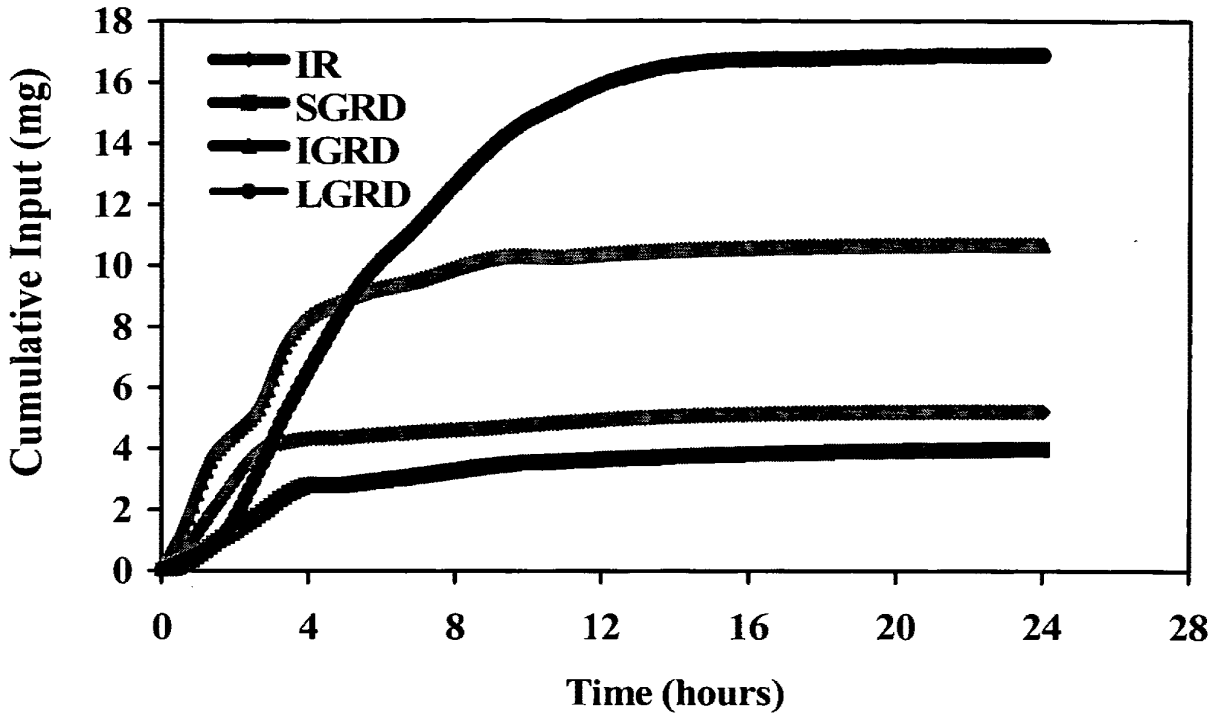

IR
SGRD
IGRD
LGRD
Cumulative Input (mg)
0
2
4
6
8
10
12
14
16
18
0
4
8
12
16
20
24
28
Time (hours)

FIG. 1

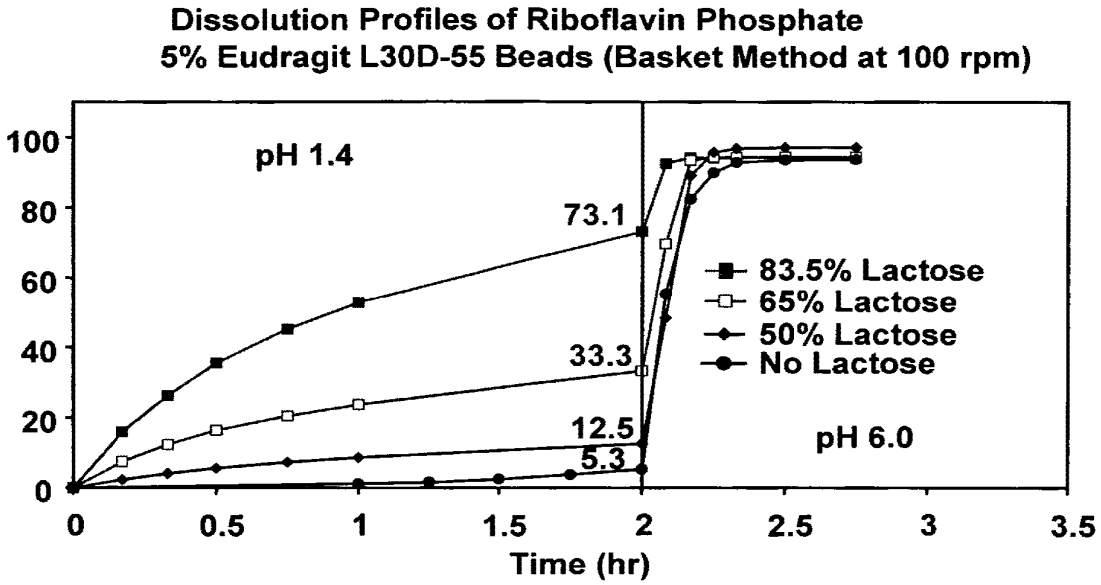

Dissolution Profiles of Riboflavin Phosphate
5% Eudragit L30D-55 Beads (Basket Method at 100 rpm)
pH 1.4
pH 6.0
73.1
33.3
12.5
5.3
83.5% Lactose
65% Lactose
50% Lactose
No Lactose
100
80
60
40
20
0
0
0.5
1
1.5
2
2.5
3
3.5
Time (hr)

FIG. 2

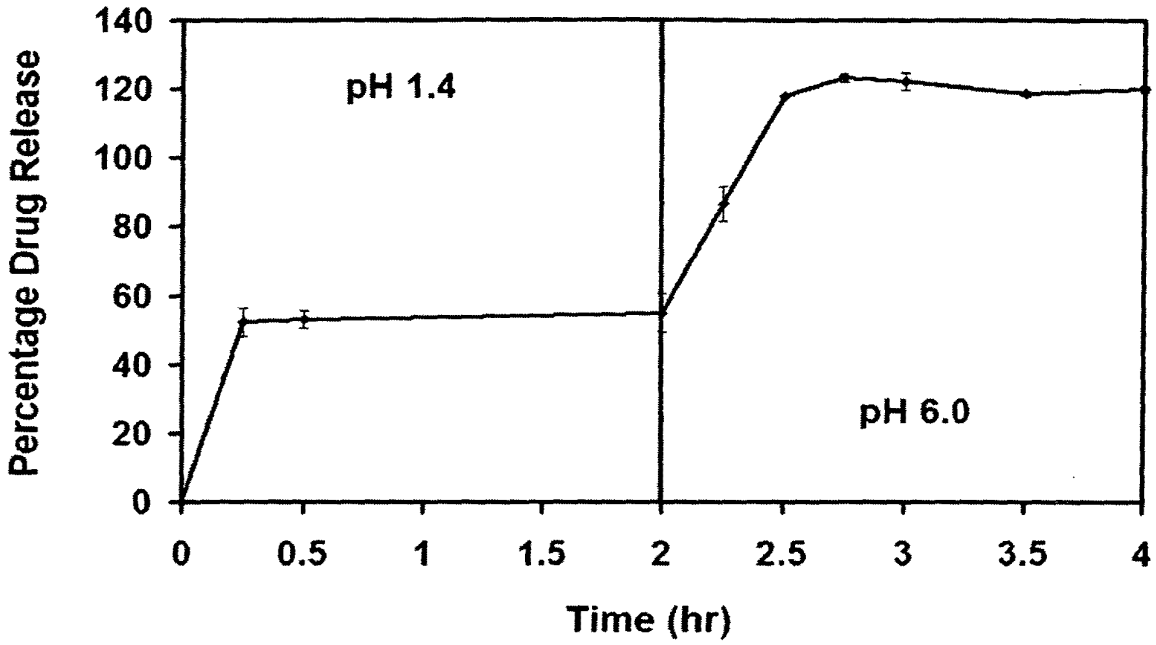

Percentage Drug Release
140
120
100
80
60
40
20
0
pH 1.4
pH 6.0
0
0.5
1
1.5
2
2.5
3
3.5
4
Time (hr)

FIG. 3

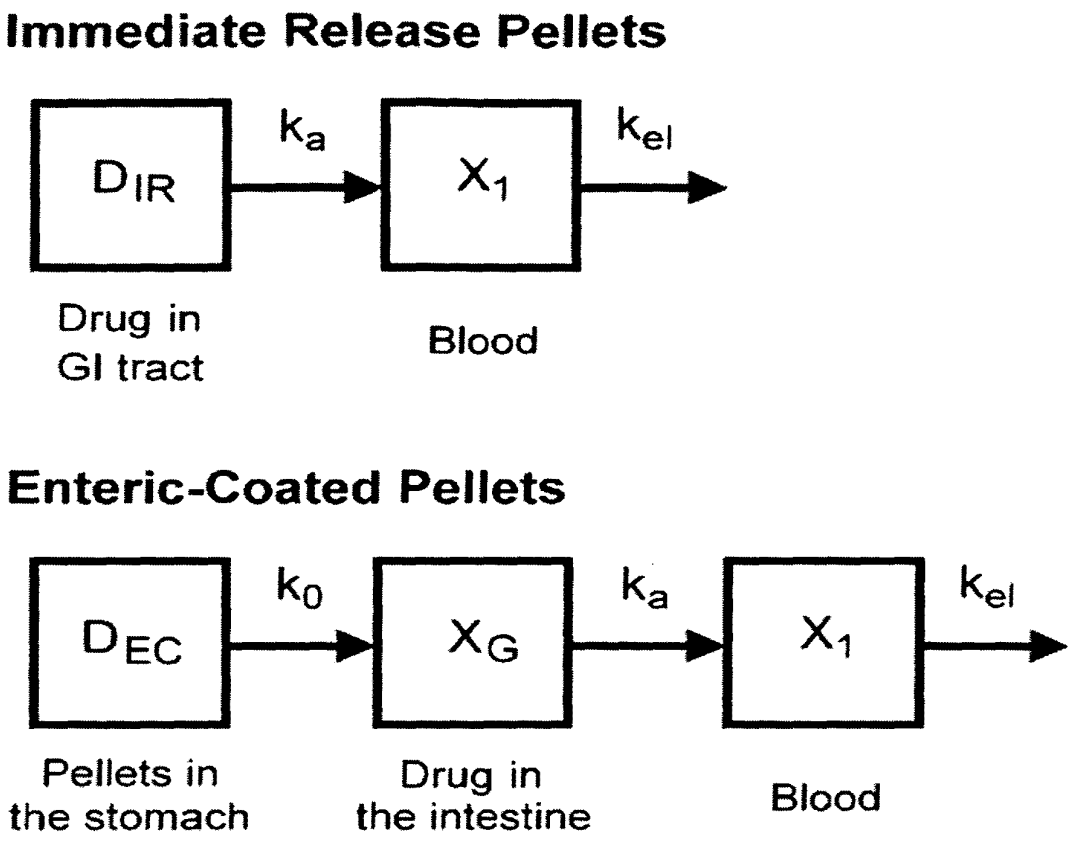
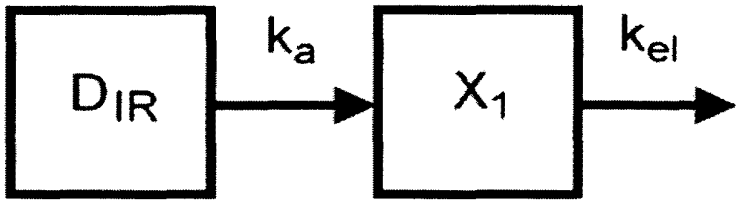
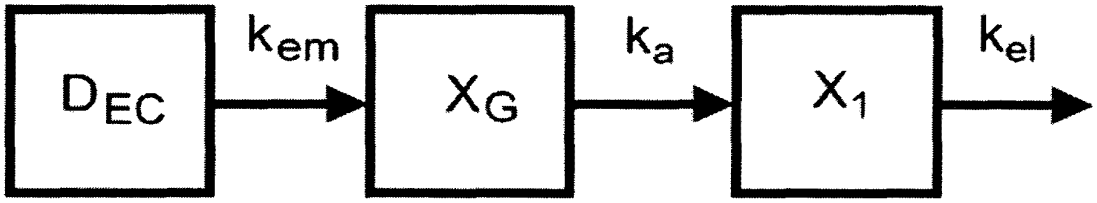

Immediate Release Pellets
D_{IR}
k_a
X_1
k_{el}
Drug in GI tract
Blood
Enteric-Coated Pellets
D_{EC}
k_0
X_G
k_a
X_1
k_{el}
Pellets in the stomach
Drug in the intestine
Blood

FIG. 4

Immediate Release Pellets



Enteric-Coated Pellets



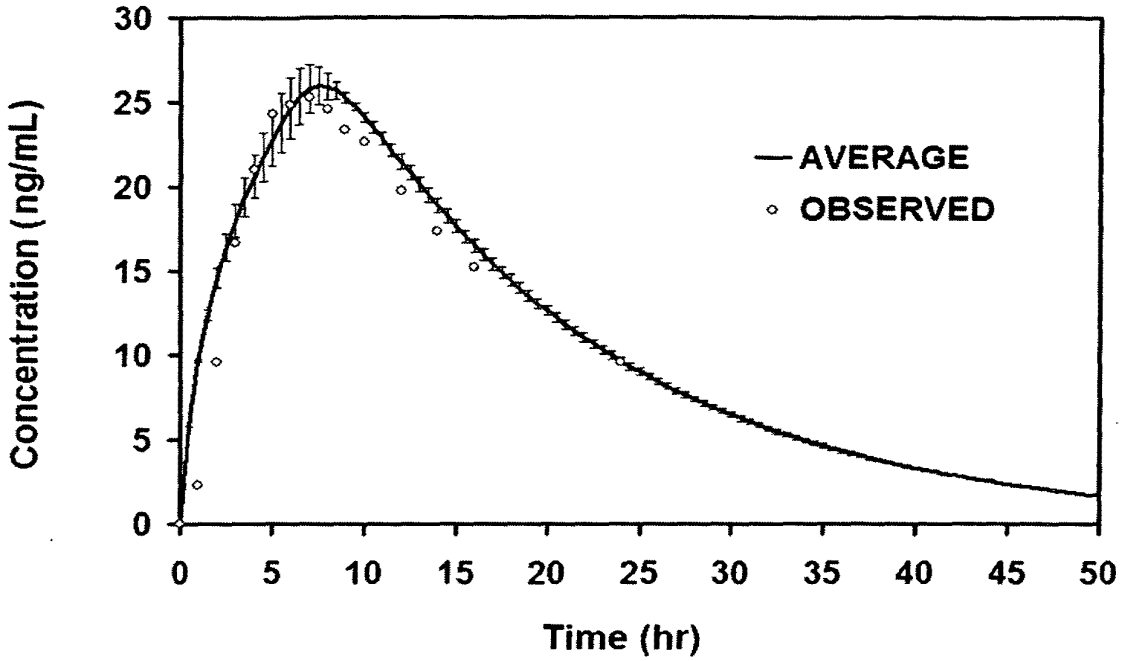

30
25
20
15
10
5
0
Concentration (ng/mL)
0
5
10
15
20
25
30
35
40
45
50
Time (hr)
AVERAGE
OBSERVED

FIG. 6

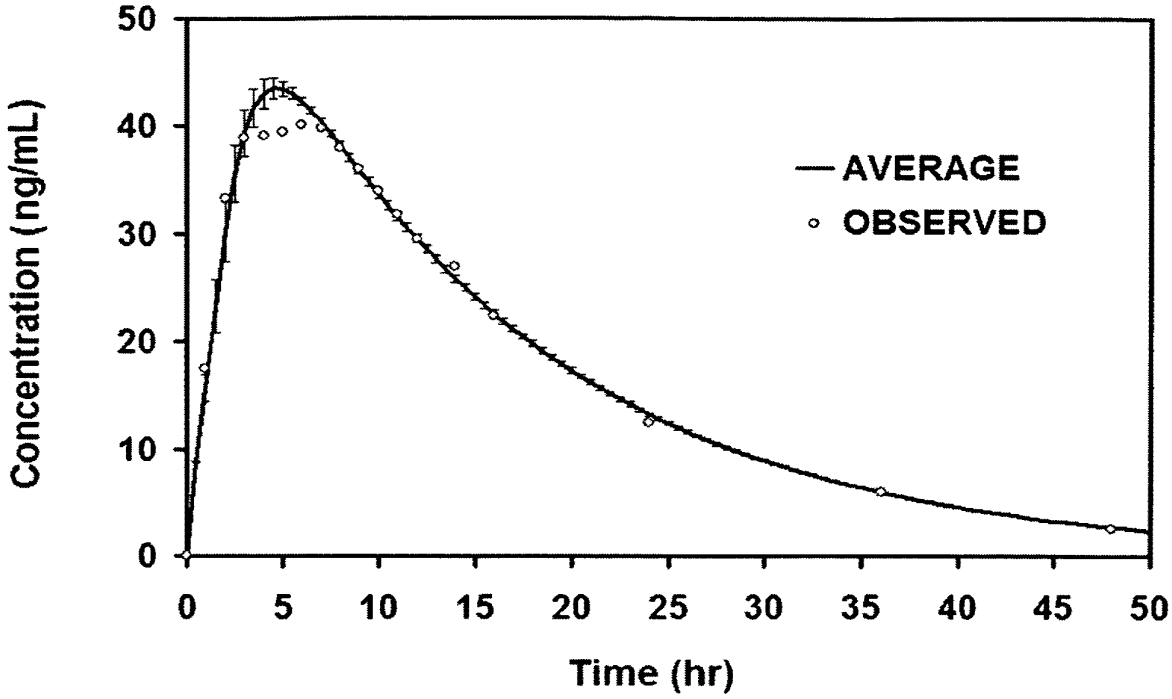

50
40
30
20
10
0
Concentration (ng/mL)
0
5
10
15
20
25
30
35
40
45
50
Time (hr)
AVERAGE
OBSERVED

FIG. 7

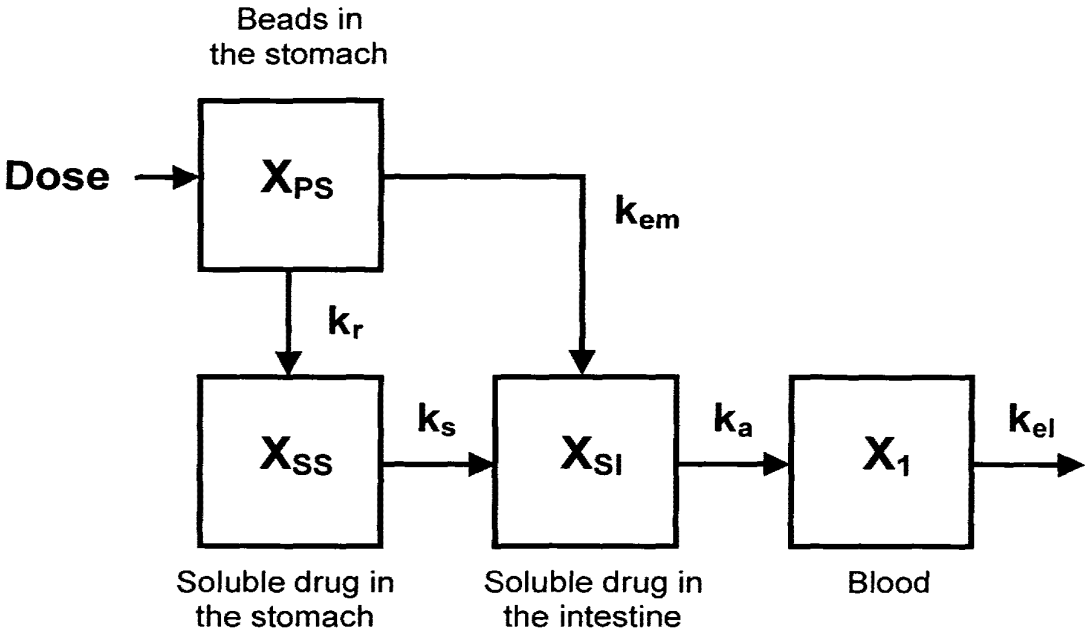

Beads in
the stomach
Dose
X_{PS}
k_{em}
k_r
X_{SS}
k_s
X_{SI}
k_a
X_1
k_{el}
Soluble drug in
the stomach
Soluble drug in
the intestine
Blood

FIG. 8

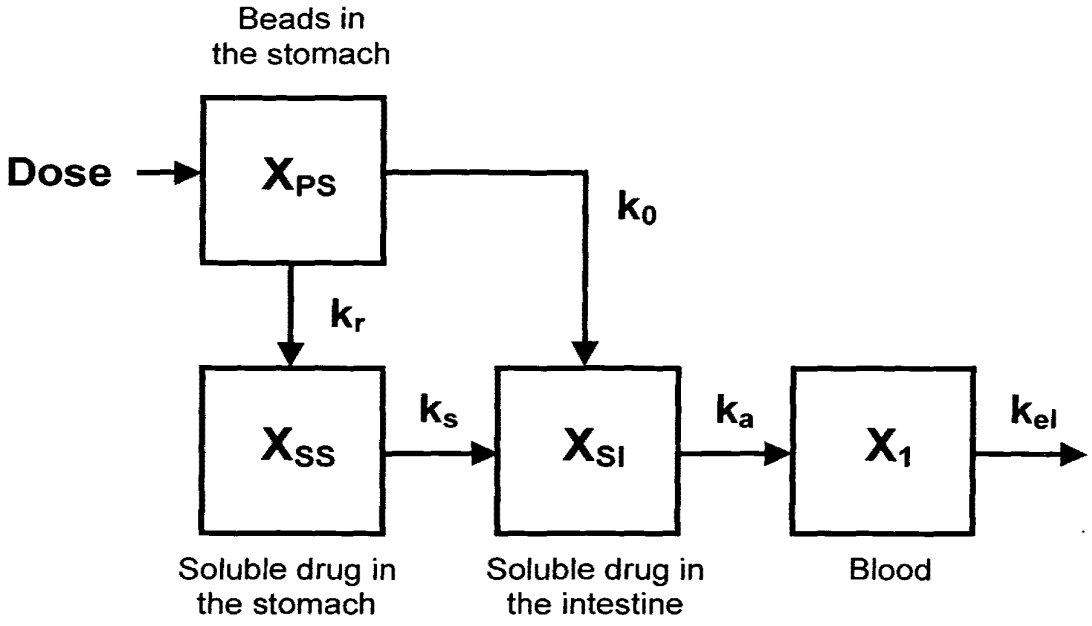

Beads in
the stomach
Dose
X_{PS}
k_0
k_r
X_{SS}
k_s
X_{SI}
k_a
X_1
k_{el}
Soluble drug in
the stomach
Soluble drug in
the intestine
Blood

FIG. 9

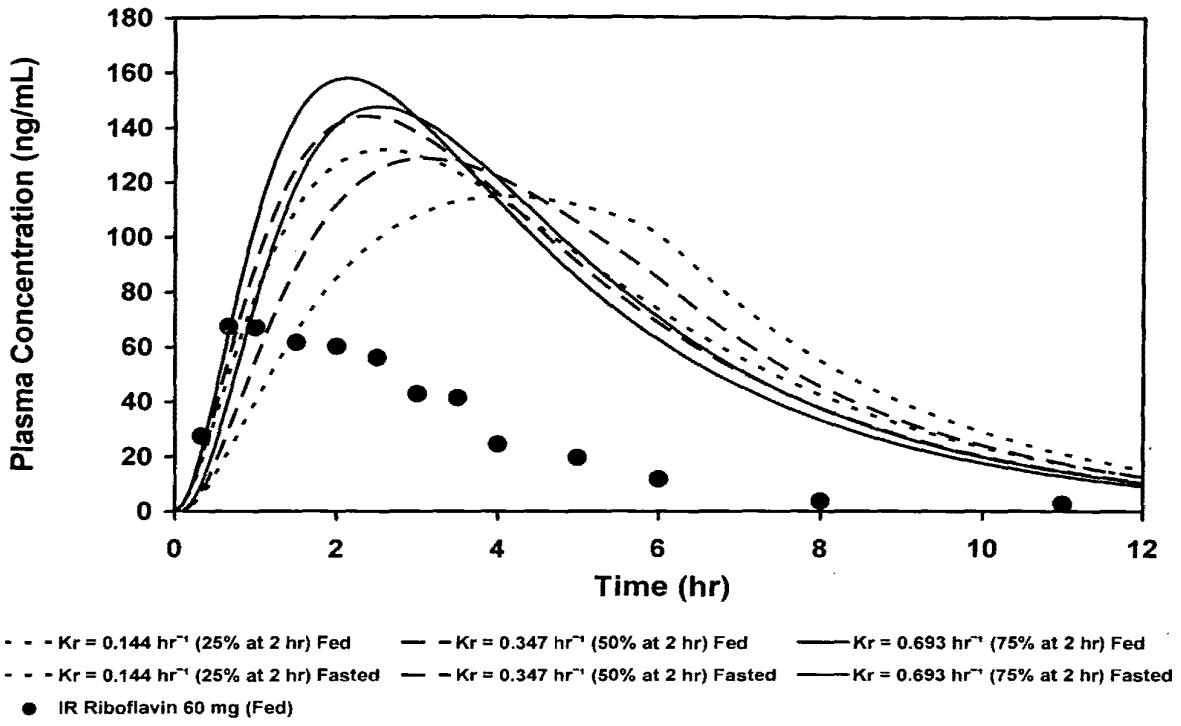

Plasma Concentration (ng/mL)
180
160
140
120
100
80
60
40
20
0
0
2
4
6
8
10
12
Time (hr)
- - - Kr = 0.144 hr⁻¹ (25% at 2 hr) Fed
— — Kr = 0.347 hr⁻¹ (50% at 2 hr) Fed
——— Kr = 0.693 hr⁻¹ (75% at 2 hr) Fed
- - - Kr = 0.144 hr⁻¹ (25% at 2 hr) Fasted
— — Kr = 0.347 hr⁻¹ (50% at 2 hr) Fasted
——— Kr = 0.693 hr⁻¹ (75% at 2 hr) Fasted
● IR Riboflavin 60 mg (Fed)

FIG. 10

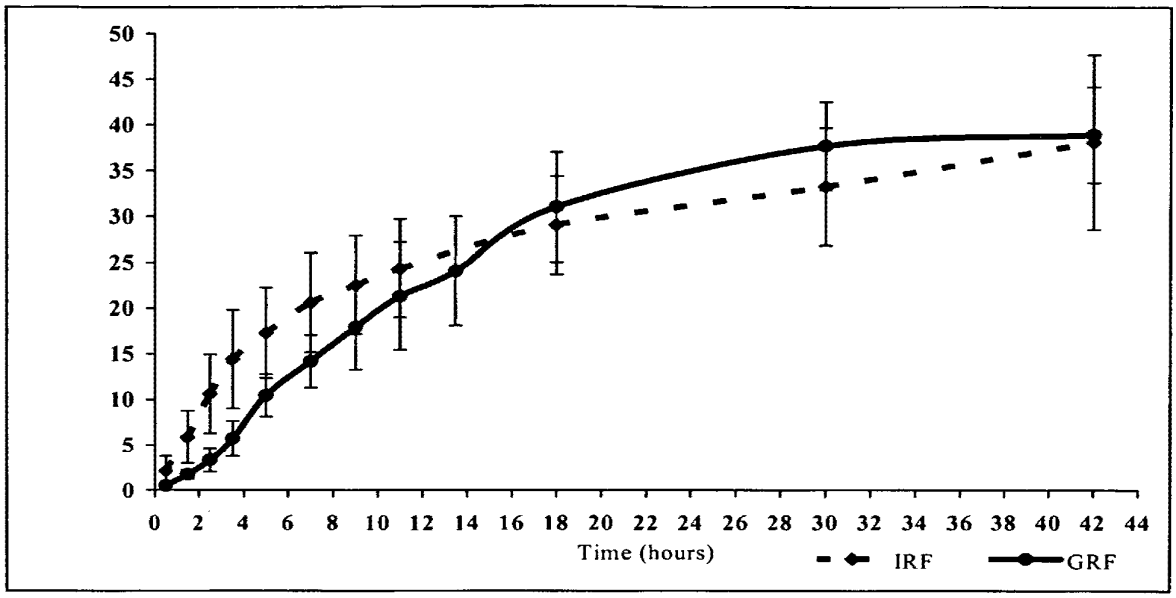

50
45
40
35
30
25
20
15
10
5
0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44
Time (hours)
IRF
GRF

FIG. 11

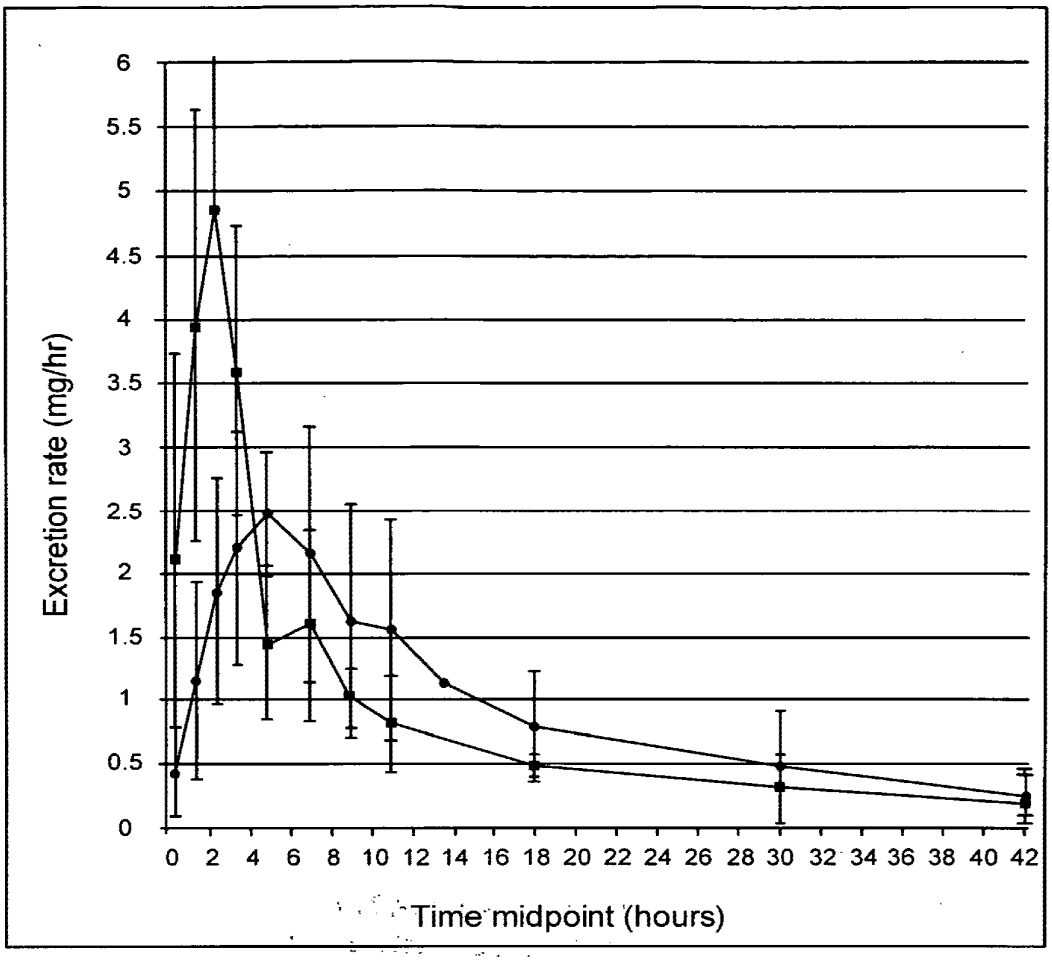

Excretion rate (mg/hr)
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42
Time midpoint (hours)

FIG. 12

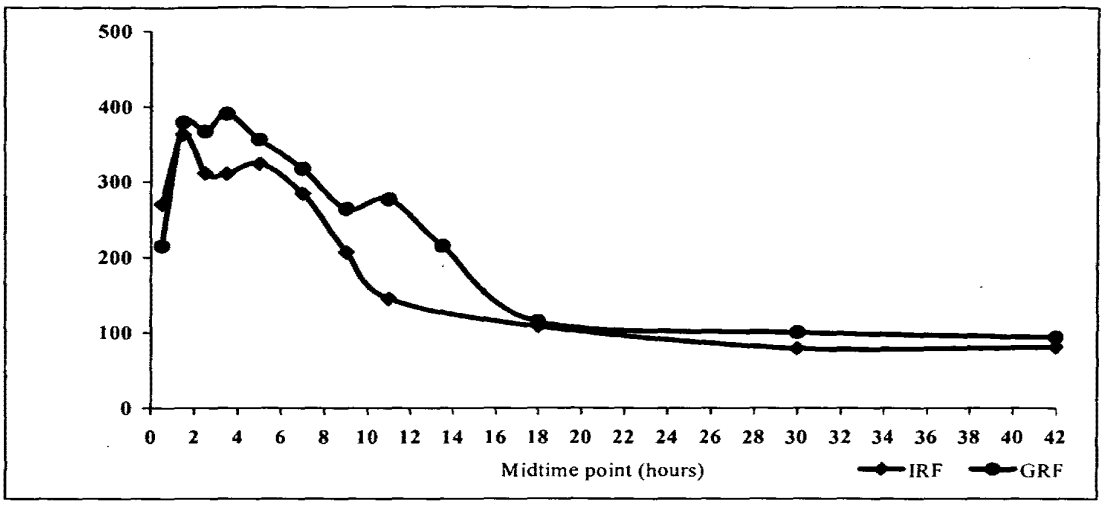

500
400
300
200
100
0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42
Midtime point (hours)
IRF
GRF

FIG. 13

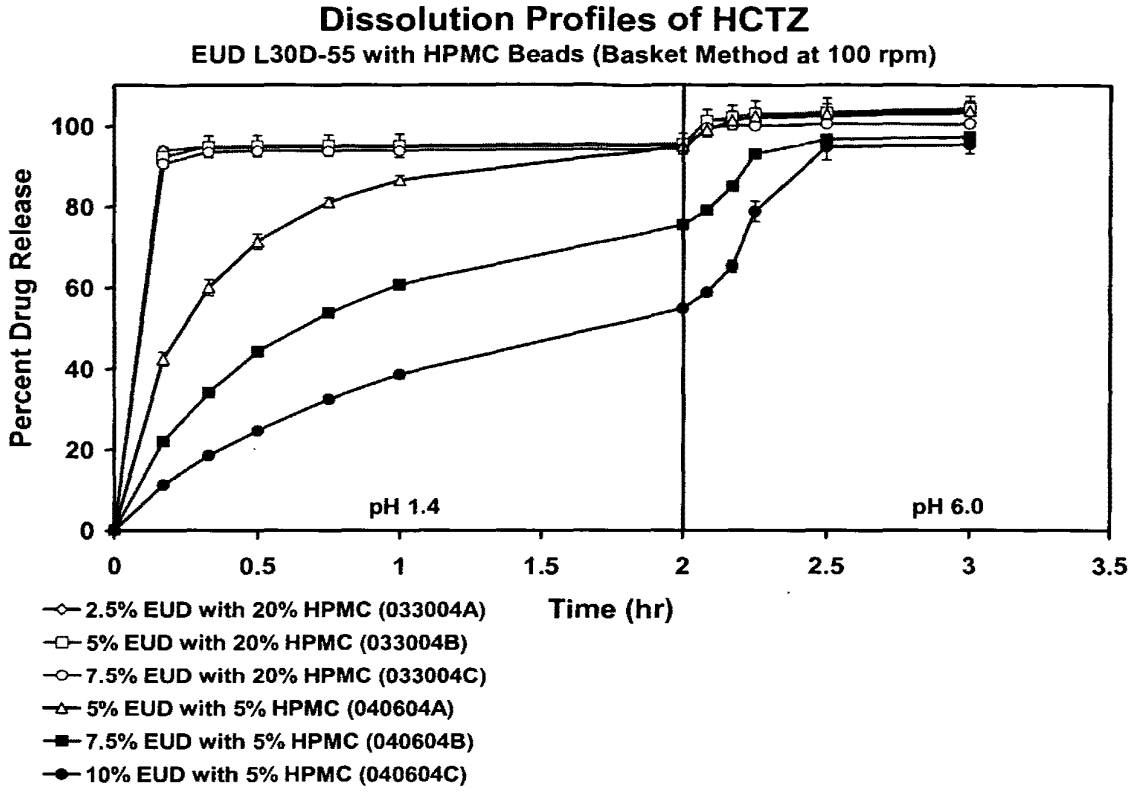

Dissolution Profiles of HCTZ
EUD L30D-55 with HPMC Beads (Basket Method at 100 rpm)
Percent Drug Release
100
80
60
40
20
0
pH 1.4
pH 6.0
0
0.5
1
1.5
2
2.5
3
3.5
Time (hr)
2.5% EUD with 20% HPMC (033004A)
5% EUD with 20% HPMC (033004B)
7.5% EUD with 20% HPMC (033004C)
5% EUD with 5% HPMC (040604A)
7.5% EUD with 5% HPMC (040604B)
10% EUD with 5% HPMC (040604C)

FIG. 14

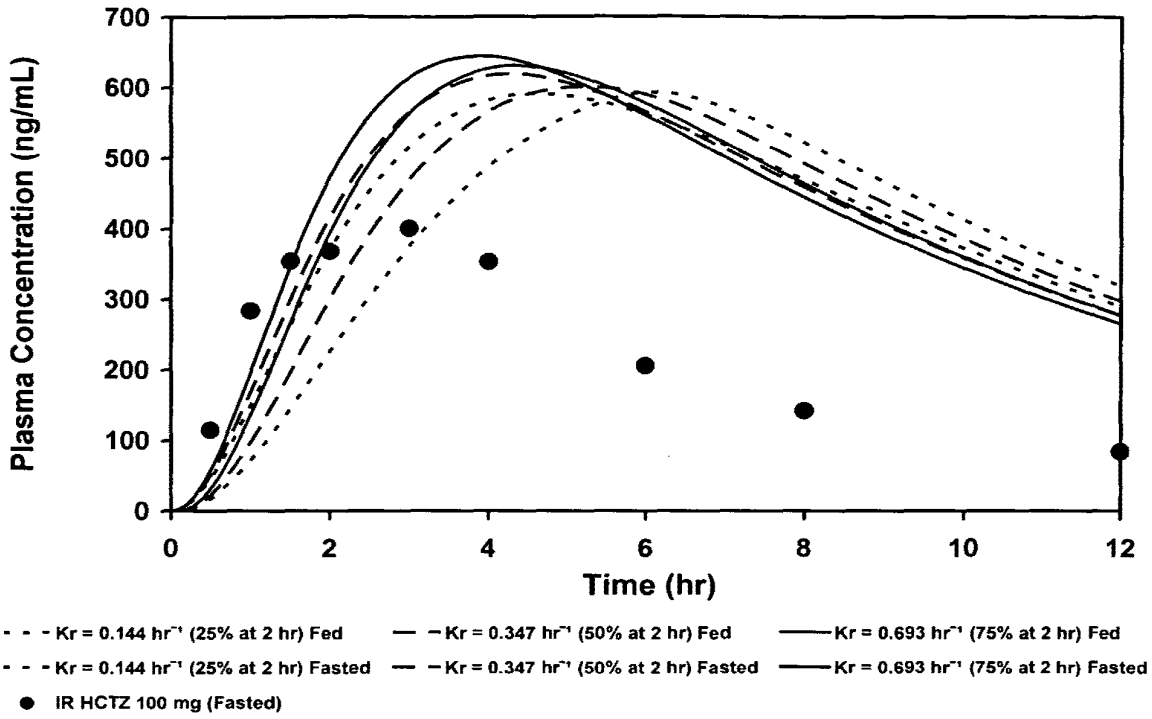

Plasma Concentration (ng/mL)
700
600
500
400
300
200
100
0
0
2
4
6
8
10
12
Time (hr)
Kr = 0.144 hr⁻¹ (25% at 2 hr) Fed
Kr = 0.347 hr⁻¹ (50% at 2 hr) Fed
Kr = 0.693 hr⁻¹ (75% at 2 hr) Fed
Kr = 0.144 hr⁻¹ (25% at 2 hr) Fasted
Kr = 0.347 hr⁻¹ (50% at 2 hr) Fasted
Kr = 0.693 hr⁻¹ (75% at 2 hr) Fasted
IR HCTZ 100 mg (Fasted)

FIG. 15

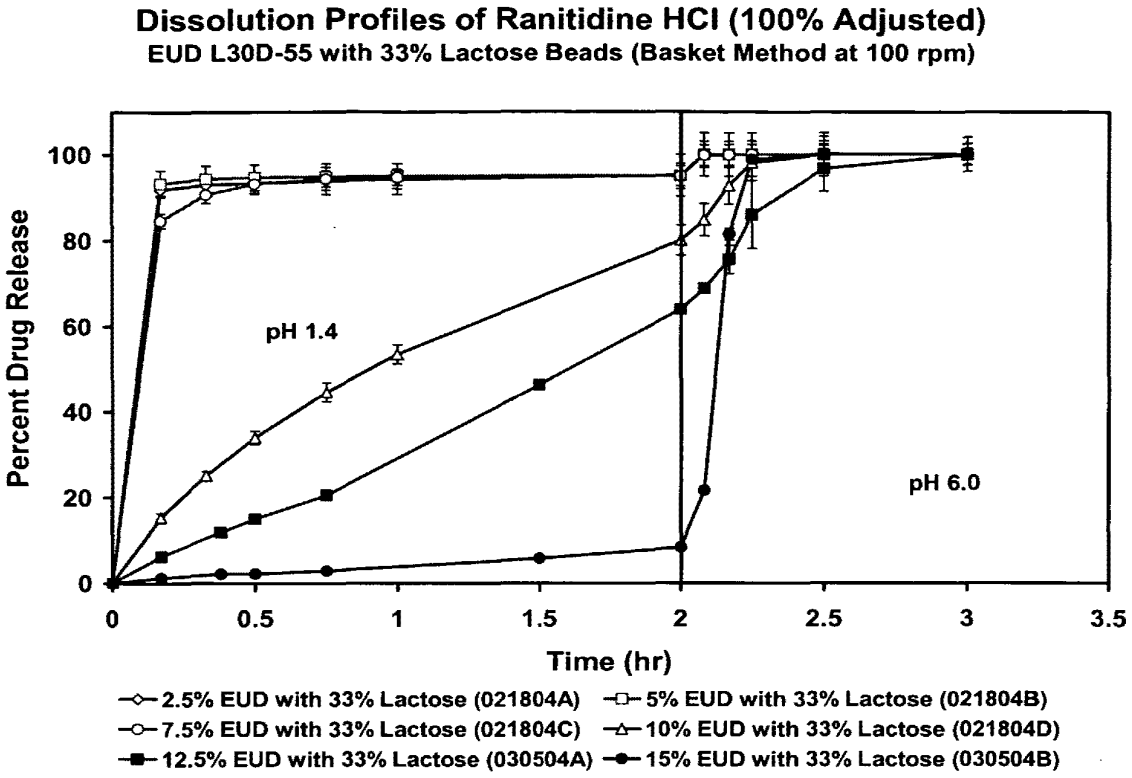

Dissolution Profiles of Ranitidine HCl (100% Adjusted)
EUD L30D-55 with 33% Lactose Beads (Basket Method at 100 rpm)
Percent Drug Release
100
80
60
40
20
0
pH 1.4
pH 6.0
0
0.5
1
1.5
2
2.5
3
3.5
Time (hr)
2.5% EUD with 33% Lactose (021804A)
5% EUD with 33% Lactose (021804B)
7.5% EUD with 33% Lactose (021804C)
10% EUD with 33% Lactose (021804D)
12.5% EUD with 33% Lactose (030504A)
15% EUD with 33% Lactose (030504B)

FIG. 16

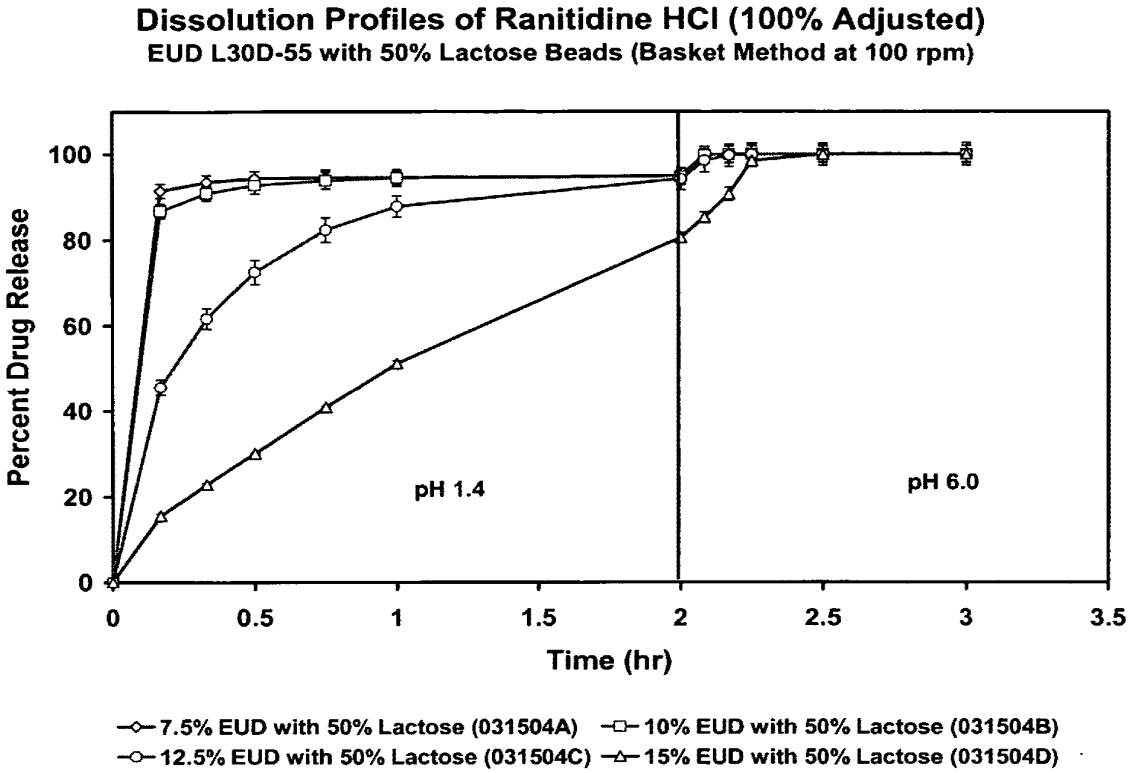

Dissolution Profiles of Ranitidine HCl (100% Adjusted)
EUD L30D-55 with 50% Lactose Beads (Basket Method at 100 rpm)
Percent Drug Release
100
80
60
40
20
0
0
0.5
1
1.5
2
2.5
3
3.5
Time (hr)
pH 1.4
pH 6.0
7.5% EUD with 50% Lactose (031504A)
10% EUD with 50% Lactose (031504B)
12.5% EUD with 50% Lactose (031504C)
15% EUD with 50% Lactose (031504D)

FIG. 17

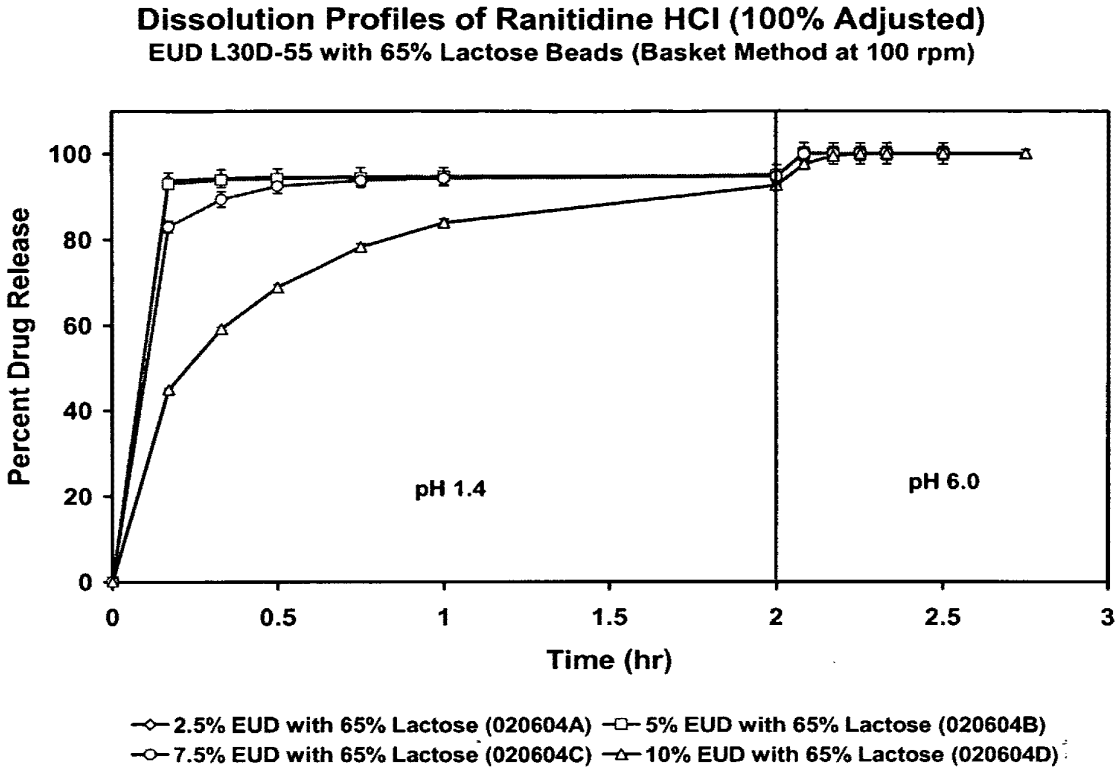

Dissolution Profiles of Ranitidine HCl (100% Adjusted)
EUD L30D-55 with 65% Lactose Beads (Basket Method at 100 rpm)
Percent Drug Release
100
80
60
40
20
0
pH 1.4
pH 6.0
0
0.5
1
1.5
2
2.5
3
Time (hr)
2.5% EUD with 65% Lactose (020604A)
5% EUD with 65% Lactose (020604B)
7.5% EUD with 65% Lactose (020604C)
10% EUD with 65% Lactose (020604D)

FIG. 18

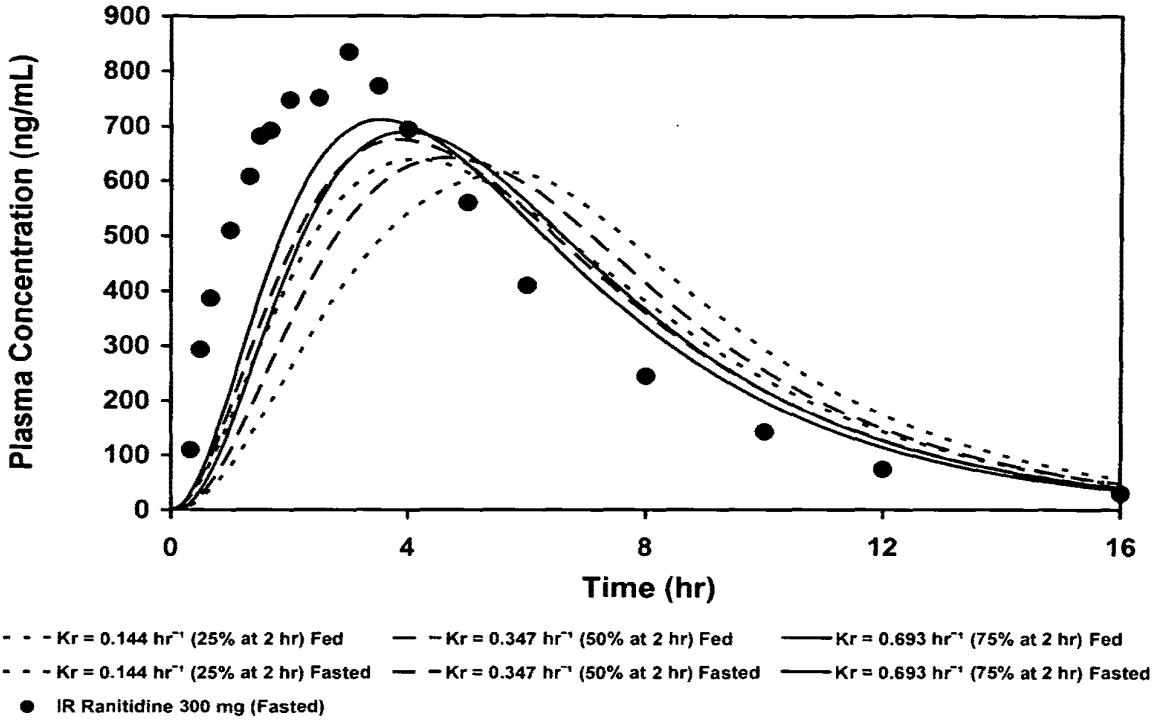

Plasma Concentration (ng/mL)
900
800
700
600
500
400
300
200
100
0
0
4
8
12
16
Time (hr)
- - - Kr = 0.144 hr⁻¹ (25% at 2 hr) Fed
— — Kr = 0.347 hr⁻¹ (50% at 2 hr) Fed
—— Kr = 0.693 hr⁻¹ (75% at 2 hr) Fed
- - - Kr = 0.144 hr⁻¹ (25% at 2 hr) Fasted
— — Kr = 0.347 hr⁻¹ (50% at 2 hr) Fasted
—— Kr = 0.693 hr⁻¹ (75% at 2 hr) Fasted
IR Ranitidine 300 mg (Fasted)

FIG. 19

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 April 2006 (27.04.2006)

PCT

(10) International Publication Number
WO 2006/044202 A3

(51) International Patent Classification:
A61K 9/28 (2006.01) *A61K 9/20* (2006.01)
A61K 9/48 (2006.01)

(21) International Application Number:
PCT/US2005/035787

(22) International Filing Date: 3 October 2005 (03.10.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/620,482 19 October 2004 (19.10.2004) US

(71) Applicant *(for all designated States except US)*: **STATE OF OREGON acting by and through THE STATE BOARD OF HIGHER EDUCATION ON BEHALF OF OREGON STATE UNIVERSITY** [US/US]; Office of Technology Transfer, 312 Kerr Administrative Building, Corvallis, OR 97331-2140 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **AYRES, James, W.** [US/US]; 1173 Charlemagne, Corvallis, OR 97330 (US).

(74) Agent: **SLATER, Stacey, C.**; Klarquist Sparkman, LLP, One World Trade Center, Suite 1600, 121 S.W. Salmon Street, Portland, OR 97204 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv))*

Published:
— *with international search report*

(88) Date of publication of the international search report:
1 March 2007

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ENTERIC COATED COMPOSITIONS THAT RELEASE ACTIVE INGREDIENT(S) IN GASTRIC FLUID AND INTESTINAL FLUID

(57) Abstract: Embodiments of a pharmaceutical formulation comprising an enteric material are disclosed. The embodiments release at least a portion of an active ingredient upon contacting gastric fluid. The remaining portion of the formulation releases active ingredient upon contacting intestinal fluid. Certain embodiments of the pharmaceutical composition comprise at least one active ingredient in a core and a leaky enteric coating, such as an enteric coating comprising a gastric fluid channeling agent. Other embodiments of the pharmaceutical composition comprise at least one active ingredient substantially homogeneously admixed with at least one enteric material, such as an enteric material comprising a gastric fluid channeling agent. Disclosed embodiments of the pharmaceutical composition may comprise a single active ingredient, or may comprise plural active ingredients. Generally, but not necessarily, the active ingredient has a window of absorption. The present disclosure also describes a method for treating a subject having a condition treatable by an active ingredient. The method comprises providing one or more embodiments of the pharmaceutical composition disclosed herein comprising an active ingredient suitable for treating the condition. The pharmaceutical composition is administered to the subject. A method for making embodiments of the disclosed composition also is described. The method comprises providing a core comprising an active ingredient. An enteric material is applied to at least a portion of the core, and generally on or about a substantial portion of the core, to form a coat. The composition is then made leaky.

WO 2006/044202 A3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/35787

A. CLASSIFICATION OF SUBJECT MATTER
IPC: A61K 9/28(2006.01)
A61K 9/48(2006.01),9/20(2006.01)

USPC: 424/464,474,451
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/464, 474, 451

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,795,644 (ZENTNER) 03 JANUARY 1989 (03.01.1989), SEE ENTIRE DOCUMENT.	1-31, 175-234, 265-364, 490-522, 555-574, 576, 578, 580 AND 581
Y	US 5,681,584 (SAVASTANO et al.) 28 OCTOBER 1997 (28.10.1997), SEE ENTIRE DOCUMENT.	578, 580 AND 581

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
24 August 2006 (24.08.2006)

Date of mailing of the international search report
26 SEP 2006

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (571) 273-3201

Authorized officer
Lakshmi S. Channavajjala

Telephone No. 571-272-1600

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/35787

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-31,175-234,265-364,490-522,555-574,576,578,580 and 581

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/35787

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

Group I, claim(s) 1-31, 175-234, 265-364, 490-522, 555-574, 576, 578, 580 and 581, drawn to drawn to a composition comprising an active agent in the core and an enteric coat.

Group II, claim(s) 32-115, 365-424, 575 and 579, drawn to a composition comprising an active agent and enteric material in a matrix.

Group III, claim(s) s 116-174, 424-489, 575 and 580, drawn to a composition comprising an active agent in the core and an enteric coat, wherein the active agent cannot be riboflavin and bisacodyl.

Group IV, claim(s) 235-264, 523-554, 577 and 582, drawn to a composition comprising a sugar bead coated with an active agent and enteric materials.

The inventions listed as Groups I, II, III and IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the release of an active from core of group I is different from the matrix (II) or the sugar bead (IV). Group I can have any active agent whereas group III cannot have riboflavin and bisacodyl.

The inventions listed as Groups II, III and IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the release of an active from core of group II is different from the matrix (II) or the sugar bead (IV).

The inventions listed as Groups III and IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the release of an active from core of group III is different from the sugar bead (IV).

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 June 2007 (07.06.2007)

PCT

(10) International Publication Number
WO 2007/064274 A1

(51) International Patent Classification:
A61K 31/60 (2006.01) ***A61P 9/10*** (2006.01)
A61K 9/20 (2006.01) *A61K 31/4184* (2006.01)
A61K 9/48 (2006.01) *A61K 31/4439* (2006.01)
A61P 1/04 (2006.01) *A61K 31/444* (2006.01)

(21) International Application Number:
PCT/SE2006/001349

(22) International Filing Date:
28 November 2006 (28.11.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/740,981 30 November 2005 (30.11.2005) US
60/818,886 6 July 2006 (06.07.2006) US

(71) Applicant *(for all designated States except US)*: **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **JOHANSSON, Dick** [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). **NILSSON, Lena** [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). **SVEDBERG, Lars-Erik** [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE).

(74) Agent: **ASTRAZENECA**; Global Intellectual Property, S-151 85 Södertälje (SE).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2007/064274 A1

(54) Title: ORAL PHARMACEUTICAL DOSAGE FORM COMPRISING AS ACTIVE INGREDIENTS A PROTON PUMP INHIBITOR TOGETHER WITH ACETYL SALICYCLIC ACID

(57) Abstract: The present invention relates to an oral pharmaceutical preparation for use in the prevention and/or reduction of gastrointestinal complications associated with the use of acetyl salicylic acid. The present preparation comprises a fixed oral dosage form comprising a proton pump inhibitor in combination with acetyl salicylic acid. Furthermore, the present invention refers to a method for the manufacture thereof and the use thereof in medicine. The present invention also relates to a specific combination comprising esomeprazole, or an alkaline salt thereof or a hydrated form of any one of them, and acetyl salicylic acid for use as a medicament for the prevention of thromboembolic vascular events, such as myocardial infarction or stroke, and for the prevention and/or reduction of gastrointestinal complications associated with the use of acetyl salicylic acid.

NEW COMBINATION DOSAGE FORMS

FIELD OF THE INVENTION

The present invention relates to an oral pharmaceutical preparation for use in the prevention and/or reduction of gastrointestinal complications associated with acetyl salicylic acid treatment. The present preparation comprises a fixed oral dosage form comprising a proton pump inhibitor (hereinafter also referred to as a PPI, i.e. a proton pump inhibitor) in combination with acetyl salicylic acid (hereinafter also referred to as ASA) or a derivative thereof. Furthermore, the present invention refers to a method for the manufacture thereof and the use thereof in medicine.

The present invention also relates to a specific combination comprising esomeprazole, or an alkaline salt thereof or a hydrated form of any one of them, and acetyl salicylic acid in an oral fixed combination dosage form comprising a group of separate physical units comprising esomeprazole, or an alkaline salt thereof or a hydrated form of any one of them, and one or more other separate physical units comprising ASA or a derivative thereof for use as a medicament for the prevention of thromboembolic vascular events, such as myocardial infarction or stroke, the risk of which is increased in the elderly population and further prevention and/or reduction of gastrointestinal complications associated with acetyl salicylic acid (ASA) treatment.

BACKGROUND OF THE INVENTION

Acetyl salicylic acid (ASA) is one of the most commonly prescribed and used drugs worldwide. Its use in prevention of thromboembolic vascular events, such as myocardial infarction or stroke have been described in "Collaborative overwiev of randomised trials of antiplatelet therapy Prevention of death, myocardial infarction, and stroke by prolonged

antiplatelet therapy in various categories of patients." [British Medical Journal 1994, 308, p. 81-106, by Antiplatelets triallists collaboration]. Despite the therapeutic benefits, its use is frequently limited by an increased risk of gastrointestinal side effects, mainly upper gastrointestinal side effects like peptic ulceration and dyspeptic symptoms. The relative risk of developing an ulcer complication like bleeding from the stomach or the duodenum is increased by all studied doses of ASA. A peptic ulcer alwaays precedes a peptic ulcer bleed. Even a daily dose as low as 75 mg doubles this risk (Weil et al BMJ 1995:310; 827-830). Epidemiological data from the UK indicate that 18% of hospital admissions due to adverse drug reactions are caused to ASA (Pirmohamed et al BMJ 2004:329; 15-19). Therefore, therapies that avoid gastrointestinal side effect caused by ASA are requested.

The most promising solution to the problem of healing and preventing ASA associated upper gastrointestinal side-effects like ulcers and dyspeptic symptoms in patients with a need for continuous treatment is to combine the ASA treatment with an anti-ulcer drug approved for the healing and/or prophylaxis of ASA associated gastrointestinal side-effects such as prostaglandin analogues, H_2-receptor antagonists or proton pump inhibitors.

"Schutzwirkung von Omeprazol gegenüber niedrig dosierter Acetylsalicylsäure" by Simon et al in Arzneimittel-Forschung, 1995 vol. 45 no. 6, p. 701-3, reports that concomitant administration of omeprazole for patients treated with ASA was found to reduce gastroduodenal lesions evoked by ASA.

In "Untersuchungen zur Schutzwirkung von Lanzoprazol auf die menschlische Magenschleimhaut gegenüber niedrig dosierter Acetylsalicylsäure" by Müller et al in Arzneimittel-Forschung, 1997 vol. 47 no. 6, p. 758-60, it was reported that concomitant administration of either lansoprazole or ranitidine for patients treated with ASA was found to reduce damages on the mucosa caused by ASA.

Established risk factors for developing ASA associated upper gastrointestinal side effects and complications are for instance high age, previous peptic ulcer and/or bleeding, high dose of ASA, co-therapy with other antithrombotic drugs, anticoagulants or Nonsteroidal

Anti-inflammatory Drugs (NSAIDs). This means that for example, fragile and elderly patients tolerating a complication like bleeding or perforation badly should receive prophylactic treatment in connection with their ASA treatment.

This has for instance been suggested by A. Lanas in Digestive and Liver Disease, 2004, 36, p.655-7.

Low-dose ASA is mainly used for the prevention of thromboembolic vascular events, such as myocardial infarction or stroke, the risk of which is increased in the elderly population. Compliance with treatment is especially important in elderly and fragile patients, who have the highest risk of developing a life-threatening complication to ASA treatment like bleeding or perforation. The importance of compliance is further supported by the finding, that peptic ulcers associated with ASA treatment are often asymptomatic until the event.

In proposed therapies comprising ASA and a proton pump inhibitor, the different active substances often are administered separately, as presented in "Clopidogrel versus Aspirin and Esomprazole to prevent recurrent bleeding." in New England Journal of Medicine, 2005, 352, p.238-44. It is well known that patient compliance is a main factor in receiving a good result in medical treatments. Therefore, administration of two or even more different tablets/capsules to the patient is not convenient or satisfactory to achieve the most optimal results.

In US 2005/0227949 A1 it is presented that a combination of an NSAID and a histamine H2-receptor antagonist is an effective treatment against viral and bacterial infections. Among the particularly preferred H2-histamine receptor antagonist is included omeprazole and esomeprazole. A kit comprising the compounds is claimed among other things. No fixed unit dosage form is disclosed.

WO 97/25064 describes an oral pharmaceutical dosage form comprising an acid susceptible proton pump inhibitor and one or more NSAIDs in a fixed formulation, wherein the proton pump inhibitor is protected by an enteric coating layer. The fixed

formulation is in the form of an enteric coating layered tablet, a capsule or a multiple unit tableted dosage form. The multiple unit dosage forms are most preferred.

Some proton pump inhibitors are susceptible to degradation in acid reacting and neutral media. In respect of the stability properties, it is obvious that when one of the active substances being a acid susceptible proton pump inhibitor it must be protected from contact with acidic gastric juice by an enteric coating layer. There are different enteric coating layered preparations of proton pump inhibitors described in the prior art, see for example US-A 4,786,505 (AB Hässle) comprising omeprazole.

US 2002/0155153 A1 discloses a fixed unit dosage form which can as one alternative be a capsule filled with more than one pharmaceutically active compound. The active compounds are preferably an acid susceptible proton pump inhibitor in combination with one or more NSAIDs and wherein at least the proton pump inhibitor is protected by an enteric coating layer.

US 2003/0069255 A1, now US patent 6,926,907, discloses a single, coordinated, unit-dose product that combines an agent that actively raises intragastric pH, and an NSAID specially formulated to be released in a coordinated way. The figures show that the NSAID is situated inside an enteric coating while the agent that actively raises intragastric pH is located outside/on the enteric coat.

US 6,554,556 B1 presents an invention that is directed to a solid oral dosage form comprising an NSAID extended release tablet and an enterically coated proton-pump inhibitor prepared without applying a separating layer between the proton pump inhibitor and the enteric coat.

US 2002/0051814 A1, now US patent 7,029,701 B2, is directed to formulations having omeprazole and aspirin comprised in the same core and further some kind of coating around said core.

FR 2845917 relates to a pharmaceutical combination comprising tenatoprazole and an NSAID or COX-2 inhibitor.

Another patent application, US 2004/0121004 A1, presents a fixed unit dosage form for an NSAID, a proton pump inhibitor and a buffer. The dosage forms are not enteric coated.

A further patent application that discloses a fixed unit dosage form which is not enteric coated, is US 2005/0147675 A1. This reference discloses a fast dissolving tablet comprising ASA and esomeprazole.

OUTLINE OF THE INVENTION

The present invention relates to an oral pharmaceutical dosage form comprising a proton pump inhibitor together with acetyl salicylic acid and optionally pharmaceutically acceptable excipients, characterized in that the dosage form is in the form of an oral fixed combination dosage form comprising a group of separate physical units comprising a proton pump inhibitor and one or more other separate physical units comprising acetyl salicylic acid or a derivative thereof.

In the present invention, the dosage form is a capsule formulation, multiple unit tablet formulation or sachet formulation, which will simplify the regimen and improve the patient compliance and which will also provide a good stability to the active substances during long-term storage.

The dosage forms according to the invention are suitable to be used especially for the prevention of thromboembolic vascular events, such as myocardial infarction or stroke, the risk of which is increased in the elderly population and further the prevention and/or reduction of gastrointestinal complications associated with acetyl salicylic acid (ASA) treatment.

DESCRIPTION OF THE INVENTION

Embodiments of the invention

A first embodiment of the present invention relates to an oral pharmaceutical dosage form comprising as active ingredients an acid susceptible proton pump inhibitor (PPI) together with acetyl salicylic acid (ASA) or a derivative thereof and optionally pharmaceutically acceptable excipients, characterized in that the dosage form is in the form of an oral fixed combination dosage form comprising a group of separate physical units comprising the acid susceptible proton pump inhibitor and one or more other separate physical units comprising the acetyl salicylic acid or a derivative thereof, and wherein at least the proton pump inhibitor is protected by an enteric coating layer.

In a second embodiment of the present invention the oral pharmaceutical dosage form is comprising an acid susceptible proton pump inhibitor together with acetyl salicylic acid and optionally pharmaceutically acceptable excipients, characterized in that the dosage form is in the form of an oral fixed combination dosage form comprising a group of separate physical units comprising the acid susceptible proton pump inhibitor and one or more other separate physical units comprising the acetyl salicylic acid or a derivative thereof, and wherein the proton pump inhibitor is protected by an enteric coating layer and the acetyl salicylic acid or a derivative thereof is not enteric coated.

In a third embodiment of the present invention the oral pharmaceutical dosage form is comprising an acid susceptible proton pump inhibitor together with acetyl salicylic acid or a derivative thereof and optionally pharmaceutically acceptable excipients, characterized in that the dosage form is in the form of an oral fixed combination dosage form comprising a group of separate physical units comprising the acid susceptible proton pump inhibitor and one or more other separate physical units comprising the acetyl salicylic acid or a derivative thereof, and wherein the proton pump inhibitor is protected by an enteric

coating layer and the acetyl salicylic acid or a derivative thereof is not enteric coated and further is present in an immediate release form.

A fourth embodiment of the invention is directed to an oral pharmaceutical dosage form which is comprising an acid susceptible proton pump inhibitor together with acetyl salicylic acid or a derivative thereof and optionally pharmaceutically acceptable excipients, characterized in that the dosage form is in the form of an oral fixed combination dosage form comprising a group of separate physical units comprising the acid susceptible proton pump inhibitor and one or more other separate physical units comprising the acetyl salicylic acid or a derivative thereof, and wherein the proton pump inhibitor comprising units are protected by an enteric coating layer and the unit comprising acetyl salicylic acid or a derivative thereof is compressed to a tablet and furthermore not is enteric coated.

A fift embodiment of the invention is directed to an oral pharmaceutical dosage form which is comprising an acid susceptible proton pump inhibitor together with acetyl salicylic acid or a derivative thereof, and optionally pharmaceutically acceptable excipients, characterized in that the dosage form is in the form of an oral fixed combination dosage form comprising a group of separate physical units comprising the acid susceptible proton pump inhibitor and one or more other separate physical units comprising the acetyl salicylic acid or a derivative thereof, and wherein the units comprising the proton pump inhibitor are protected by an enteric coating layer and the unit comprising the acetyl salicylic acid or a derivative thereof is mildly compressed to a plug and furthermore not is enteric coated. The mild compression of ASA is beneficial for its stability and dissolution rate.

In one special embodiment of the invention, the mildly compressed plug of ASA has a friability as measured for tablets in US Pharmacopoeia 24, official from 1 January, 2000, in the range of 2%-50 % (w/w), preferably 2%-30% (w/w) and more preferably 2-10% (w/w).

In another special embodiment of the invention, the mildly compressed plug of ASA has a friability as measured for tablets in US Pharmacopoeia 24, official from 1 January, 2000, in the range of 4%-50 % (w/w), preferably 4%-30% (w/w) and more preferably 4-10% (w/w).

In a further special embodiment of the invention, the mildly compressed plug of ASA has a friability as measured for tablets in US Pharmacopoeia 24, official from 1 January, 2000, in the range of 6%-50 % (w/w), preferably 6%-30% (w/w) and more preferably 6-10% (w/w).

Terms used:

The physical units, when used as a starting material for coating, are also referred to as "cores", or as "core material".

The term "dosage form" as used herein, is limited to capsule, tablet, "multiple unit tablet" (see p. 22) or sachet.

Thus the term "fixed combination dosage form" in the present invention is excluding a blister pack arrangement comprising separate dosage forms of PPI and ASA respectively, e.g. one capsule or tablet comprising the acid susceptible proton pump inhibitor and another capsule or tablet comprising the acetyl salicylic acid, packed together. This does not exclude that it is envisaged to pack the dosage forms of the invention in a blister pack cartridge.

The term "unit(s)", as used herein, is intended to include "pellet(s)", "granule(s)", "bead(s)", "mildly compacted plug(s)" and "tablet(s)".

The term "tablet" is the normal, meaning any compressed tablet, which also fulfills the requirement regarding friability being less than 1% (w/w), as measured and required for tablets in US Pharmacopoeia 24, official from 1 January, 2000.

The term "mildly compacted plug" considers a material that have been compressed into a unit form like e.g. a tablet, but not enough compressed to fulfill the requirement of friability for tablets in US Pharmacopoeia 24, official from 1 January, 2000. The mildly compacted plugs are having a friability as measured for tablets, according to US Pharmacopoeia 24, official from 1 January, 2000, being 2% (w/w) or more. In special embodiments the friability is a range which might be situated starting from 2% (w/w) or above and upwards.

The term "gastrointestinal complications", as used herein, is intended to include ulcer in the stomach or duodenum, complications to said ulcers, such as bleeding, perforation and/or obstruction, and dyspeptic symptoms, such as epigastric pain and/or discomfort.

The term "prevention", as used herein, also includes the inhibition of "gastrointestinal complications". The term "reduction" as used herein, is intended to also include the risk reduction of "gastrointestinal complications".

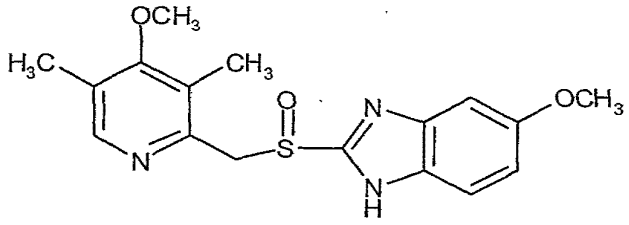
The term "ASA", as used herein, is an abbreviation of acetyl salicylic acid.

The term "PPI", as used herein, is an abbreviation of proton pump inhibitor, and thus encompasses esomeprazole, or an alkaline salt thereof or a hydrated form of any one of them, as well as omeprazole, or an alkaline salt thereof or a hydrated form of any one of them.

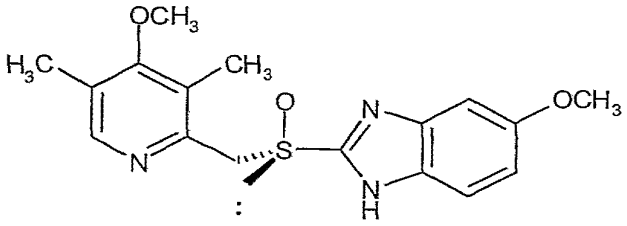
The expressions "low dose acetyl salicylic acid" or "low dose ASA", as used herein, is in one embodiment defined as doses in the range of 10 mg to 500 mg of ASA. In another embodiment it is defined as doses in the range of 25 mg to 450 mg of ASA. In a further embodiment it is defined as doses in the range of 60 mg to 350 mg of ASA.

Active ingredients:

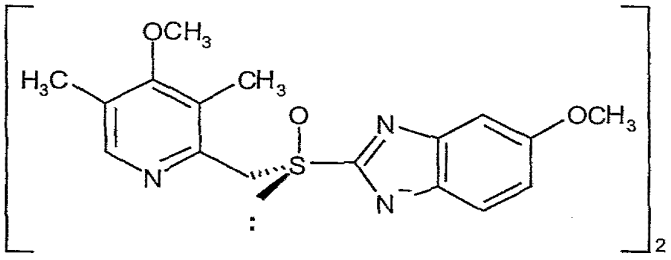
The acid susceptible proton pump inhibitors suitable for the present invention are H^+K^+-ATPase inhibitors and they are selected from:



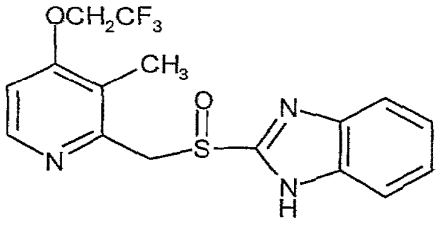
omeprazole



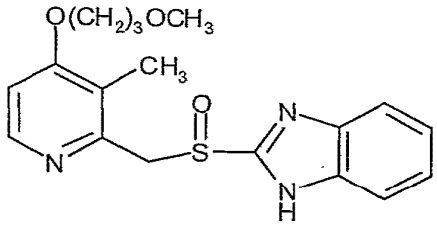
esomeprazole



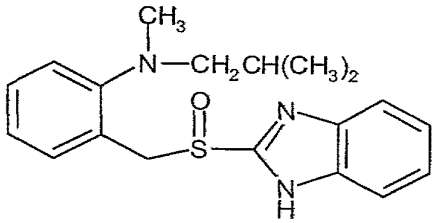
Mg^{2+} esomeprazole magnesium



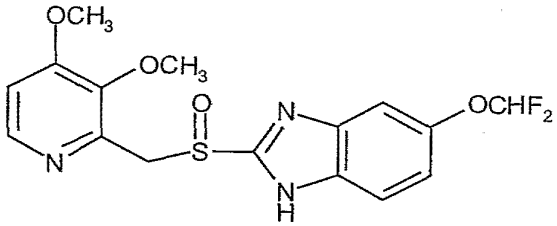
lansoprazole



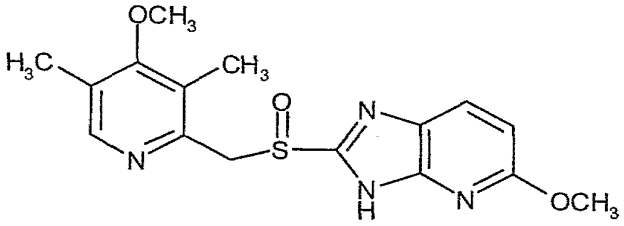
rabeprazole
(pariprazole)



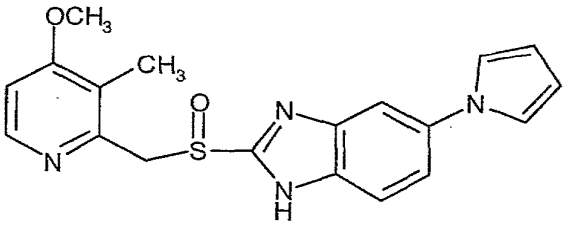
leminoprazole



pantoprazole



tenatoprazole



ilaprazole

The acid susceptible proton pump inhibitors used in the dosage form of the present invention may be used in their neutral form or in the form of a pharmaceutically acceptable salt such as an alkaline salt selected from any one of their Mg^{2+}, Ca^{2+}, Na^{+}, K^{+}, Li^{+} or TBA (tert-butyl ammonium) salts. Further a given chemical formula or name shall encompass all stereo and optical isomers and racemates thereof as well as mixtures in different proportions of the separate enantiomers, where such isomers and enantiomers exist, as well as pharmaceutically acceptable salts thereof and solvates thereof, such as for instance hydrates. The above-listed compounds can also be used in their tautomeric form. Also included in the present invention are derivatives of the compounds listed above which have the biological function of the compounds listed, such as prodrugs.

Proton pump inhibitors are for example disclosed in EP-A1-0005129, EP-A1-174 726, EP-A1-166 287, GB 2 163 747 and WO90/06925, WO91/19711, WO91/19712, WO95/01977, WO98/54171 and WO94/27988.

The acetyl salicylic acid (ASA) can be selected from its free acid form, derivatives thereof or any other possible forms, for example, but not limiting to scope of the present invention, acetyl salicylic amid or acetyl salicylic complex(s).

In a further special embodiment of the present invention the acetyl salicylic acid is in its free acid form. In another further special embodiment of the present invention the acetyl salicylic acid is present as acetyl salicylic amid or acetyl salicylic complex(s) like e.g. a cyclodextrin complex.

Anyone of the different embodiments of ASA can be combined with anyone of the earlier presented embodiments of the oral pharmaceutical dosage form of the invention.

According to one embodiment of the invention, the acid susceptible PPI is omeprazole or an alkaline salt thereof or the acid susceptible PPI is esomeprazole, an alkaline salt thereof or a hydrate form of any one of them.

According to another embodiment of the invention, the acid susceptible PPI is omeprazole or an alkaline salt thereof.

According to yet another embodiment of the present invention the acid susceptible PPI is esomeprazole, an alkaline salt thereof or a hydrate form of any one of them.

According to a further embodiment of the present invention the acid susceptible PPI is lansoprazole or a pharmaceutically acceptable salt thereof or a single enantiomer of either one of them.

In another embodiment of the present invention the acid susceptible PPI is pantoprazole or a pharmaceutically acceptable salt thereof or a single enantiomer of either one of them.

In yet another embodiment of the present invention, the acid susceptible PPI is rabeprazole or a pharmaceutically acceptable salt thereof or a single enantiomer of either one of them.

In a further embodiment of the present invention, the acid susceptible PPI is ilaprazole or a pharmaceutically acceptable salt thereof or a single enantiomer of either one of them.

In yet a further embodiment of the present invention, the acid susceptible PPI is tenatoprazole or a pharmaceutically acceptable salt thereof or a single enantiomer of either one of them.

Anyone of the different embodiments of acid susceptible PPI can be combined with anyone of the earlier presented embodiments of ASA in anyone of the earlier presented embodiments of the oral pharmaceutical dosage form of the invention.

An active ingredient combination especially foreseen to be included in anyone of the earlier presented embodiments of the oral pharmaceutical dosage form is esomeprazole, an alkaline salt thereof or a hydrate form of any one of them and the acetyl salicylic acid is in its free acid form.

Another active ingredient combination especially foreseen to be included in anyone of the earlier presented embodiments of the oral pharmaceutical dosage form is omeprazole, an alkaline salt thereof or a hydrate form of any one of them and the acetyl salicylic acid is in its free acid form.

Core material

The core material for the individually enteric coating layered units can be constituted according to different principles. Seeds layered with the proton pump inhibitor, optionally mixed with alkaline substances, can be used as the core material for the further processing.

The seeds which are to be layered with the proton pump inhibitor may be water insoluble seeds comprising different oxides, celluloses, organic polymers and other materials, alone or in mixtures. The seeds may also be water-soluble seeds comprising different inorganic salts, sugars, non-pareils and other materials, alone or in mixtures. Further, the seeds may comprise the proton pump inhibitor in the form of crystals, agglomerates, compacts etc. The size of the seeds is not essential for the present invention but may vary from approximately 0.1 to 2 mm. In a preferred embodiment of the invention the average diameter of the seeds is from 0.1 mm up to 1.0 mm. The seeds layered with the proton pump inhibitor are produced either by powder or solution/suspension layering. Granulation or spray coating layering equipment may be used.

Before the seeds are layered, the proton pump inhibitor may be mixed with further components. Such components can be binders, surfactants, fillers, disintegrating agents, alkaline additives and/or other pharmaceutically acceptable ingredients , alone or in mixtures. The binders are for example polymers such as hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), carboxymethylcellulose sodium, polyvinyl pyrrolidone (PVP), or sugars, starches or other pharmaceutically acceptable substances

with cohesive properties. Suitable surfactants are found in the groups of pharmaceutically acceptable non-ionic or ionic surfactants such as for instance sodium lauryl sulfate.

Alternatively, the proton pump inhibitor optionally mixed with alkaline substances and further mixed with suitable constituents can be formulated into a core material. Extrusion/spheronization, balling or compression utilizing conventional process equipment may produce said core material. The size of the formulated core material is in one embodiment of the invention approximately from 0.1 mm to 4 mm in diameter, and in another embodiment of the invention from 0.1 mm to 2 mm in diameter. The manufactured core material can further be layered with additional ingredients comprising the proton pump inhibitor and/or be used for further processing.

The proton pump inhibitor is mixed with pharmaceutical constituents to obtain suitable handling and processing properties and a suitable concentration of the proton pump inhibitor in the final preparation. Pharmaceutical constituents such as fillers, binders, lubricants, disintegrating agents, surfactants and other pharmaceutically acceptable additives may be used.

Further, the proton pump inhibitor may also be mixed with an alkaline, pharmaceutically acceptable substance (or substances). Such substances can be chosen among, but are not restricted to, substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminium hydroxide/sodium bicarbonate co precipitate; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $Al_2O_3.6MgO.CO_2.12H_2O$, $(Mg_6Al_2(OH)_{16}CO_3.4H_2O)$, $MgO.Al_2O_3.2SiO_2.nH_2O$ or similar compounds; organic pH-buffering substances such as trihydroxymethylaminomethane, basic amino acids and their salts or other similar, pharmaceutically acceptable pH-buffering substances.

Alternatively, the aforementioned core material can be prepared by using spray drying or spray congealing technique.

Enteric coating layer(s)

Before applying the enteric coating layer(s) onto the core material in the form of individual units, the units may optionally be covered with one or more separating layer(s) comprising pharmaceutical excipients optionally including alkaline compounds such as pH-buffering compounds. This/these separating layer(s), separate(s) the core material from the outer layers being enteric coating layer(s). This/these separating layer(s) protecting the core material of proton pump inhibitor should be water soluble or rapidly disintegrating in water.

The separating layer(s) can be applied to the core material by coating or layering procedures in suitable equipments, such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating process. As an alternative, the separating layer(s) can be applied to the core material by using powder coating technique. The materials for the separating layers are pharmaceutically acceptable compounds selected from any one of sugar, polyethylene glycol, polyvinyl pyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methylcellulose, carboxymethyl cellulose sodium, water soluble salts of enteric coating polymers and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers anti-tacking and anti-static agents (such as magnesium stearate, titanium dioxide, talc) and other additives may also be included into the separating layer(s).

When the optional separating layer is applied to the core material, it may constitute a variable thickness. The maximum thickness of the separating layer(s) is normally only limited by processing conditions. The separating layer may serve as a diffusion barrier and it may also act as a pH-buffering zone. The pH-buffering properties of the separating layer(s) can be further strengthened by introducing into the layer(s) substances chosen from a group of compounds usually used in antacid formulations such as, for instance,

magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds such as $Al_2O_3.6MgO.CO_2.12H_2O$, $(Mg_6Al_2(OH)_{16}CO_3 .4H_2O)$, $MgO.Al_2O_3.2SiO_2.nH_2O$, aluminium hydroxide/sodium bicarbonate coprecipitate or similar compounds; or other pharmaceutically acceptable pH-buffering compounds such as, for instance the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, carbonic, citric or other suitable, weak, inorganic or organic acids; or suitable organic bases, including basic amino acids and salts thereof. Talc or other compounds may also be added to increase the thickness of the layer(s) and thereby strengthen the diffusion barrier. The optionally applied separating layer(s) is not essential for the invention. However, the separating layer(s) may improve the chemical stability of the active substance and/or the physical properties of the claimed oral fixed dosage form.

Alternatively, the separating layer may be formed in situ by a reaction between an enteric coating polymer layer applied on the core material and an alkaline reacting compound in the core material. Thus, the separating layer formed comprises a water soluble salt formed between the enteric coating layer polymer(s) and an alkaline reacting compound, which is in the position to form a salt.

One or more enteric coating layers are applied onto the core material or onto the core material covered with separating layer(s) by using a suitable coating technique. The enteric coating layer material may be dispersed or dissolved in either water or in suitable organic solvents or suitable mixtures of water plus solvent when applicable, like e.g. water plus ethanol in certain proportions can be used to dissolve hydroxypropyl methylcellulose phthalate. As enteric coating layer polymers one or more, separately or in combination, of the following can be used, e.g. solutions or dispersions of methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethyl ethylcellulose, shellac or other suitable enteric coating polymer(s).

The enteric coating layers may contain pharmaceutically acceptable plasticizers to obtain the desired mechanical properties, such as flexibility and hardness of the enteric coating

layers. Such plasticizers are selected from e.g. triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene glycols, polysorbates or other plasticizers.

The amount of plasticizer is optimized for each enteric coating layer formula, in relation to selected enteric coating layer polymer(s), selected plasticizer(s) and the applied amount of said polymer(s), in such a way that the mechanical properties, i.e. flexibility and hardness of the enteric coating layer(s) fulfill the desired requirements. The amount of plasticizer is usually above 10 % by weight of the enteric coating layer polymer(s), alternatively 15 - 50 %, or alternatively 20 - 50 %. Additives such as dispersants, colorants, pigments polymers e.g. poly (ethylacrylat, methylmethacrylat), anti-tacking and anti-foaming agents may also be included into the enteric coating layer(s). Other compounds may be added to increase film thickness and to decrease diffusion of acidic gastric juices into the acid susceptible material. To protect the acid susceptible substance, the proton pump inhibitor, and to obtain an acceptable acid resistance of the dosage form according to the invention, the enteric coating layer(s) constitutes a thickness of approximately at least 10 μm or alternatively more than 20 μm. The maximum thickness of the applied enteric coating is normally only limited by processing conditions and the desired dissolution profile.
In one embodiment of the invention the enteric coating layer thickness is in the range of 15 – 45 micron. In a preferred embodiment of the invention the enteric coating layer thickness is in the range of 20 – 35 micron.

Over-coating layer

Units comprising either proton pump inhibitor or ASA and covered with enteric coating layer(s) may further be covered with one or more over-coating layer(s). The over-coating layer(s) should be water soluble or rapidly disintegrating in water. The over-coating layer(s) can be applied to the enteric coating layered units by coating or layering procedures in suitable equipments, such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating or layering process. The materials for over-coating layers are chosen among pharmaceutically acceptable

compounds selected from any one of sugar, polyethylene glycol, polyvinyl pyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methyl cellulose, carboxymethylcellulose sodium and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers, anti-tacking and anti-static agents (such as magnesium stearate, titanium dioxide and talc) and other additives may also be included into the over-coating layer(s). Said over-coating layer may further prevent potential agglomeration of enteric coating layered units. The maximum thickness of the applied over-coating layer(s) is normally limited by processing conditions and the desired dissolution profile.

In one embodiment of the present invention the proton pump inhibitor is protected by two layers, an enteric coating layer and a subcoating layer separating the enteric coating from the proton pump inhibitor.

For filling enteric coated units or overcoated enteric coated units into capsules, it is sometimes an advantage to admix a lubricant or a glidant. Such lubricants or glidants include Mg-Stearate, sodium stearyl fumarate, glyceryl behenate, talk and fumed silica, thereby not excluding the possibility to use other non-mentioned pharmaceutically acceptable lubricants or glidants.

In one embodiment of the invention the lubricant is Mg-Stearate.
In another embodiment of the invention the lubricant is sodium stearyl fumarate.
In a further embodiment of the invention the lubricant is glyceryl behenate.

The different forms of acetyl salicylic acid (ASA)

The ASA can be present in the following forms:

- Powder of ASA (ASA-substance as such);
- Agglomerates of ASA;
- Spherical agglomerates of ASA;
- Solid dispersions or solutions of ASA in polymers;

These solid dispersions or solutions of may be accomplished by melting the dispersing/dissolving agent and adding the ASA, or by dissolving the dispersing/dissolving agent and ASA in a common solvent, where after the solvent is evaporated.

- Cyclodextrin complexes of ASA (as powder);

  These complexes may comprise α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin or derivates thereof such as e.g. β-hydroxypropyl cyclodextrin. The complexing cyclodextrin may be chosen to affect the release rate, for instance to give extended release (β-hydroxypropyl cyclodextrin) or immediate release (β-cyclodextrin).

- Cyclodextrin complexes of ASA granulated together with pharmaceutical excipients;

  These complexes may comprise α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin or derivates thereof such as e.g. β-hydroxypropyl cyclodextrin. The complexing cyclodextrin may be chosen to affect the release rate, for instance to give extended release (β-hydroxypropyl cyclodextrin) or immediate release (β-cyclodextrin).

- Units for immediate release, comprising ASA together with pharmaceutical excipients;
- Units for extended release, comprising ASA together with pharmaceutical excipients. These units may be constructed according to the hydrophilic gel matrix principle, hydrophobic matrix principle or diffusion membrane layered pellets/granules principle;
- Units for enteric release (enteric coated granules or pellets), comprising ASA together with pharmaceutical excipients;
- Units for pH-independent time delayed release ((not enteric coated) granules or pellets), comprising ASA together with pharmaceutical excipients;
- Units comprising ASA together with effervescent pharmaceutical excipients for immediate release;

- Units layered with an enteric coating layer, such as the enteric coating layer described above, comprising ASA;
- Minitablets comprising ASA ;
- Coated Minitablets comprising ASA
- Mildly compacted plug of ASA, which considers a material that have been compressed into a unit form like e.g. a tablet, with a friability that does not fulfill the requirement of friability for tablets in US Pharmacopoeia 24, official from 1 January, 2000 (requirement: less than 1%). See previously explainations.

Process for preparing the claimed fixed dosage form

The present invention also relates to a process for the manufacture of an oral fixed combination dosage form comprising an acid susceptible proton pump inhibitor and acetyl salicylic acid, characterized in that the proton pump inhibitor is prepared in the form of enteric coating layered units and that the units are mixed with acetyl salicylic acid and this mixture is optionally mixed with pharmaceutically acceptable excipients, and then the obtained mixture is filled into a capsule or a sachet. The acetyl salicylic acid can be in any of the forms disclosed above.

One embodiment of the present invention relates to a process for the manufacture of an oral fixed combination dosage form comprising an acid susceptible proton pump inhibitor and acetyl salicylic acid, characterized in that said proton pump inhibitor is prepared in the form of enteric coating layered units and that the units are filled into a capsule or a sachet together with one or more other separate physical units comprising acetyl salicylic acid optionally mixed with pharmaceutically acceptable excipients.

One example on a process for the manufacture of the present fixed dosage form, but which should not in any way limit the scope of the present invention, is to dry mix the PPI and ASA and then fill those active compounds into a capsule or sachet. The proton pump inhibitor is in the form of enteric coating layered units and the acetyl salicylic acid is in the form of units that may either be used as such or be in the form of modified release

formulated units such as enteric coating layered units or in the form of units formulated to achieve an extended release e.g. by being coated with an extended release coating layer.

As another example of a manufacturing process, but which should not in anyway limit the scope of the present invention, is wet massed granulation. The acetyl salicylic acid is dry mixed with excipients, wherein one or more of the excipients optionally is a disintegrant. Suitable excipients for the acetyl salicylic acid granulation may be selected from any one of sodium starch glycolate, corn starch, crosslinked polyvinylpyrrolidone, low substituted hydroxypropyl cellulose, microcrystalline cellulose, mannitol, lactose and colloidal silicon dioxide anhydrous (Aerosil®).

The mixture is wet massed with a granulation liquid comprising a binder selected from any one of polyvinyl pyrrolidone, hydroxypropyl methyl cellulose, polyethylene glycol, hydroxypropyl cellulose and optionally one or more wetting agents, such as sodium lauryl sulphate, and a solvent such as purified water or a suitable alcohol or a mixture thereof. In one embodiment of the invention, the wet mass is dried to a loss on drying of less than 3% by weight. In another embodiment of the invention, the wet mass is dried to a loss on drying of less than 2% by weight.
After the drying the dry mass is milled to a suitable size for the granules, such as smaller than 4 mm, alternatively smaller than 1 mm.

The dry granules are then mixed with the proton pump inhibitor, which PPI is in the form of enteric coating layered units, and then filled into a capsule or a sachet or compressed, optionally together with suitable pharmaceutical excipients, to a "multiple unit tablet".

In an alternative manufacturing process ASA, or granules of ASA and optionally pharmaceutical excipients, are compressed into a mildly compacted plug (definition according to above) and filled into a capsule, together with the PPI wherein the latter is in the form of enteric coating layered units.

The plug may be positioned in the lower part of the capsule, i.e. the body part, or in the upper part of the capsule, i.e. the cap. In both situations the plug is in tight connection to the inner walls of the capsule, restricting the free movement of PPI comprising units within the capsule. This is favourable for reducing intracapsular attrition.

The PPI comprising units may be positioned under the plug or on top of the plug, (in both situations within the capsule).

Thus, in one embodiment of the invention, the ASA comprising plug is positioned in the body part of the capsule in tight connection to the inner walls of the capsule and the PPI comprising units are positioned on top of the plug within the capsule.

In a further embodiment of the invention, the ASA comprising plug is positioned in the body part of the capsule in tight connection to the inner walls of the capsule and the PPI comprising units are positioned below the plug within the capsule.

In an even further embodiment of the invention, the ASA comprising plug is positioned in the cap (i.e. upper) part of the capsule in tight connection to the inner walls of the capsule cap and the PPI comprising units are positioned below the plug within the capsule body.

The acetyl salicylic acid may also be mixed with a gelling agent during the granulation, such as hydrophilic polymer(s) to obtain extended relase. Suitable gelling hydrophilic polymers may be selected from any one of hydroxypropyl methylcellulose with a viscosity higher or equal to 50 mPas (cps), polyoxyethylene (polyethylene glycol) with a molecular weight above 50000 u, hydroxypropyl cellulose not including low-substituted hydroxypropyl cellulose, hydroxyethyl cellulose and xantan or combinations thereof.

The obtained units may also comprise suitable buffering substances.

Capsule or sachet material

The capsule or sachet comprises any water-soluble or gastric soluble polymeric material, such as gelatin or hydroxypropyl methylcellulose. However, this list should however not be interpreted as exhaustive. The capsules or sachet may be produced by molding.

Use of the claimed invention

The dosage forms according to the present invention are especially advantageous in the prevention and/or reduction of gastrointestinal complications caused by acetyl salicylic acid, for example in a continuous treatment with acetyl salicylic acid.

According to one embodiment of the present invention, the claimed dosage form has an amount of proton pump inhibitor in the range of from 5 to 300 mg and an amount of acetyl salicylic acid in the range of from 10 to 500 mg.

According to yet another embodiment the amount of proton pump inhibitor is in the range of from 10 to 200 mg or from 10 to 100 mg or from 10 to 80 mg. In an alternative embodiment of the present invention the amount of proton pump is selected from about: 5, 10, 20, 30, 40, 50, 60, 70, 80, 90 and 100 mg. According to yet another embodiment of the present invention, the amount of proton pump inhibitor is selected from 20, 40 and 80 mg.

In further embodiments of the present invention the amount of acetyl salicylic acid is in the range of from 25 to 450 mg, from 50 to 400, from 60 to 350 mg or from 75 to 325 mg. In an alternative embodiment of the present invention the amount of acetyl salicylic acid is selected from about: 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 205, 210, 215, 220, 225, 230, 235, 240, 245, 250, 255, 260, 265, 270, 275, 280, 285, 290, 295, 300, 305, 310, 315, 320, and 325 mg, for example 81, 101, 124, 126, 181, 204, 301, 311 and 321.

In another embodiment of the present invention the oral fixed combination dosage form comprises 20 mg of esomeprazole and 325 mg of acetyl salicylic acid.

In a second other embodiment of the present invention the oral fixed combination dosage form comprises 20 mg of esomeprazole and 75 mg of acetyl salicylic acid.

In a third other embodiment of the present invention the oral fixed combination dosage form comprises 40 mg of esomeprazole and 325 mg of acetyl salicylic acid.

In a fourth other embodiment of the present invention the oral fixed combination dosage form comprises 40 mg of esomeprazole and 75 mg of acetyl salicylic acid.

In a fifth other embodiment of the present invention the oral fixed combination dosage form comprises 20 mg of esomeprazole and 81 mg of acetyl salicylic acid.

In a sixth other embodiment of the present invention the oral fixed combination dosage form comprises 40 mg of esomeprazole and 81 mg of acetyl salicylic acid.

The present invention also relates to a method for the prevention of thromboembolic vascular events, such as myocardial infarction or stroke and the reduction and/or prevention of gastrointestinal complications associated with acetyl salicylic acid treatment, such as e.g. esophagitis associated with low dose ASA treatment, in mammals or man by administering to a mammals or man in need thereof a therapeutically effective dose of the claimed oral fixed combination dosage form. According to further embodiments of the present invention said complication is an upper gastrointestinal complication, a peptic ulcer in the stomach or a peptic ulcer in the duodenum. Upper gastrointestinal complications include bleeding, perforation and gastric outlet obstruction.

According to yet another embodiment of the present invention, the man is a patient of 60 years or older.

According to an alternative embodiment of the present invention the claimed method comprises administration of a capsule or a sachet comprising acetyl salicylic acid and proton pump inhibitor. The administration is either once or twice daily.

The present invention also relates to the use of a dosage form comprising a proton pump inhibitor and acetyl salicylic acid for the manufacture of a medicament for the prevention of thromboembolic vascular events, such as myocardial infarction or stroke, and for the prevention and/or reduction of gastrointestinal complications associated with acetyl salicylic acid treatment. According to further embodiments of the present invention, the complication is, as mentioned above, an upper gastrointestinal complication or is a peptic ulcer in the stomach or a peptic ulcer in the duodenum.

The present invention also relates to an oral pharmaceutical fixed combination dosage form comprising esomeprazole or an alkaline salt thereof or a hydrated form of any one of them and acetyl salicylic acid for the prevention of thromboembolic vascular events, such as myocardial infarction or stroke, and for the prevention and/or reduction of gastrointestinal complications associated with acetyl salicylic acid treatment. Any oral dosage form can be used for administration of this pharmaceutical combination, for instance a capsule, sachet, tablet or multiunit tablet, including effervescent forms thereof. However, this list should however not be interpreted as exhaustive.

An alternative embodiment of the present invention relates to a pharmaceutical oral fixed combination dosage form comprising esomeprazole or an alkaline salt thereof or a hydrated form of any one of them and acetyl salicylic acid, which dosage form is comprising a group of separate physical units comprising the acid susceptible proton pump inhibitor and one or more other separate physical units comprising the acetyl salicylic acid or a derivative thereof, and wherein at least the proton pump inhibitor is protected by an enteric coating layer, for the prevention of thromboembolic vascular events, such as myocardial infarction or stroke, and for the prevention and/or reduction of gastrointestinal complications associated with acetyl salicylic acid treatment.

In a further alternative embodiment of the invention, the unit (ASA comprising unit mentioned in the paragraph above) comprising the acetyl salicylic acid is compressed and used for the prevention of thromboembolic vascular events, such as myocardial infarction

or stroke, and for the prevention and/or reduction of gastrointestinal complications associated with acetyl salicylic acid treatment.

In an even further alternative embodiment of the invention, the unit (ASA comprising unit mentioned in the penultimate paragraph above) comprising the acetyl salicylic acid is mildly compressed to a plug, and used for the prevention of thromboembolic vascular events, such as myocardial infarction or stroke, and for the prevention and/or reduction of gastrointestinal complications associated with acetyl salicylic acid treatment.

In one embodiment of the present invention, the claimed pharmaceutical combination has an amount esomeprazole or an alkaline salt thereof or a hydrated form of any one of them in the range of from 5 to 300 mg and an amount of acetyl salicylic acid of from 10 to 500 mg.

According to a further embodiment of the present invention, the amount of esomeprazole or an alkaline salt thereof or a hydrated form of any one of them is in the range of from 10 to 80 mg. According to yet another embodiment the amount of esomeprazole or an alkaline salt thereof or a hydrated form of any one of them is selected from 20, 40 or 80 mg.

In further embodiments of the present invention the amount of acetyl salicylic acid is in the range of from 25 to 450 mg, from 50 to 400, from 60 to 350 mg or from 75 to 325 mg. In an alternative embodiment of the present invention the amount of acetyl salicylic acid is selected from about: 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 205, 210, 215, 220, 225, 230, 235, 240, 245, 250, 255, 260, 265, 270, 275, 280, 285, 290, 295, 300, 305, 310, 315, 320, and 325 mg, for example 81, 101, 124, 126, 181, 204, 301, 311 and 321.

A further embodiment of the present invention relates to a method for the prevention of thromboembolic vascular events, such as myocardial infarction or stroke, and for preventing and/or reducing gastrointestinal complications associated with acetyl salicylic

acid treatment in mammals or man by administering to a mammals or man in need thereof the claimed pharmaceutical combination.

EXAMPLES

The present invention is described in more detail by the following examples, which should not in any way limit the scope of the present invention.

Example 1

Male or female *Helicobacter pylori*-negative patients ≥60 years, who had a moderate-to-high risk of developing gastroduodenal ulcers were included in this randomized, double-blind, multicenter, placebo-controlled trial. Patients were randomized to receive either esomeprazole 20 mg (administered as esomeprazole magnesium, i.e. Nexium® owned by AstraZeneca AB) or placebo once daily for 26 weeks. The primary outcome variable was the presence of gastric and/or duodenal ulcers at endoscopy over the 26-week period. A total of 991 patients, all receiving ASA in doses varying between 75-325 mg/day (57.1% male, mean age 69.3 years, mean acetyl salicylic acid (ASA) dose 124.0 mg/day) were included in the intent-to-treat population. The cumulative proportion of patients without either gastric or duodenal ulcer at 26 weeks was 98.2% with esomeprazole, compared with 93.8% with placebo (life table estimates, p=0.0007). The incidence of gastric ulcers was lower in patients taking esomeprazole than in those taking placebo (1.2% vs. 3.8%), as was the incidence of duodenal ulcers (0.4% and 1.6% for esomeprazole and placebo, respectively). Eight patients (1.6%) had developed an ulcer, in the esomeprazole group by 6 months, compared with 27 patients (5.4%) in the placebo group. This corresponded to a relative reduction of developing an ulcer of 70% when taking esomeprazole rather than placebo. A total of 95.6% of patients treated with esomeprazole had no esophageal lesions at week 26, compared with 81.7% of patients treated with placebo ($p<0.0001$). The proportion of patients without esophageal lesions at 6 months was higher with esomeprazole than with placebo for patients with no lesions and for those with Los Angeles grade A lesions at baseline. Resolution of investigator-assessed upper gastrointestinal symptoms was higher with esomeprazole than with placebo for all symptoms. Esomeprazole was safe and well tolerated.

Example 2

Capsule comprising Esomeprazole 20 mg and ASA granules 325 mg.

Principle: enteric coated pellets comprising Esomeprazole-Mg trihydrate corresponding to 20 mg Esomeprazole were manufactured and mixed with Mg-Stearate.
This mixture and ASA granules were filled into hard gelatine capsules.

Manufacturing of Enteric coated Esomeprazole pellets

Core material

Sugar sphere seeds 0.25 to 0.35 mm approx. diameter	300 g

(suspension for) Active layer

Esomeprazole-Mg trihydrate	445 g
Hydroxypropyl methylcellulose	67 g
Polysorbate 80	9 g
Purified water	2100 g

(suspension for) Subcoating layer

Hydroxypropyl cellulose	90 g
Talc	340 g
Magnesium stearate	22 g
Purified water	3100 g

(dispersion for) Enteric coating layer

Methacrylic acid copolymer type C, 30 % dispersion	1270 g
Triethyl citrate	38 g
Mono- and diglycerides	19 g
Polysorbate 80	2 g
Purified water	500 g

Esomeprazole-Mg trihydrate was suspended in a water solution containing the dissolved binder hydroxypropyl methyl cellulose and the surfactant polysorbate 80. The suspension was sprayed onto sugar spheres seeds in a fluidized bed coating apparatus using bottom spray (Wurster) technique.

The prepared core material was covered with the subcoating layer in a fluid bed apparatus by spraying a hydroxypropyl cellulose solution containing suspended talc and magnesium stearate.

The enteric coating layer was sprayed as a water dispersion onto the subcoated pellets obtained above, in a fluid bed apparatus.

Mixture of enteric coated Esomeprazole pellets and Mg-Stearate.
Enteric coated pellets according to above was mixed with Mg-Stearate in the weight proportions given below;

Esomeprazole gastro-resistant pellets	100
Magnesium stearate	0.2

Capsule filling

	Per capsule
Mixture of enteric coated Esomeprazole pellets and Mg-Stearate (acc. to above)	86.2 mg
ASA granules*	325 mg
Hard gelatin capsule size 0	1 piece

* Rhodine ® 3118 ASA granules, Ba 0407231, from Rhodia France. The majority of the granules passes a sieve having apertures of 1000 micron and is retained on a sieve having apertures of 125 micron.

Capsules according to above was placed in plastic (High Density Poly Ethylene, also referred to as HDPE) bottles with desiccant, and checked for stability. The results obtained can be seen in the Table below;

Environment	Time	desiccant	% released in pH 6.8 after	Sum degradation products,	Amount degradation

			preexposure** Esomeprazole	(%) of Esomeprazole	of ASA. (%) SA*
	0		93%	0.2	0.3
40/75	2 weeks	5 g		0.3	NT
40/75	4 weeks	5g		0.3	NT
30/75	3 months	0.5 g		0.4	NT
25/60	6 months	0.5g	93%	0.4	NT

* SA = salicylic acid

NT= Not tested

**Dissolution of esomeprazole was measured in USP dissolution apparatus No 2 (paddle, 100 rpm) after preexposure in 300 ml 0.1 M HCl for 2 hrs, whereafter 700 ml of phosphate buffer was added giving a 1000 ml resulting testmedium having pH 6.8. After 30 minutes in pH 6.8 the released amount of nominal dose was measured.

Example 3

Capsule comprising Esomeprazole 20 mg and ASA powder 325 mg.

Principle: enteric coated pellets comprising Esomeprazole-Mg trihydrate corresponding to 20 mg Esomeprazole were manufactured and mixed with Mg-Stearate, according to Ex. 2. This mixture and ASA powder were filled into hard gelatine capsules.

Capsule filling

	Per capsule
Mixture of enteric coated Esomeprazole pellets and Mg-Stearate (acc. to Example 2, above)	86.2 mg
ASA powder	325 mg
Hard gelatin capsule size 0	1 piece

Capsules according to above was placed in plastic (High Density Poly Ethylene, also referred to as HDPE) bottles with desiccant, and checked for stability. The results obtained can be seen in the Table below;

Environment	Time	desiccant	Sum degradation products, (%) of Esomeprazole	Amount degradation of ASA. (%) SA
	0		0.2	0.2
25/60	3 months	0.5g	0.2	<0.1
25/60	6 months	0.5g	0.2	NT

NT= Not tested

Example 4

Capsule comprising Esomeprazole 20 mg and ASA (comprised in tablet) 75 mg.

Principle: enteric coated pellets comprising Esomeprazole-Mg trihydrate corresponding to 20 mg Esomeprazole were manufactured and mixed with Mg-Stearate, according to Ex. 2. This mixture and ASA tablets were filled into hard gelatine capsules.

Capsule filling

	Per capsule
Mixture of enteric coated Esomeprazole pellets and Mg-Stearate (acc. to Example 2, above)	86.2 mg
ASA tablet comprising 75 mg ASA*	Approx. 97 mg
Hard gelatin capsule size 1	1 piece

* Trombyl ®, Ba B 811A from Pfizer. Flat, hart-shaped uncoated tablets, approximazed size 6-7 mm in diameter, weight 97 mg (as average of 10 tablets).

Capsules according to above was placed in plastic (High Density Poly Ethylene, also referred to as HDPE) bottles with desiccant, and checked for stability. The results obtained can be seen in the Table below;

Environment	Time	desiccant	% released in pH 6.8 after preexposure** Esomeprazole	Sum degradation products, (%) of Esomeprazole	Amount degradation of ASA. (%) SA
	0		93%	0.2	2.3
40/75	1 month	0.5g		0.5	2.9
25/60	5 months	0.5 g	94%	0.3	NT

**Dissolution of esomeprazole was measured in USP dissolution apparatus No 2 (paddle, 100 rpm) after preexposure in 300 ml 0.1 M HCl for 2 hrs, whereafter 700 ml of phosphate buffer was added giving a 1000 ml resulting testmedium having pH 6.8. After 30 minutes in pH 6.8 the released amount of nominal dose was measured.

Example 5

Capsule comprising Esomeprazole 20 mg and ASA (comprised in enteric coated pellets) 100 mg.

Principle: enteric coated pellets comprising Esomeprazole-Mg trihydrate corresponding to 20 mg Esomeprazole were manufactured and mixed with Mg-Stearate, according to Ex. 2. This mixture and ASA enteric coated pellets were filled into hard gelatine capsules.

Capsule filling

	Per capsule
Mixture of enteric coated Esomeprazole pellets and Mg-Stearate (acc. to Example 2, above)	86.2 mg
ASA enteric coated pellets comprising 100 mg ASA*	117.9 mg
Hard gelatin capsule size 1	1 piece

* content of capsules "Astrix®", ba 298140, manufactured by Faulding & Co Ltd, Australia.

Capsules according to above was placed in plastic (High Density Poly Ethylene, also referred to as HDPE) bottles with desiccant, and checked for stability. The results obtained can be seen in the Table below;

Environment	Time	desiccant	% released in pH 6.8 after preexposure** Esomeprazole	Sum degradation products, (%) of Esomeprazole	Amount degradation of ASA. (%) SA
	0		93%	0.2	2.7
40/75	1 month	0.5g		0.3	3.9
25/60	5 months	0.5 g	95%	0.2	NT

**Dissolution of esomeprazole was measured in USP dissolution apparatus No 2 (paddle, 100 rpm) after preexposure in 300 ml 0.1 M HCl for 2 hrs, whereafter 700 ml of phosphate buffer was added giving a 1000 ml resulting testmedium having pH 6.8. After 30 minutes in pH 6.8 the released amount of nominal dose was measured.

Example 6

Capsule comprising Esomeprazole 20 mg and ASA granules 75 mg.

Principle: enteric coated pellets comprising Esomeprazole-Mg trihydrate corresponding to 20 mg Esomeprazole were manufactured and mixed with Mg-Stearate, according to Ex. 2. This mixture and a mildly compacted plug of ASA were filled into hard gelatine capsules.

Manufacturing of Enteric coated Esomeprazole pellets

Was done according to Ex. 2.

Mixture of enteric coated Esomeprazole pellets and Mg-Stearate.

Enteric coated pellets according to above was mixed with Mg-Stearate in the weight proportions given below;

Esomeprazole gastro-resistant pellets	100
Magnesium stearate	0.2

Capsule filling

	Per capsule
Mixture of enteric coated Esomeprazole pellets and Mg-Stearate (acc. to above)	86.2 mg
ASA granules, compacted into a plug*	75 mg
Hard gelatin capsule size 2	1 piece

* Rhodine ® 3118 ASA granules, Ba FRH 0528131, from Rhodia France. The majority of the granules passes a sieve having apertures of 1000 micron and is retained on a sieve having apertures of 125 micron. The plug was positioned in the lower part of the capsule, i.e. the body part, in tight connection to the inner walls of the capsule.

Capsules according to above was packed in blister cartridges, having a three-layer film of PVC/Aclar®*/PVC and an Al-foil backing.

(* = Aclar® film is polychlorotrifluoroethylene film presently manufactured by Honeywell International Inc.)

Such capsules were also placed in plastic (High Density Poly Ethylene, also referred to as HDPE) bottles with desiccant, and checked for stability. The results obtained can be seen in the Table below;

Environment	Time	desiccant	Sum degradation products, (%) of Esomeprazole	Amount degradation of ASA. (%) SA*
	0		0.1	NT
40/75	3 months	0.5g	0.7	0.1
30/75	3 months	0.5 g	0.1	0.1

* SA = salicylic acid

NT= Not tested

Example 7

Tablet comprising Esomeprazole 20 mg and ASA 100 mg.

Principle: enteric coated pellets comprising Esomeprazole-Mg trihydrate corresponding to 20 mg Esomeprazole are prepared and overcoated with a layer of hydroxypropyl methyl cellulose, and then mixed with ASA granules and tablet excipients and compressed into multiple unit tablets.

Manufacturing of Enteric coated Esomeprazole pellets

Core material	
Sugar sphere seeds 0.25 to 0.35 mm approx. diameter	300 g
(suspension for) Active layer	
Esomeprazole-Mg trihydrate	445 g
Hydroxypropyl methylcellulose	67 g
Polysorbate 80	9 g
Purified water	2100 g
(suspension for) Subcoating layer	
Hydroxypropyl cellulose	90 g
Talc	340 g
Magnesium stearate	22 g
Purified water	3100 g
(dispersion for) Enteric coating layer	
Methacrylic acid copolymer type C, 30 % dispersion	1270 g
Triethyl citrate	114 g
Mono- and diglycerides	19 g
Polysorbate 80	2 g
Purified water	500 g

Esomeprazole-Mg trihydrate was suspended in a water solution containing the dissolved binder hydroxypropyl methyl cellulose and the surfactant polysorbate 80. The suspension was sprayed onto sugar spheres seeds in a fluidized bed coating apparatus using bottom spray (Wurster) technique.

The prepared core material was covered with the subcoating layer in a fluid bed apparatus by spraying a hydroxypropyl cellulose solution containing suspended talc and magnesium stearate.

The enteric coating layer was sprayed as a water dispersion onto the subcoated pellets obtained above, in a fluid bed apparatus.

(solution for) Overcoating layer	
Hydroxypropyl methyl cellulose 5-6 cps (mPas)	90 g
Purified water	2400 g

The prepared enteric coated pellets from Example 2 are covered with the overcoating layer in a fluidized bed apparatus by spraying the hydroxypropyl methyl cellulose solution according to above onto them and drying when the spraying is completed.

The overcoated enteric coated Esomeprazole pellets are used for tableting;

Ingredients	Per 1000 tablets
Overcoated enteric coated esomeprazole pellets	103 g
ASA granules *	100 g
Microcrystalline cellulose (Avicel PH 102)	100 g
Sodium Stearyl fumarate (Pruv®)	2.9 g
Sum	305.9 g

* example given, granules from Rhodia as in example 2.

The ingredients above are mixed in a laboratory mixer, type Kenwood for 3-4 minutes then compressed into tablets in a suitable tabletting machine, non-limiting example given is Korsch Pharmapress 106, using 9 mm circular biconvex punches, adjusting the average tablet weight to 306 mg/tablet.

CLAIMS

1. An oral pharmaceutical dosage form comprising as active ingredients an acid susceptible proton pump inhibitor (PPI) together with acetyl salicylic acid (ASA) or a derivative thereof and optionally pharmaceutically acceptable excipients, characterized in that the dosage form is in the form of an oral fixed combination dosage form comprising a group of separate physical units comprising the acid susceptible proton pump inhibitor and one or more other separate physical units comprising the acetyl salicylic acid or a derivative thereof, and wherein at least the proton pump inhibitor is protected by an enteric coating layer.

2. A dosage form according to claim 1, wherein the proton pump inhibitor is protected by an enteric coating layer and the acetyl salicylic acid or a derivative thereof is not enteric coated.

3. A dosage form according to claim 2, wherein the acetyl salicylic acid or a derivative thereof further is present in an immediate release form.

4. A dosage form according to claim 3, wherein the proton pump inhibitor comprising units are protected by an enteric coating layer and the unit comprising acetyl salicylic acid or a derivative thereof is compressed to a tablet.

5. A dosage form according to claim 4, wherein the unit comprising acetyl salicylic acid or a derivative thereof is mildly compressed to a plug.

6. A dosage form according to claim 5, wherein the plug of ASA has a friability in the range of 2%-50 % (w/w).

7. A dosage form according to any of claims 1-6, wherein said dosage form is a capsule formulation or a sachet formulation.

8. A dosage form according to any of claims 1-3, wherein said dosage form is a multiple unit tablet formulation.

9. A dosage form according to any of claims 1-8, wherein the proton pump inhibitor is protected by two layers, an enteric coating layer and a subcoating layer separating the enteric coating from the proton pump inhibitor.

10. A dosage form according to any one of claims 1 - 9, wherein the proton pump inhibitor is omeprazole or an alkaline salt thereof.

11. A dosage form according to any one of claims 1 - 9, wherein the proton pump inhibitor is esomeprazole or an alkaline salt thereof or a hydrated form of any one of them.

12. A dosage form according to any one of claims 1- 9, wherein the proton pump inhibitor is lansoprazole or a pharmaceutically acceptable salt thereof or a single enantiomer of any one of them.

13. A dosage form according to any one of claims 1 - 9, wherein the proton pump inhibitor is pantoprazole or a pharmaceutically acceptable salt thereof or a single enantiomer of any one of them.

14. A dosage form according to any one of claims 1 - 9, wherein the proton pump inhibitor is rabeprazole or a pharmaceutically acceptable salt thereof or a single enantiomer of either one of them.

15. A dosage form according to any one of claims 1 - 9, wherein the proton pump inhibitor is ilaprazole or a pharmaceutically acceptable salt thereof or a single enantiomer of either one of them.

16. A dosage form according to any one of claims 1 - 9, wherein the proton pump inhibitor is tenatoprazole or a pharmaceutically acceptable salt thereof or a single enantiomer of either one of them.

17. A dosage form according to any one of claims 1 - 16, wherein the amount of proton pump inhibitor is in the range of from 5 to 300 mg and the amount of acetyl salicylic acid is in the range of from 10 to 500 mg.

18. A dosage form according to any one of claims 1 - 17, wherein the amount of proton pump inhibitor is in the range of from 10 to 200 mg.

19. A dosage form according to any one of claims 1 - 18, wherein the amount of proton pump inhibitor is selected from 5, 10, 20, 30, 40, 50, 60, 70, 80, 90 and 100 mg.

20. A dosage form according to claim any one of claims 1-19, wherein the amount of acetyl salicylic acid is in the range of from 25 to 450 mg.

21. A dosage form according to any one of claims 1-20, wherein the amount of acetyl salicylic acid is in the range of from 50 to 400.

22. A dosage form according to any one of claims 1-21, wherein the amount of acetyl salicylic acid is in the range of from 60 to 350 mg.

23. A dosage form according to any one of claims 1-22, wherein the amount of acetyl salicylic acid is in the range of from 75 to 325 mg.

24. A process for the manufacture of an oral fixed combination dosage form comprising an acid susceptible proton pump inhibitor and acetyl salicylic acid, characterized in that said proton pump inhibitor is prepared in the form of enteric coating layered units and that the units are filled into a capsule or a sachet together with one or

more other separate physical units comprising acetyl salicylic acid optionally mixed with pharmaceutically acceptable excipients.

25. A method for the prevention of thromboembolic vascular events, such as myocardial infarction or stroke, and the reduction and/or prevention of gastrointestinal complications associated with acetyl salicylic acid treatment in mammals or man by administering to a host in need thereof a therapeutically effective dose of a fixed dosage form according to any of claims 1 to 23.

26. A method according to claim 25, wherein said method comprises administration of a capsule or a sachet comprising acetyl salicylic acid and proton pump inhibitor.

27. A method according to claim 26, wherein the capsule or sachet is administered once daily.

28. A method according to claim 26, wherein the capsule or sachet is administered twice daily.

29. Use of a dosage form according to any one of claims 1-23, for the manufacture of a medicament for the prevention of thromboembolic vascular events, such as myocardial infarction or stroke, and for the prevention and/or reduction of gastrointestinal complications associated with acetyl salicylic acid treatment.

30. A pharmaceutical oral fixed combination dosage form comprising esomeprazole or an alkaline salt thereof or a hydrated form of any one of them and acetyl salicylic acid, which dosage form is comprising a group of separate physical units comprising the acid susceptible proton pump inhibitor and one or more other separate physical units comprising the acetyl salicylic acid or a derivative thereof, and wherein at least the proton pump inhibitor is protected by an enteric coating layer, wherein said dosage form is for the prevention of thromboembolic vascular events, such as myocardial infarction or stroke,

and for the prevention and/or reduction of gastrointestinal complications associated with acetyl salicylic acid treatment.

31. A dosage form according to claim 30, wherein the unit comprising the acetyl salicylic acid or a derivative thereof is compressed, wherein said dosage form is for the prevention of thromboembolic vascular events, such as myocardial infarction or stroke, and for the prevention and/or reduction of gastrointestinal complications associated with acetyl salicylic acid treatment.

32. A dosage form according to claim 30 or 31, wherein the amount of esomeprazole or an alkaline salt thereof or a hydrated form of any one of them is in the range of from 5 to 300 mg and the amount of acetyl salicylic acid is in the range of from 10 to 500 mg.

33. A dosage form according to anyone of claims 30 to 32, which comprises 20 mg of esomeprazole and 325 mg of acetyl salicylic acid.

34. A dosage form according to anyone of claims 30 to 32, which comprises 20 mg of esomeprazole and 75 mg of acetyl salicylic acid.

35. A dosage form according to anyone of claims 30 to 32, which comprises 40 mg of esomeprazole and 325 mg of acetyl salicylic acid.

36. A dosage form according to anyone of claims 30 to 32, which comprises 40 mg of esomeprazole and 75 mg of acetyl salicylic acid.

37. A dosage form according to anyone of claims 30 to 32, which comprises 20 mg of esomeprazole and 81 mg of acetyl salicylic acid.

38. A dosage form according to anyone of claims 30 to 32, which comprises 40 mg of esomeprazole and 81 mg of acetyl salicylic acid.

39. Use of a dosage form according to any one of claims 30-38 for the manufacture of a medicament for administration to a mammal or man, wherein said medicament is for the prevention of thromboembolic vascular events, such as myocardial infarction or stroke, and for the prevention and/or reduction of gastrointestinal complications associated with acetyl salicylic acid treatment.

40. A method for the prevention of thromboembolic vascular events, such as myocardial infarction or stroke, and for prevention and/or reduction of gastrointestinal complications associated with acetyl salicylic acid treatment in mammal or man by administration to a mammal or man in need thereof a therapeutically effective dose of a combination according to any one of claims 30-38.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2006/001349

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 25-28 and 40
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 25-28, 40 relate to a method of treatment of the human or animal body by surgery or by therapy, as well as diagnostic methods /Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the dosage forms.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2006/001349

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, MEDLINE, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 20020155153 A1 (HELENE DEPUI ET AL), 24 October 2002 (24.10.2002), See the whole document ---	1-40
X	US 6544556 B1 (CHIH-MING CHEN ET AL), 8 April 2003 (08.04.2003), See the whole document ---	1-40
X	US 20040121004 A1 (RAJNEESH TANEJA), 24 June 2004 (24.06.2004), claims 1-7, paragraphs 1,4, 6-11, 19, 24-25; examples 1-3; tables 1-2 ---	1-40

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 February 2007	26 -02- 2007
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Andreas Gustafsson/Els Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2006/001349

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 20020051814 A1 (CHIH-MING CHEN), 2 May 2002 (02.05.2002), claims 1-30, paragraphs 1-24, 62, 64, 76-77; example 1	1-40
A	US 20030069255 A1 (JOHN R. PLACHETKA), 10 April 2003 (10.04.2003), claims 1-50, paragraphs 1, 10-14, 20,24,41; examples 5-8; figures 1-3	1-40
A	FR 2845917 A1 (NEGMA GILD), 23 April 2004 (23.04.2004), page 1, line 1 - line 30; page 2, line 27 - page 3, line 30; page 4, line 32 - page 5, line 25, page 6, lines 1-13; page 8, lines 32-35; claims 1-10	1-40
A	US 20050147675 A1 (EDWARD J. PETRUS), 7 July 2005 (07.07.2005), claims 1,6,12,15, paragraphs 6,23, 25, 57-60	1-40
A	WO 2004062552 A2 (GALEPHAR M/F), 29 July 2004 (29.07.2004), page 2, line 23 - page 4, line 5; page 4, line 20 - page 6, line 13, claims 1-28, examples 1-3	1-40
A	US 20050227949 A1 (NASROLA EDALATPOUR), 13 October 2005 (13.10.2005), claims 1,3,5-6,11-12; paragraphs 9-10,14,21,24	1-40
A	Simon, B. et al "Schutzwirkung von Omeprazol gegenuber niedrig dosierter Acetylsalicylsäure". Arzneimittel-Forschung./Drug Res, 1995, vol. 45, no.6, p. 701-703	1-40

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2006/001349

International patent classification (IPC)

A61K 31/60 (2006.01)
A61K 9/20 (2006.01)
A61K 9/48 (2006.01)
A61P 1/04 (2006.01)
A61P 9/10 (2006.01)
A61K 31/4184 (2006.01)
A61K 31/4439 (2006.01)
A61K 31/444 (2006.01)

Download your patent documents at www.prv.se
The cited patent documents can be downloaded at www.prv.se by following the links:

- In English/Searches and advisory services/Cited documents (service in English) or
- e-tjänster/anförda dokument (service in Swedish).

Use the application number as username.
The password is **IXIUUSZHVZ**.

Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.

US	20020155153	A1	24/10/2002	US	6613354	B	02/09/2003
				US	20040022846	A	05/02/2004
				AT	242006	T	15/06/2003
				AU	712571	B	11/11/1999
				AU	1323997	A	01/08/1997
				BR	9607476	A	23/12/1997
				CA	2213987	A,C	17/07/1997
				CN	1116899	B,C	06/08/2003
				CN	1183048	A	27/05/1998
				CZ	294255	B	10/11/2004
				CZ	9702748	A	14/01/1998
				DE	69628551	D,T	06/05/2004
				DK	814839	T	22/09/2003
				EE	4003	B	15/04/2003
				EE	9700194	A	16/02/1998
				EP	0814839	A,B	07/01/1998
				SE	0814839	T3	
				EP	1352660	A	15/10/2003
				ES	2201211	T	16/03/2004
				HK	1001761	A	10/10/2003
				HK	1017991	A	23/04/2004
				HU	9904095	A	28/06/2000
				IL	121650	A	12/03/2003
				IS	4546	A	19/08/1997
				JP	11501948	T	16/02/1999
				NO	974069	A	17/10/1997
				NZ	325975	A	25/02/1999
				PL	187074	B	31/05/2004
				PL	322174	A	19/01/1998
				PT	814839	T	31/10/2003
				RU	2158138	C	27/10/2000
				SE	9600070	D	00/00/0000
				SI	814839	T	31/12/2003
				SK	117797	A	08/04/1998
				SK	283871	B	02/03/2004
				TR	9700915	T	21/11/1997
				TW	452495	B	01/09/2001
				US	6365184	B	02/04/2002
				WO	9725064	A	17/07/1997
				ZA	9610936	A	08/07/1997
US	6544556	B1	08/04/2003	AU	8899801	A	26/03/2002
				EP	1330238	A	30/07/2003
				JP	2004508396	T	18/03/2004
				US	6869615	B	22/03/2005
				US	20030129235	A	10/07/2003
				WO	0222108	A	21/03/2002
US	20040121004	A1	24/06/2004	CA	2506930	A	22/07/2004
				EP	1594499	A	16/11/2005
				JP	2006514049	T	27/04/2006
				MX	PA05006629	A	30/09/2005
				PL	375900	A	12/12/2005
				WO	2004060372	A	22/07/2004

US	20020051814	A1	02/05/2002	US	7029701	B	18/04/2006
US	20030069255	A1	10/04/2003	US	D466620	S	03/12/2002
				US	6926907	B	09/08/2005
				US	20050249811	A	10/11/2005
				AU	2006235929	A	30/11/2006
				CA	2449098	A	12/12/2002
				EA	6398	B	29/12/2005
				EP	1411900	A	28/04/2004
				IL	159129	D	00/00/0000
				JP	2004536809	T	09/12/2004
				MX	PA03011017	A	29/04/2005
				NO	20035275	D	00/00/0000
				WO	02098352	A	12/12/2002
FR	2845917	A1	23/04/2004	AT	326968	T	15/06/2006
				AU	2003285424	A	13/05/2004
				BR	0315455	A	23/08/2005
				CA	2503211	A	06/05/2004
				CN	1744897	A	08/03/2006
				DE	60305522	D	00/00/0000
				DK	1553942	T	02/10/2006
				EP	1553942	A,B	20/07/2005
				SE	1553942	T3	
				JP	2006506376	T	23/02/2006
				KR	20050090375	A	13/09/2005
				PT	1553942	T	31/10/2006
				US	20060287284	A	21/12/2006
				WO	2004037254	A	06/05/2004
US	20050147675	A1	07/07/2005	US	6930099	B	16/08/2005
				US	20030215430	A	20/11/2003
				US	6596708	B	22/07/2003
WO	2004062552	A2	29/07/2004	NONE			
US	20050227949	A1	13/10/2005	NONE			

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 July 2007 (12.07.2007)

PCT

(10) International Publication Number
WO 2007/078874 A2

(51) International Patent Classification:
A61K 9/48 (2006.01) *A61P 29/00* (2006.01)
A61K 9/50 (2006.01) *A61K 31/4439* (2006.01)
A61K 9/70 (2006.01) *A61K 31/5415* (2006.01)
A61K 45/06 (2006.01)

(21) International Application Number:
PCT/US2006/047886

(22) International Filing Date:
15 December 2006 (15.12.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/755,131 30 December 2005 (30.12.2005) US

(71) Applicant *(for all designated States except US)*: **COGENTUS PHARMACEUTICALS, INC.** [US/US]; 301 RAVENSWOOD AVENUE, SUITE 100, Menlo Park, CA 94025 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **TANANBAUM, James, B.** [US/US]; COGENTUS PHARMACEUTICALS, INC., 301 RAVENSWOOD AVENUE, SUITE 100, Menlo Park, CA 94025 (US). **VADAS, Elizabeth** [CA/US]; COGENTUS PHARMACEUTICALS, INC., 301 RAVENSWOOD AVENUE, SUITE 100, Menlo Park, CA 94025 (US). **GOLDSMITH, Mark, A.** [US/US]; COGENTUS PHARMACEUTICALS, INC., 301 RAVENSWOOD AVENUE, SUITE 100, Menlo Park, CA 94025 (US).

(74) Agent: **BREZNER, David, J.**; MORGAN, LEWIS & BOCKIUS LLP, ONE MARKET, SPEAR STREET TOWER, San Francisco, CA 94105 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*
— *of inventorship (Rule 4.17(iv))*

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) **Title:** ORAL PHARMACEUTICAL FORMULATIONS CONTAINING NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND ACID INHIBITORS

(57) **Abstract:** The present disclosure provides enteric coated capsules and orally dissolving films comprising non-steroidal anti-inflammatory drugs and acid inhibitors, as well as methods of treating treatment humans for pain and/or inflammation while reducing gastrointestinal side effects.

WO 2007/078874 A2

ORAL PHARMACEUTICAL FORMULATIONS CONTAINING NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND ACID INHIBITORS

1. FIELD

[0001] The present teaching relates to oral pharmaceutical compositions comprising non-steroidal anti-inflammatory drugs and acid inhibitors and methods for their use in the treatment for pain and/or inflammation while reducing gastrointestinal side effects.

2. INTRODUCTION

[0002] Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat a variety of indications including mild to moderate pain such as dental, muscular, post-operative pain, and rheumatoid arthritis, osteoarthritis, gouty arthritis and ankylosing spondylitis. Generally NSAIDs inhibit the enzyme cyclooxygenase (COX). The COX enzyme has two forms: COX-1 and COX-2. The COX-1 enzyme is the constitutive isoform and is mainly responsible for the synthesis of cytoprotective prostaglandins in the gastrointestinal tract. The COX-2 enzyme is the inducible isoform, and plays a major role in prostaglandin biosynthesis in inflammatory cells such as monocytes and macrophages. Consequently NSAIDs reduce inflammation, but at the same time, inhibit an enzyme partly responsible for protecting the gastrointestinal tract. Thus, the administration of NSAIDs are associated with gastrointestinal side effects such as

perforations, ulcers and gastrointestinal bleeding. Patients in need of long term NSAID therapy often cannot receive such therapy due to its propensity to cause gastrointestinal side effects and as a result patients are deprived of beneficial NSAID therapy.

[0003] Clinical studies demonstrate an improvement in NSAID tolerability when patients are simultaneously administered acid inhibitors such as proton pump inhibitors (PPIs) or histamine H_2 receptor antagonists (H_2 blockers). Proton pump inhibitors suppress gastric acid secretion by inhibiting the H^+, K^+-ATPase enzyme system at the surface of the gastric parietal cell. H_2 blockers inhibit the action of histamine on stomach cells, and thus reduce stomach acid production.

[0004] Recognizing the potential benefits of administering acid inhibitors for the prevention of NSAID-induced gastrointestinal side effects, others have disclosed combining the two active agents for therapeutic purposes. Proton pump inhibiting agents are typically acid-labile compounds unstable in acidic environments such as those typically found in the stomach and are typically administered in a variety of enteric coated dosage forms. See for example U.S. Pat. Nos. 4,786,505, 6,613,354, 6,365,184, and 6,926,907. In addition, orally dissolvable films can be used to carry pharmaceutically active ingredients. See for example, U.S. Pat. No. 4,136,145; and 6,923,981. However, there remains a need for oral pharmaceutical combination formulations to reduce or eliminate the gastrointestinal side effects of NSAID therapy.

3. SUMMARY

[0005] The present invention relates to pharmaceutical compositions comprising one or more non-steroidal anti-inflammatory drugs (NSAIDs) and one or more acid inhibitors as active agents, termed "actives". In some embodiments, the composition is an enteric coated capsule containing a NSAID and a proton pump

inhibitor. In a specific embodiment, the composition is an enteric coated capsule containing meloxicam and omeprazole.

[0006] Another embodiment of the invention relates to pharmaceutical compositions with actives comprising one or more NSAIDs and one or more reversible proton pump inhibitors, wherein the reversible proton pump inhibitor is not enteric coated.

[0007] In another embodiment, the invention relates to orally dissolvable films including one or more non-steroidal anti-inflammatory drugs and one or more acid inhibitors as actives. In one embodiment, the actives comprise a combination of one or more NSAIDs and one or more proton pump inhibitors. In a specific embodiment, the proton pump inhibitor is enteric coated on dispersed fine particulates. In a specific embodiment, the orally dissolvable film contains meloxicam and enteric coated omeprazole. In another embodiment, the orally dissolvable film comprises a combination an NSAID and a non-enteric coated reversible proton pump inhibitor.

[0008] The pharmaceutical compositions are particularly useful in treating pain and/or inflammation in a patient. The invention also relates to methods of protecting the gastrointestinal tract from side effects associated with NSAID therapy using the compositions described herein. These and other features of the present teachings are set forth herein.

4. DESCRIPTION OF VARIOUS EMBODIMENTS

4.1 Definitions

[0009] As used herein, the following terms have the following meanings:

[0010] The phrase "acid inhibitor" means an agent capable of inhibiting or decreasing gastric acid secretion and includes antiulcerative compounds. The term

acid inhibitor includes, but is not limited to, proton pump inhibitors, including reversible proton pump inhibitors, and H_2 blockers.

[0011] The term "NSAID" means a non-steroidal anti-inflammatory agent suitable for the treatment of pain, inflammation and/or fever.

[0012] The phrase "pharmaceutically acceptable" means moieties or compounds that are, within the scope of medical judgment, suitable for use in humans without undue toxicity, irritation, allergic response, and the like.

[0013] The phrase "therapeutically effective amount" means a sufficient quantity of NSAID and acid inhibitor which is effective in treating the targeted disorder, disease or condition, at a reasonable benefit/risk ratio.

~~**[0014]** The term "substrates" means pharmaceutically acceptable particulate~~ materials such as beads, particles, granules, pellets, and the like.

4.2 Compositions

4.2.1 Actives

[0015] The compositions provided herein can be administered in any dosage form suitable for oral administration. The dosage form generally comprise a combination of one or more NSAIDs and one or more acid inhibitors. Exemplary acid inhibitors include, but are not limited to proton pump inhibitors, reversible proton pump inhibitors, and H_2 blockers.

[0016] In some embodiments, the dosage form comprises one or more NSAIDs and one or more proton pump inhibitors. In some embodiments, the dosage form comprises one or more NSAIDs, one or more proton pump inhibitors and one or

more H_2 blockers. In some embodiments, the dosage form comprises one or more NSAIDs and one or more H_2 blockers.

[0017] Any compound having NSAID-like activity can be used in the present dosage forms. Suitable compounds having NSAID activity include, but are non-limited to, the non-selective COX inhibitors, selective COX-2 inhibitors, selective COX-1 inhibitors, and COX-LOX inhibitors, as well as pharmaceutically acceptable salts, isomers, enantiomers, polymorphic crystal forms including the amorphous form, co-crystals, derivatives, prodrugs thereof.

[0018] Exemplary NSAIDs include, but not limited to, celecoxib (Celebrex™); rofecoxib (Vioxx™), etoricoxib (Arcoxia™), meloxicam (Mobic™), valdecoxib, diclofenac (Voltaren™, Cataflam™), etodolac (Lodine™), sulindac (Clinori™), aspirin, alclofenac, fenclofenac, diflunisal (Dolobid™), benorylate, fosfosal, salicylic acid including acetylsalicylic acid, sodium acetylsalicylic acid, calcium acetylsalicylic acid, and sodium salicylate; ibuprofen (Motrin), ketoprofen, carprofen, fenbufen, flurbiprofen, oxaprozin, suprofen, triaprofenic acid, fenoprofen, indoprofen, piroprofen, flufenamic, mefenamic, meclofenamic, niflumic, salsalate, rolmerin, fentiazac, tilomisole, oxyphenbutazone, phenylbutazone, apazone, feprazone, sudoxicam, isoxicam, tenoxicam, piroxicam(Feldene™), indomethacin(Indocin™), nabumetone (Relafen™), naproxen (Naprosyn™), tolmetin, lumiracoxib, parecoxib, licofelone (ML3000), including pharmaceutically acceptable salts, isomers, enantiomers, derivatives, prodrugs, crystal polymorphs, amorphous modifications, co-crystals and combinations thereof.

[0019] Any compound having acid inhibitor-like activity can be used as an acid inhibitor in the present dosage forms. One type of acid inhibitor comprises any compound having proton pump inhibitor activity. Suitable non-limiting examples of proton pump inhibitors include omeprazole (Prilosec™), esomeprazole

(Nexium™), lansoprazole (Prevacid™), leminoprazole, rabeprazole (Aciphex™), and pantoprazolem (Protonix™), including pharmaceutically acceptable salts, isomers, enantiomers, derivatives, prodrugs, crystal polymorphs, amorphous modifications, co-crystals and combinations thereof.

[0020] In addition to compounds described above, the acid inhibitor may include compounds which reversibly bind to the enzyme responsible for gastric acid secretion, H^+/K^+ ATPase, the so called "reversible proton pump inhibitors" or "acid pump antagonists". Suitable non-limiting examples include Sch-28080 (Schering Plough); Sch-32651 (Schering Plough), AZD-0865, AR-H047108, CS-526, pumaprazole, revaprazan (see WO 1998018784;US 6,252,076; US 5,990,311 and US 5,750,531) soraprazan (see WO9605177 and WO9605199), H-335/25 (AstraZeneca) and SK&F-96067 (GlaxoSmithKline), and the reversible proton pump inhibitors disclosed, for example, in the documents U.S. Pat. No. 4,833,149, U.S. Pat. No. 5,041,442, U.S. Pat. No. 4,464,372, U.S. Pat. No. 6,132,768, including pharmaceutically acceptable salts, isomers, polymorphs, amorphous modifications, co-crystals and derivatives thereof, and combinations thereof.

[0021] Additional suitable non-limiting examples of acid inhibitors include SK&F-95601, SK&F-96067 and SK&F-97574 (GlaxoSmithKline), NC-1300 and NC-1300-B (Nippon Chemiphar); Hoe-731 (Saviprazole) (Sanofi-Aventis); IY-81149 (Ilaprazole); H-405/02 (AstraZeneca); CS-526 and R-105266 (Novartis; Sankyo;Ube); TY-11345 or nepaprazole sodium (Toa Eiyo); BY-841 (Altana Pharma), and TU-199 (TAP; Takeda), including pharmaceutically acceptable salts, isomers, polymorphs, amorphous modifications, co-crystals and derivatives thereof, and combinations thereof.

[0022] The acid inhibitor may also comprise any compound having H_2 blocker or H_2 antagonist activity. Suitable non-limiting examples include ranitidine, cimetidine, nizatidine, famotidine, as well as pharmaceutically acceptable salts,

isomers, polymorphs, amorphous modifications, co-crystals, derivatives, prodrugs, enantiomers, and combinations thereof.

[0023] The oral pharmaceutical compositions described herein comprise one or more NSAIDs and one or more acid inhibitors in therapeutically effective amounts. As with other pharmaceuticals, it will be understood that the total daily usage of a pharmaceutical composition of the invention will be decided by a patient's physician. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and other factors known to those of ordinary skill in the medical arts. For example, it is well within the skill of the art to start doses of the compound at levels lower than required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

[0024] The skilled artisan can adjust the amount of active ingredient in the pharmaceutical compositions or administered to a patient based upon standard techniques well known in the art. The dosage form can be administered at a dosage level up to and above conventional dosage levels for NSAIDs. General guidelines for dosing NSAIDS and acid inhibitors are know in the art. *See* for example U.S. Patent Nos. 6,264,984; 6,610,701; and 6,926,907.

[0025] Suitable dosage levels will depend in part upon the effectiveness of the chosen actives and condition to be treated. Generally, the daily pharmaceutically effective amount of the compounds administered to a patient in doses typically range from about 0.1 to about 100 mg/kg body weight. In some embodiments,

each dosage form will comprise 0.1-200 mg of the acid inhibitor and 0.1-1,000 mg of the NSAID(s). Preferably, each dosage form will comprise 10-80 mg of the acid inhibitor and 10-800 mg of the NSAID(s), and more preferably 10-40 mg acid inhibitor and 10-500 mg of the NSAID(s), respectively.

[0026] In some embodiment, the oral pharmaceutical composition comprises 1-500 mg of NSAID and 1-500 mg of acid inhibitor. In a specific embodiments, the oral pharmaceutical composition comprises 1-50 mg of meloxicam. and 5-100mg of omeprazole. In some embodiment, the oral pharmaceutical composition comprises 5-50mg of H_2 blocker.

[0027] All of the components used in the pharmaceutical compositions, including actives such as NSAIDs and acid inhibitors, or other excipients should be pharmaceutically acceptable.

[0028] In addition to the actives described herein, various additives may be added to the pharmaceutical compositions. These include, but are not limited to, pharmaceutically acceptable flavoring agents, sweeteners, stabilizing agents, preservatives, anti-microbial agents, coloring agents, antioxidants, wetting agents, surfactants, emulsifiers, efflux inhibitors and other excipients know to one skilled in the art.

[0029] Sweetening or flavoring agents, when present, may be in an amount of from 0.1 to 80% by weight based on the total weight of the composition. Suitable sweetening or flavoring agents are well known in the art. Exemplary sweetening agents include, but are not limited to, dextrose, mannitol, saccharine, sorbitol, sucrose, aspartame, or xylitol.

[0030] The pharmaceutical compositions optionally contain pharmaceutically acceptable coloring agents, water-soluble dyes or pigments, and opacifiers.

Typical coloring agents include, among others, synthetic iron oxides, *e.g.*, FD&C Red, and FD&C Blue.

[0031] In some embodiments, the pharmaceutical compositions described herein provide controlled release of one or more actives using one or more controlled release agents. The term "controlled release" is intended to mean the release of actives at a pre-selected or desired rate. This rate will vary depending upon the application. Desirable rates include fast or immediate release profiles as well as delayed, sustained or sequential release. Combinations of release patterns, such as initial release followed by lower levels of sustained release of active are specifically contemplated.

[0032] The active agent could be in the form of a powder, a liquid, a blended powder(s) with inactive agent(s), granules or pellets with or without enteric coating, a solution in a suitable solvent(s), a suspension with or without a suspending agent(s), or an emulsion with or without an emulsifier(s). The pharmaceutical compositions can be provided in various forms, such as in the form of a capsule, tablet or orally dissolvable film, in single unit dosage form, and multiunit dosage form. The pharmaceutical compositions may be provided in packets, bottles, blisters, sachets, and other types of containers, and where appropriate, accompanied by a desiccant to provide moisture protection or a device for providing a measured dose.

4.2.2 Enteric coated capsules

[0033] In one embodiment, an enteric coated capsule comprises one or more NSAIDs and one or more acid inhibitors. The enteric coated capsules are generally provided as orally administrable hard, soft or gel capsules, or other encapsulated dosage forms known in the art. The capsules to be enteric coated can include any of the various materials conventionally used in the pharmaceutical industry, including, by way of example and not limitation, gelatin, carrageen,

polysaccharide (*e.g.*, agar, hydroxypropyl methycellulose, hydroxyethycellulose, pectin, starch etc. or mixtures thereof). The capsule can include a plasticizer, such as glycerin, triacetin, sorbitol, polyethylene glycol, propylene glycol, citrate, and phthalate, to impart form and flexibility where desired.

[0034] The capsules are chosen to be compatible with the actives (*e.g.*, NSAID and acid inhibitors) and with the enteric coating. In some embodiments, the capsule is enteric coated with an enteric material. Generally, the enteric material is insoluble in acid environments, such as the stomach, but is soluble in near-neutral environments such as the small intestine. Because of the enteric properties of the capsule, the capsule can pass through the stomach undissolved and the actives can be released in the intestinal tract. In some embodiments, the enteric coated capsule dissolves at a pH of between 5 and 7.5.

[0035] Various enteric materials are known in the art, a number of which are commercially available. The enteric coated capsule can be any enteric material known to those skilled in the art. The enteric materials usually comprises a polymer with enteric properties. Suitable non-limiting examples include methacrylic acid copolymers such as methacrylic acid/methyl methacrylate copolymers, methacrylic acid/ethyl acrylate copolymers, methacrylic acid/methyl acrylate/methyl methacrylate copolymers, shellac, hydroxypropyl methylcellulose phthalate, hydroxypropyl methyl cellulose acetate-succinates, hydroxypropylmethylcellulose trimellitate, cellulose acetate-phthalates, carboxymethylethylcellulose, polyvinyl acetate phthalate or a mixture of these components, or other suitable enteric polymer(s).

[0036] In some embodiments, enteric coating layer(s) can be applied using standard coating technique. The enteric coating is applied using a variety of methods known in the art, such as spraying or layering (see, *e.g.*, U.S. Pat. No. 4,287,221). The thickness of the enteric coating is designed based on the nature of

the coating material and the desired lag time or delay in release of the pharmaceutical composition. The enteric coating(s) may be applied to the capsule, or another coating, using a suitable coating technique. The enteric coating layer material may be dispersed or dissolved in either water or in suitable organic solvents for coating the capsule.

[0037] In some embodiments the enteric coating may contain effective amounts of pharmaceutically acceptable plasticizers to obtain the desired mechanical properties, such as flexibility of the enteric coating layers. Such plasticizers are, for example and without limitation, triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, diethyl phthalate, triethyl citrate, polyethylene glycols, polysorbates or other plasticizers. The amount of plasticizer is optimized for the particular situation. The amount of plasticizer is usually above 10% by weight of the enteric coating polymer(s), preferably 15-50%, and more preferably 20-50%. Additives such as dispersants, colorants, pigments, anti-tacking agents may also be included into the enteric coating layer(s). Other compounds may be added to increase film thickness or opacity and to decrease diffusion of acidic gastric juices into the dosage form.

[0038] As will be appreciated by one skilled in the art, overcoating may be applied to the enteric coated capsule, for example, as a protective layer, flavor, and the like. Suitable overcoating materials include, but are not limited to, sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methyl cellulose, carboxymethylcellulose sodium and the like. Additives such as plasticizers, colorants, pigments, fillers, anti-tacking and anti-static agents, such as for instance magnesium stearate, titanium dioxide, talc and other additives may also be included in the over-coating layer(s).

[0039] Several benefits are derived from the enteric coated capsules provided herein. For example, the enteric coating protects the actives, for example proton pump inhibitors, from acid degradation in the stomach. In addition, manufacturing costs can be significantly reduced and productivity increased because there is no need to enteric coat the individual active agents of the pharmaceutical compositions. Also, there is no need to enteric coat individual units of the proton pump inhibitor and formulate the enteric coated proton pump inhibitor with the other ingredients in such a way as to not compromise the integrity of the protective enteric coating. Accordingly, NSAIDs can be delivered in a enteric coated capsule with a minimum of gastrointestinal side effects typically associated with NSAIDs.

4.2.3 Non-Enteric Coated Formulations

[0040] In another embodiments, the formulation comprises a combination of one or more NSAIDs and one or more non-enteric protected acid inhibitors. Suitable formulations include, but non-limited to, capsules, tablets or films for oral administration to a subject.

[0041] The non-enteric formulations can comprise one or more NSAIDs and one or more proton pump inhibitors. Any compound having NSAID activity described herein can be used in the non-enteric coated formulations described herein.

[0042] In some embodiments, the non-enteric coated formulations comprises one or more NSAIDs and one or more reversible proton pump inhibitors or acid pump antagonists. Suitable non-limiting examples of such reversible compounds include Sch-28080 (Schering Plough); Sch-32651 (Schering Plough), AZD-0865, AR-H047108, CS-526, pumaprazole, revaprazan (see WO 1998018784;US 6,252,076; US 5,990,311 and US 5,750,531) soraprazan (see WO9605177 and WO9605199),

H-335/25 (AstraZeneca) and SK&F-96067 (GlaxoSmithKline), and the reversible proton pump inhibitors disclosed, for example, in the documents U.S. Pat. No. 4,833,149, U.S. Pat. No. 5,041,442, U.S. Pat. No. 4,464,372, U.S. Pat. No. 6,132,768, including pharmaceutically acceptable salts, isomers, polymorphs, amorphous modifications, co-crystals and derivatives thereof, and combinations thereof.

[0043] In some embodiments, the non-enteric coated formulation comprises one or more NSAIDs and one or more H_2 blockers. Any of the compounds described herein having H_2 blocker activity can be used in the present formulation.

[0044] In some embodiments, the non-enteric coated formulation comprises one or more NSAIDs, one or more proton pump inhibitors and one or more H_2 blockers.

4.2.4 Orally Dissolving Films

[0045] The orally dissolving films provided herein generally comprise a combination of one or more NSAIDs and one or more acid inhibitors. It is specifically contemplated that the orally dissolving films described herein can comprise a single film layer or multiple film layers. For example, it may be desirable to form an orally dissolving film comprising a first active and a second film comprising a second active which may be layered onto the first film.

[0046] Any compound having NSAIDs activity can be used in the present formulation and suitable non-limiting examples are described herein. In some embodiments, the orally dissolving films comprises one or more NSAIDs and one or more proton pump inhibitors. Any compound having proton pump inhibitor activity can be used as the acid inhibitor in the present formulation and suitable non-limiting examples described herein.

[0047] In some embodiments, the orally dissolving films comprises one or more NSAIDs and one or more H_2 blockers. Any compound having H_2 blocker activity can be used in the present formulation and suitable non-limiting examples are described herein. In some embodiments, the orally dissolving films comprise one or more NSAIDs and one or more H_2 blockers, wherein the H_2 blocker is not enteric coated.

[0048] In some embodiments, the orally dissolving films comprises one or more NSAIDs and one or more reversible proton pump inhibitors. Any compound having reversible proton pump inhibitors activity can be used in the present formulation and suitable non-limiting examples are described herein. In some embodiments, the orally dissolving films comprises one or more NSAIDs and one or more reversible proton pump inhibitors, wherein the reversible proton pump inhibitors is not enteric coated.

[0049] Orally dissolving films and methods for making such films are well know in the art. See for example, the following references each of which is hereby incorporated by references in its entirety: U.S. Pat. Nos. 4,136,145; 4,713,243; 5,166,233; 5,700,478; 5,800,832, 5,948,430; 6,419,903, 6,177,096; 6,284,264; 6,596,298; 6,656,493; 6,709,671; 6,824,829; 6,923,981, and United States Patent Application Publication Nos.: US 2001/0046511; US 2001/0022964; US 2002/0131990; US 2003/0107149; US 2004/0151756, US 2004/0241242; US 2004/0247649; US 2004/0258896;US 2005/0184427; US 2005/0196358; US 2005/0075432 and US 2005/0037055.

[0050] Generally, the orally dissolving film can be prepared as described in U.S. patent no. 6,709,671; polyalcohol, surfactants, plasticizers, and possible other ingredients except the water-soluble or water-dispersible polymer(s) are dissolved in a sufficient amount of a solvent which is compatible with them. Examples of compatible solvents include water, alcohols or mixtures thereof. After a clear

solution has been formed, the water-dispersible polymer or mixture of water-dispersible polymers is slowly added with stirring, and heat if necessary, until a clear and homogeneous solution has been formed, followed by the addition of actives and flavors. The solution is coated onto a suitable carrier material and dried to form a film.

[0051] In some embodiments, the orally dissolving film can be prepared as described in U.S. patent publication no: 20050184427. Briefly, the desired components are combined to form a multi-component matrix, including the polymer, water, and an active or other components as desired, and the combination is formed into a sheet or film, by any method known in the art such as extrusion, coating, spreading, casting or drawing the multi-component matrix. If a multi-layered film is desired, this may be accomplished by co-extruding more than one combination of components which may be of the same or different composition. A multi-layered film may also be achieved by coating, spreading, or casting a combination onto an already formed film layer.

[0052] As described above, the desired actives can be mixed with the film forming solution to form the desired orally dissolving film. The actives can be uniformly dispersed in the film forming solution in the form of insoluble solid particles together an/or soluble actives. In some embodiments NSAID and enteric coated proton pump inhibitor granules are added to the film forming solution. In other embodiments meloxicam powder and enteric coated omeprazole granules are added to the film forming solution.

[0053] In some embodiments, NSAIDs maybe added to the film forming polymer solutions in the form of granules together with the enteric coated proton pump inhibitors granules. In some embodiments, meloxicam maybe added to the film forming polymer solutions in the form of granules together with the enteric coated omeprazole granules.

[0054] In some embodiments, the NSAID and/or acid inhibitor may be incorporated into the film-forming mixture in liquid form, such as in solution or suspension rather than as a coating on solid particles. This is particularly useful for acid inhibitors, such as reversible proton pump inhibitors, that do not require an enteric coat.

[0055] The orally dissolving films generally, comprise one or more polymers as well as fillers as desired. Film-forming polymers are well know in the art. See for example, U.S. Patent Appl. No. 11/092217. Generally, the polymer can be water soluble, water insoluble, water swelleable or a combination thereof. In some, embodiments the polymer can include cellulose or a cellulose derivative. Suitable non-limiting examples of water soluble polymers include carboxymethyl cellulose, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol, pullulansodium aginate, polyethylene glycol, acacia gum, arabic gum, xanthan gum, tragancanth gum, guar gum, , polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, and combinations thereof. Suitable non-limiting examples of water insoluble polymers include cellulose acetate, hydroxypropyl ethyl cellulose, hydroxypropyl methyl cellulose, phthalateethyl cellulose, phthalate and combinations thereof.

[0056] Also provided herein are orally dissolving films comprise one or more enteric coated pharmaceutical agents. Enteric coated pharmaceutical agents and methods for making such agents are well know in the art, see for example the following references each of which is hereby incorporated by references in its entirety 4,786,505; 6,013,281; 6,365,184; 6,296,876; 6,780,435; and 6,926,907 . In some embodiments, the orally dissolving film comprising one or more NSAIDs and one or more acid inhibitors, in which one or more acid inhibitors is enteric coated. In some embodiments, the acid inhibitor can be coated onto the surface of particulate substrates and overcoated with an enteric coating.

[0057] The concentration of enteric coated actives in the orally dissolving films should be suitable for therapeutic benefit without causing adverse feeling in the mouth. The amount of enteric coated actives in the orally dissolving films depends on the kind of active and is usually between 0.01 and 20% (w/w), but it can be higher if necessary to achieve the desired effect.

[0058] In some embodiments, the orally dissolving film comprising one or more NSAIDs and one or more acid inhibitors, wherein one or more of the actives is coated onto the surface of particulate substrates. In some embodiments, the orally dissolving film comprising one or more NSAIDs and one or more acid inhibitors, wherein one ore more of the actives is coated onto the surface of particulate substrates and the acid inhibitor is not enteric coated. This embodiment can be used for an acid inhibitor that does not require an enteric coating, *e.g.* a reversible proton pump inhibitor or H_2 blocker. In a specific embodiment, the orally dissolving film comprising one or more NSAIDs and one or more reversible proton pump inhibitors, wherein the reversible proton pump inhibitor is coated onto the surface of particulate substrates and the reversible proton pump inhibitor is not enteric coated.

[0059] In another embodiment, the orally dissolving films comprise a combination of one or more NSAIDs and one or more acid inhibitors, in which one or more acid inhibitors are enteric coated. Suitable non-limiting examples of proton pump inhibitors, that can be enteric coated, include omeprazole (Prilosec™), esomeprazole (Nexium™), lansoprazole (Prevacid™), leminoprazole, rabeprazole (Aciphex™), and pantoprazolem (Protonix™), as well as pharmaceutically acceptable salts, polymorphic crystal forms, isomers, amorphous modifications, co-crystals, derivatives, prodrugs, enantiomers, and combinations thereof.

[0060] In a specific embodiment, the orally dissolving film comprises meloxicam and enteric coated omeprazole.

[0061] Various enteric coatings are known in the art, a number of which are commercially available. The enteric coating comprises a polymer with pH dependent solubility properties. The enteric coating can be any enteric material known to those skilled in the art and may be the same type of enteric materials described above.

[0062] Enteric coating layer(s) can be applied using standard coating technique. The enteric coating is applied using a variety of methods known in the art, such as spraying or layering (see, e.g., U.S. Pat. No. 4,287,221). The thickness of the enteric coating is designed based on the nature of the coating material and the desired lag time or delay in release of the pharmaceutical composition. The enteric coating(s) may be applied to the capsule, or another coating, using a suitable coating technique. The enteric coating layer material may be dispersed or dissolved in either water or in suitable organic solvents for coating.

[0063] The enteric coating may contain effective amounts of pharmaceutically acceptable plasticizers to obtain the desired mechanical properties, such as flexibility of the enteric coating layers, of the type described above.

[0064] In some embodiments, orally dissolving films provide controlled release of one or more actives using one or more controlled release agents. The polymers in orally dissolving films may also be chosen to be the agents for controlled release of one or more pharmaceutical ingredients. In some embodiments, controlled release can be achieved by providing a substantially water insoluble film that incorporates one or more pharmaceutical ingredients that will be released from the film over time. In some embodiments, a variety of different water soluble or insoluble polymers can be used and optionally include biodegradable polymers in combination.

[0065] In some embodiments, one or more pharmaceutical ingredients employed in the present invention can be incorporated into the film in a controlled release

form. For example, pharmaceutical ingredients can be coated with polymers such as ethyl cellulose or polymethacrylate.

[0066] Additional components can be incorporated into the films of the present invention include, without limitation, colorants, flavors, fragrances, mouthwash components, preservatives, sweetening agents, vitamins and combinations thereof. Additional components can include, without limitation, surfactants and plasticizers for compartmentalizing the components within the mixture; polyalcohols; and thermo-setting gels such as pectin, carageenan, and gelatin, which can help maintain the dispersion of components. Citric acid, or other suitable agent, can be added to stimulate saliva production and facilitate rapid dissolution of the film in the oral cavity, and/or provide an acidic environment for an enteric coated proton pump inhibitor.

[0067] In some embodiments, the dissolving film can be adhered to the oral cavity thereby releasing a pharmaceutically active agents, for example NSAIDs and acid inhibitors. In some embodiments, the dissolving film can be adhered to the oral cavity thereby releasing some of the pharmaceutically active agents locally in the oral cavity. For example, a dissolving film comprising a NSAID and enteric coated proton pump inhibitor, in which the NSAID is released into the oral cavity, while the enteric coated proton pump inhibitor remains insoluble in the oral cavity and stomach, but is soluble in near-neutral environments such as the small intestine.

[0068] Optionally, the formulation may contain a combination of plasticizers, surfactants, colorants, sweetening agents, flavors, flavor enhancers, and/or other excipients commonly used to modify the taste of formulations intended for application to the oral cavity.

[0069] The orally dissolving films provided herein can accommodate a wide range of amounts of the active ingredients. As understood by one skilled on the art, the

amount of actives incorporated into the film depend in part on the on the type of film, polymer, surface area, and thickness of the film. In some embodiments, the amount of actives to film is between 0.01 and 50% (w/w), but it can be higher if necessary to achieve the desired effect.

[0070] The oral pharmaceutical compositions can be packaged in sealed, air and moisture resistant packages to protect the actives from exposure to the environment and from oxidation, hydrolysis, volatilization resulting from interaction with the environment. The packaged oral pharmaceutical compositions can contain a full supply of the medication typically prescribed for the intended therapy. A series of unit doses can be packaged together in accordance with the prescribed regimen or treatment, e.g., a 3-90 day supply, depending on the particular therapy.

[0071] A number of benefits are derived from orally dissolving films provided herein. For example, the oral film strip formulations can be administered without water. This method of drug administration, without the need for water, is also particularly well suited for a mobile society. The orally dissolving films provided herein can be particularly appealing to subjects with difficulty in swallowing pharmaceuticals, such as children, elderly, and also in veterinary practice. In addition, the orally dissolving films provided herein provide for an accurate dosage amount. The dosage amount can be determined by the size of the film and concentration of the active in the original polymer/water or polymer/solvent combination.

4.3 Methods

[0072] Also provided is a method for protecting the gastrointestinal tract from the detrimental effects of NSAID therapy. The oral formulations described herein can be used for treatment of almost any physiological disorders for which the pharmaceutical compounds are indicated. The formulations provided herein can be administered to any subject in need of a therapy includes without limitation,

humans(male or female), companion animals, including, but not limited to dogs, cats, ferrets, birds, food-source animals, including, but not limited to cows, pigs, and sheep, and zoo animals, and other similar animal species.

[0073] The formulations provided herein can be administered to subject in need of a therapy for disorders for which NSAIDs are typically indicated such as, for example, angina, aorto-pulmonary shunt occlusion, arthritis, bursitis, cognative decline, cancer, such as esophageal cancer and colon cancer, coronary artery disease, dementia, dysmenorrhea, ischemia, inflammation, fever, gout, headache, migraine headache, musculoskelatal disorders, myocardial infarction, osteoarthritis, pain, pericarditis, rheumatoid arthritis, soft tissue injury, stroke, thrombocythemia, post-operative thromboembolism, and the like.

[0074] Certain types of pain contemplated by this invention arise from pre-operative, post-operative, and both pre- and post-operative procedures. Examples of pain that are treated by this invention thus include anogenital, minor arthritic, dental, topical, associated with an upper respiratory infection, general, joint, menstrual, mild, mild to moderate, acute musculo-skeletal, moderate to moderately severe, moderate to severe, muscular, neurogenic, obstetrical, ocular, oral mucosal and gingival, post operative, pre-operative, pre- and post-operative, severe, short term, urinary tract, and pain associated with gastric hyperacidity

[0075] The formulations according to the invention are advantageous in minimizing or avoiding gastrointestinal side-effects caused by NSAID(s), such as in a continuous treatment with NSAID(s). The formulations can be administered one to several times a day. The daily dose of the active substances varies and will depend on various factors such as the individual requirements of the patients, properties of the actives, the mode of administration and disorder.

[0076] The oral film strip formulations described herein dissolve upon contact with saliva or mucosal membrane areas, eliminating the need to wash the dose

down with a liquid. Generally, the oral film strip formulations are used to orally administer to a patient a combination of one or more NSAIDs and one or more acid inhibitors.

5. EXAMPLES

5.1 Example 1. Omeprazole and meloxicam enteric coated hard gelatin and HPMC capsules

[0077] Omeprazole is wet granulated with excipients, which can include, but not limited to microcrystalline cellulose, mannitol, sodium starch glycolate, sodium stearyl fumarate and hydroxypropyl methylcellulose. The granules can be prepared by high shear granulation or by extrusion and spheronization.

[0078] Meloxicam is either wet granulated or roller compacted with excipients that include but not limited to microcrystalline cellulose, lactose, crospovidone and magnesium stearate.

[0079] The omeprazole and meloxicam granules are blended in the appropriate proportion and filled into either hard gelatin or HPM capsules using conventional capsule filling equipment.

[0080] The filled capsules are enteric coated using conventional film coating technology, such as side vented pans or fluidized bed coaters. The polymers used to enteric coat the capsules may include but are not limited to methacrylic acid copolymers, polyvinyl acetate phthalate or cellulose acetate phthalate plasticized to provide the appropriate flexibility to the film to coat the capsule with a uniform and coherent film.

5.2 Example 2. Omeprazole and meloxicam non-enteric coated hard gelatin and HPMC capsules

[0081] Omeprazole is wet granulated with excipients, which include but not limited to microcrystalline cellulose, mannitol, sodium starch glycolate, sodium

stearyl fumarate and hydroxypropyl methylcellulose. The granules can be prepared by high shear granulation or by extrusion and spheronization. The dried granules are sized and film coated preferably by fluidized bed coating technology using polymers of known pH dependent solubility to provide protection against chemical degradation of omeprazole in the acidic environment of the upper GI tract. These polymers may include but not limited to methacrylic acid copolymers, cellulose acetate phthalate or polyvinyl acetetate phthalate.

[0082] Meloxicam is either wet granulated or roller compacted with excipients that include but not limited to microcrystalline cellulose, lactose, crospovidone and magnesium stearate.

[0083] The enteric coated omeprazole granules and uncoated meloxicam granules are blended in the appropriate proportion and filled into hard gelatin or HPMC capsules using conventional capsule filling equipment.

[0084] Alternatively, the enteric coated omeprazole granules and uncoated meloxicam granules are blended in the appropriate proportion and with excipients that include but not limited to microcrystalline cellulose, lactose, magnesium stearate, and croscarmellose sodium and are filled into hard gelatin or HPMC capsules using conventional capsule filling equipment.

5.3 Example 3. Omeprazole and meloxicam orally dissolvable films (ODT)

[0085] The film-forming natural polymers, including but not limited to xanthan gum, pullulan and carrageenan are mixed and hydrated in purified water. An aqueous solution of wetting agent, sweetener, flavoring agent and citric acid is added to the hydrated polymers and mixed to homogeneity. The citric acid is added to stimulate saliva production and facilitate rapid dissolution of the film in the oral cavity. It also provides an acidic environment for the enteric coated omeprazole. To this film forming solution are added meloxicam powder and

enteric coated omeprazole granules. The wetting agent in the film forming polymer solution aids the dispersion of the water insoluble meloxicam and the enteric coated omeprazole granules. The suspension is mixed to homogeneity, cast on a suitable carrier and dried to form a film. The dried film is cut into appropriately sized pieces to provide the required dosage of the two active medicaments.

[0086] ·Alternatively, meloxicam maybe added to the film forming polymer solutions in the form of granules together with the enteric coated omeprazole granules.

[0087] ·Alternatively, the film former maybe hydroxypropyl methylcellulose, which is hydrated in an aqueous solution of surfactant, flavoring and sweetening agents and citric acid. Glycerol is added to plasticize the film. The solution is stirred until a clear, homogeneous solution is formed. Meloxicam powder is dispersed in the film forming solution, then enteric coated omeprazole granules are mixed in, the film is cast onto a suitable support, dried and cut into appropriately sized pieces.

[0088] ·Alternatively the film maybe formed from a mixture of hydroxypropyl methyl cellulose and polyvinyl pirrolidone, which is hydrated in the presence of surfactant, sweetening and flavoring agents. Once a homogeneous solution is obtained the medicaments in the form of meloxicam powder or meloxicam granules and enteric coated omeprazole particles are added, the film is cast onto a suitable carrier, dried and cut to the desired size.

[0089] ·Alternatively, the acid inhibitor maybe an H_2 antagonist without the need for enteric coating. The medicament maybe uniformly dispersed in the film forming solution in the form of insoluble solid particles together with the particles of the NSAID. Once a homogeneous dispersion is obtained the film is cast on a suitable carrier, dried and cut into the desired size.

[0090] The foregoing descriptions of specific embodiments of the present invention have been presented for purposes of illustration and description. They are not intended to be exhaustive or to limit the invention to the precise forms disclosed, and obviously many modifications and variations are possible in light of the above teaching. The embodiments were chosen and described in order to best explain the principles of the invention and its practical application, to thereby enable others skilled in the art to best utilize the invention and various embodiments with various modifications as are suited to the particular use contemplated. It is intended that the scope of the invention be defined by the Claims appended hereto and their equivalents.

[0091] All patents, patent applications, publications, and references cited herein are expressly incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

CLAIMS

What is claimed is:

1. An enteric coated capsule comprising a non-steroidal anti-inflammatory drug and an acid inhibitor.

2. The enteric coated capsule of Claim 1, wherein said enteric coating is selected from methacrylic acid copolymers, hydroxopropyl methylcellulose phthalate, cellulose acetate phthalate and combinations thereof .

3. The enteric coated capsule of Claim 1, wherein the amount of non-steroidal anti-inflammatory drug is between 1 mg and 500 mg.

4. The enteric coated capsule of Claim 1, wherein the non-steroidal anti-inflammatory drug is meloxicam.

5. The enteric coated capsule of Claim 4, wherein the meloxicam is at an amount between 1 mg and 50 mg.

6. The enteric coated capsule of Claim 1, wherein the acid inhibitor is a proton pump inhibitor.

7. The enteric coated capsule of Claim 6, wherein the amount of proton pump inhibitor is between 1 mg and 500 mg.

8. The enteric coated capsule of Claim 7, wherein the acid inhibitor is omeprazole.

9. The enteric coated capsule of Claim 8, wherein the wherein the omeprazole is at an amount between 1 mg and 100 mg.

10. A pharmaceutical composition comprising a non-steroidal anti-inflammatory drug and a reversible proton pump inhibitor.

11. The pharmaceutical composition of Claim 10 in which said inhibitors is not enteric coated.

12. An orally dissolvable film comprising a combination of pharmaceutically active agents, wherein said agents are a non-steroidal anti-inflammatory drug and an acid inhibitor.

13. The film of Claim 12, wherein the amount of non-steroidal anti-inflammatory drug is between 1 mg and 100 mg.

14. The film of Claim 12, wherein the non-steroidal anti-inflammatory drug is meloxicam.

15. The film of Claim 12, wherein the acid inhibitor is enteric coated.

16. The film of Claim 12, wherein the acid inhibitor is not enteric coated.

17. The film of Claim 12, wherein the acid inhibitor is a proton pump inhibitor.

18. The film of Claim 17, wherein the amount of proton pump inhibitor is at an amount between 1 mg and 100 mg.

19. The film of Claim 17, wherein the wherein the proton pump inhibitor is omeprazole.

20. The film of Claim 19, wherein omeprazole is enteric coated.

21. The film of Claim 20, wherein the wherein the omeprazole is at an amount between 1 mg and 100 mg.

22. The film of Claim 12, wherein the acid inhibitor is an H_2 antagonist.

23. The film of Claim 22, wherein the H_2 antagonist is at an amount between 5 mg and 50 mg.

24. The film of Claim 22 wherein the H_2 antagonist is famotidine.

25. An orally dissolvable film comprising meloxicam and enteric coated omeprazole.

26. A method of treating pain and/or inflammation in a patient comprising administering to said patient a composition of any one of Claims 1-25.

27. A method of protecting the gastrointestinal tract from side effects associated with non-steroidal anti-inflammatory drug therapy in a patient comprising administering to said patient a composition of any one of Claims 1-25.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 July 2007 (12.07.2007)

PCT

(10) International Publication Number
WO 2007/078874 A3

(51) International Patent Classification:
A61K 9/48 (2006.01) *A61P 29/00* (2006.01)
A61K 9/50 (2006.01) *A61K 31/4439* (2006.01)
A61K 9/70 (2006.01) *A61K 31/5415* (2006.01)
A61K 45/06 (2006.01)

(21) International Application Number:
PCT/US2006/047886

(22) International Filing Date:
15 December 2006 (15.12.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/755,131 30 December 2005 (30.12.2005) US

(71) Applicant *(for all designated States except US)*: **COGENTUS PHARMACEUTICALS, INC.** [US/US]; 301 RAVENSWOOD AVENUE, SUITE 100, Menlo Park, CA 94025 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **TANANBAUM, James, B.** [US/US]; COGENTUS PHARMACEUTICALS, INC., 301 RAVENSWOOD AVENUE, SUITE 100, Menlo Park, CA 94025 (US). **VADAS, Elizabeth** [CA/US]; COGENTUS PHARMACEUTICALS, INC., 301 RAVENSWOOD AVENUE, SUITE 100, Menlo Park, CA 94025 (US). **GOLDSMITH, Mark, A.** [US/US]; COGENTUS PHARMACEUTICALS, INC., 301 RAVENSWOOD AVENUE, SUITE 100, Menlo Park, CA 94025 (US).

(74) Agent: **BREZNER, David, J.**; MORGAN, LEWIS & BOCKIUS LLP, ONE MARKET, SPEAR STREET TOWER, San Francisco, CA 94105 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*
— *of inventorship (Rule 4.17(iv))*

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
6 March 2008

(54) Title: ORAL PHARMACEUTICAL FORMULATIONS CONTAINING NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND ACID INHIBITORS

(57) Abstract: The present disclosure provides enteric coated capsules and orally dissolving films comprising non-steroidal anti-inflammatory drugs and acid inhibitors, as well as methods of treating treatment humans for pain and/or inflammation while reducing gastrointestinal side effects.

WO 2007/078874 A3

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/047886

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/48 A61K9/50 A61K9/70 A61K45/06 A61P29/00
A61K31/4439 A61K31/5415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97/25064 A (ASTRA AB [SE]; DEPUI HELENE [SE]; LUNDBERG PER JOHAN [SE]) 17 July 1997 (1997-07-17) cited in the application page 1, paragraph 1 page 3, last paragraph - page 4, paragraph 2 page 6, last paragraph - page 13, paragraph 3 page 16, paragraph 2 - page 18, paragraph 3; examples 8,9	1-9,15, 20,21, 26,27

-/--

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 December 2007	08/01/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Marttin, Emmeline

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/047886

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2004/062552 A (GALEPHAR M F [BE]; VANDERBIST FRANCIS [BE]; SERENO ANTONIO [BE]; BAUDI) 29 July 2004 (2004-07-29) page 1, paragraph 1 - page 7, paragraph 2 page 8, last paragraph - page 10, paragraph 1; examples	1-9,14, 15, 19-21, 25-27
Y	EP 1 352 660 A (ASTRAZENECA AB [SE]) 15 October 2003 (2003-10-15) paragraphs [0009], [0011], [0012], [0014], [0019], [0021], [0024], [0026], [0006] - [0038], [0051] - [0058]; example 6	1-9,26, 27
Y	EP 0 960 620 A1 (RANBAXY LAB LTD [IN]) 1 December 1999 (1999-12-01) examples	1-9,15, 20,21, 26,27
Y	WO 01/66088 A (ASTRAZENECA AB [SE]; HOLMBERG CHRISTINA [SE]; SIEKMANN BRITTA [SE]) 13 September 2001 (2001-09-13) page 21, line 13 - page 24, line 8; examples 16,17	1-9,26, 27
X	WO 01/70194 A (WARNER LAMBERT CO [US]) 27 September 2001 (2001-09-27)	12,13, 17-19, 22-24
Y	page 3, line 15 - page 5, last line ; claims 1,4,6,12,13; table A	12-15, 19-21, 25-27
Y	US 2004/229038 A1 (COOPER EUGENE R [US] ET AL) 18 November 2004 (2004-11-18) paragraphs [0185] - [0191]	12-14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/047886

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 26 and 27 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [X] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

1-9, 12-25, 26-27 partially

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-9, 26-27 partially

An enteric coated capsule comprising a non-steroidal anti-inflammatory drug and an acid inhibitor. A method of treating pain and/or inflammation in a patient comprising administering to said patient said enteric coated capsule. A method of protecting the gastrointestinal tract from side effects associated with non-steroidal anti-inflammatory drug therapy in a patient comprising administering to said patient said enteric coated capsule.

---

2. claims: 10-11, 26-27 partially

A pharmaceutical composition comprising a non-steroidal anti-inflammatory drug and a reversible proton pump inhibitor. A method of treating pain and/or inflammation in a patient comprising administering to said patient said composition. A method of protecting the gastrointestinal tract from side effects associated with non-steroidal anti-inflammatory drug therapy in a patient comprising administering to said patient said composition.

---

3. claims: 12-25, 26-27 partially

An orally dissolvable film comprising a combination of pharmaceutically active agents, wherein said agents are a non-steroidal anti-inflammatory drug and an acid inhibitor. An orally dissolvable film comprising meloxicam and enteric coated omeprazole. A method of treating pain and/or inflammation in a patient comprising administering to said patient said orally dissolvable film. A method of protecting the gastrointestinal tract from side effects associated with non-steroidal anti-inflammatory drug therapy in a patient comprising administering to said patient said orally dissolvable film.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2006/047886

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9725064 A	17-07-1997	AT	242006 T	15-06-2003
		AU	712571 B2	11-11-1999
		AU	1323997 A	01-08-1997
		BR	9607476 A	23-12-1997
		CA	2213987 A1	17-07-1997
		CN	1183048 A	27-05-1998
		CZ	9702748 A3	14-01-1998
		DE	69628551 D1	10-07-2003
		DE	69628551 T2	06-05-2004
		DK	814839 T3	22-09-2003
		EE	9700194 A	16-02-1998
		EP	0814839 A1	07-01-1998
		ES	2201211 T3	16-03-2004
		HK	1001761 A1	10-10-2003
		HK	1017991 A1	23-04-2004
		HU	9904095 A2	28-06-2000
		IL	121650 A	12-03-2003
		IS	4546 A	19-08-1997
		JP	11501948 T	16-02-1999
		NO	974069 A	17-10-1997
		NZ	325975 A	25-02-1999
		PL	322174 A1	19-01-1998
		PT	814839 T	31-10-2003
		RU	2158138 C2	27-10-2000
		SK	117797 A3	08-04-1998
		TR	9700915 T1	21-11-1997
		TW	452495 B	01-09-2001
		US	6365184 B1	02-04-2002
		ZA	9610936 A	08-07-1997
WO 2004062552 A	29-07-2004	NONE		
EP 1352660 A	15-10-2003	SI	814839 T1	31-12-2003
EP 0960620 A1	01-12-1999	AT	315396 T	15-02-2006
		AU	1979699 A	13-12-1999
		BR	9910723 A	12-06-2001
		CN	1237415 A	08-12-1999
		DE	69833157 T2	31-08-2006
		ES	2256910 T3	16-07-2006
		WO	9961022 A1	02-12-1999
		RU	2216321 C2	20-11-2003
		US	2002128293 A1	12-09-2002
		ZA	9810765 A	06-08-1999
WO 0166088 A	13-09-2001	AT	268162 T	15-06-2004
		AU	3787601 A	17-09-2001
		BR	0109014 A	03-06-2003
		CA	2401498 A1	13-09-2001
		CN	1416335 A	07-05-2003
		CZ	20023005 A3	12-02-2003
		DE	60103627 D1	08-07-2004
		DE	60103627 T2	16-06-2005
		DK	1267832 T3	30-08-2004
		EE	200200500 A	16-02-2004
		EP	1267832 A1	02-01-2003
		ES	2220728 T3	16-12-2004
		HK	1050632 A1	18-03-2005

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2006/047886

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0166088 A		HU 0300882 A2	29-09-2003
		IS 6539 A	03-09-2002
		JP 2003525894 T	02-09-2003
		MX PA02008657 A	24-02-2003
		NO 20024272 A	05-11-2002
		NZ 521009 A	25-06-2004
		PL 358595 A1	09-08-2004
		PT 1267832 T	30-09-2004
		SK 12572002 A3	02-05-2003
		TR 200401906 T4	21-09-2004
		US 2003161846 A1	28-08-2003
		ZA 200206740 A	24-11-2003
WO 0170194 A	27-09-2001	AR 029494 A1	02-07-2003
		AT 324864 T	15-06-2006
		AU 2972001 A	03-10-2001
		AU 2006201888 A1	25-05-2006
		AU 2006201899 A1	25-05-2006
		BR 0109378 A	03-06-2003
		CA 2402988 A1	27-09-2001
		CN 1419441 A	21-05-2003
		CN 1651092 A	10-08-2005
		CZ 20023108 A3	16-04-2003
		DE 60119298 T2	31-08-2006
		DK 1267829 T3	11-09-2006
		EP 1267829 A1	02-01-2003
		ES 2261455 T3	16-11-2006
		HU 0300035 A2	28-05-2003
		IS 6523 A	23-08-2002
		JP 2003527410 T	16-09-2003
		MX PA02008425 A	13-12-2002
		NO 20024513 A	20-09-2002
		NZ 520961 A	31-10-2003
		PL 357135 A1	12-07-2004
		PT 1267829 T	31-07-2006
		SK 13432002 A3	03-06-2003
		US 2006204559 A1	14-09-2006
		US 7067116 B1	27-06-2006
		UY 26628 A1	29-06-2001
		ZA 200206963 A	21-07-2003
US 2004229038 A1	18-11-2004	NONE	

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 August 2008 (21.08.2008)

PCT

(10) International Publication Number
WO 2008/101060 A1

(51) International Patent Classification:
A61K 38/00 (2006.01) *A61K 39/08* (2006.01)

(21) International Application Number:
PCT/US2008/053932

(22) International Filing Date:
14 February 2008 (14.02.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/889,777 14 February 2007 (14.02.2007) US

(71) Applicant *(for all designated States except US)*: **LOGICAL THERAPEUTICS, INC.** [US/US]; 300 Second Avenue, Waltham, Massachusetts 02451 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **FINK, Mitchell, P.** [US/US]; 109 Rockwood Drive, Pittsburgh, Pennsylvania 15238 (US). **SEWELL, Kathryn, Lea** [US/US]; 22 Bostonia Avenue, Brighton, Massachusetts 02215 (US).

(74) Agent: **MILLER, Raymond, A.**; Pepper Hamilton LLP, 500 Grant Street, One Mellon Bank Center, 50th floor, Pittsburgh, PA 15219 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

WO 2008/101060 A1

(54) Title: METHOD OF TREATING ARTHRITIS, PAIN OR INFLAMMATION WITH NAPROXEN 2(METHANESULFONYL)ETHYL ESTER AND A PROTON PUMP INHIBITOR

(57) Abstract: Embodiments of the present invention provide methods of treating pain, arthritis and inflammation comprising administering naproxen 2(methanesulfonyl)ethyl ester and a proton pump inhibitor. Further embodiments provide pharmaceutical compositions comprising naproxen 2(methanesulfonyl)ethyl ester and a proton pump inhibitor.

A. Title: Method of treating arthritis, pain or inflammation with naproxen 2(methanesulfonyl)ethyl ester and a proton pump inhibitor

B. Cross-Reference to Related Applications

[0001] This application claims the benefit of U.S. Provisional Application No. 60/889,777, filed February 14, 2007, which is herein incorporated by reference in its entirety.

C. Government Interests: Not applicable

D. Parties to a Joint Research Agreement: Not applicable

E. Incorporation by Reference of Material submitted on a Compact Disc: Not applicable

F. Background

1. Field of Invention: Not applicable

2. Description of Related Art

[0002] Despite the advent of modern pharmaceutical technology, many drugs still possess untoward toxicities which often limit the therapeutic potential thereof. For example, although nonsteroidal anti-inflammatory drugs (NSAIDs) are a class of compounds which are widely used for the treatment of inflammation, pain and fever, NSAIDs (e.g., naproxen, aspirin, ibuprofen and ketoprofen) can cause gastrointestinal ulcers, a side effect that remains the major limitation to the use of NSAIDs.

[0003] There are two major ulcerogenic effects of NSAIDs: (1) irritant effects on the epithelium of the gastrointestinal tract and (2) suppression of gastrointestinal prostaglandin synthesis. In recent years, numerous strategies have been attempted to design and develop new NSAIDs that reduce the damage to the gastrointestinal tract. These efforts, however, have not fully satisfied the medical need. For example, enteric coating or slow release formulations designed to reduce the topical irritant properties of NSAIDs have been shown to be ineffective in terms of reducing the incidence of clinically significant side effects, including perforation and bleeding.

[0004] It is well recognized that aspirin and other NSAIDs exert their pharmacological effects through the non-selective inhibition of cyclooxygenase (COX) enzymes, thereby blocking prostaglandin synthesis. There are two types of COX enzymes, namely COX1 and COX2. COX1 is expressed constitutively in many tissues, including the stomach, kidney, and platelets, whereas COX2 is expressed only at the site of inflammation. The prostagladins derived from COX1 are responsible for many of the physiological effects, including maintenance of gastric

mucosal integrity. Many attempts have been made to develop NSAIDs that only inhibit COX2, without impacting the activity of COX1. There are several NSAIDs (e.g., rofecoxib and celecoxib) that show marked selectivity for COX2. These drugs appear to have reduced gastrointestinal toxicity relative to other NSAIDs. However, the physiological functions of COX1 and COX2 are not always well defined. Thus, there is a possibility that prostaglandins produced as a result of COX1 expression may also contribute to inflammation, pain and fever. On the other hand, prostaglandins produced by COX2 have been shown to play important physiological functions, including the initiation and maintenance of labor and in the regulation of bone resorption, thus inhibition of this pathway may not always be beneficial. Considering these points, highly selective COX2 inhibitors have been known to product cardiovascular side effects and may produce additional side effects above and beyond those observed with standard NSAIDs, therefore such inhibitors may not be highly desirable.

[0005] In general, various acid inhibitors may be useful during administration of NSAIDs. For example, more potent and longer lasting acid inhibitors, such as proton pump inhibitors, and shorter acting agents, *e.g.*, histamine H_2 receptor antagonists (H-2 blockers) are two classes of acid inhibitors, with different effects. Gastric pH fluctuates widely throughout the dosing interval with short acting acid inhibitors leaving the mucosa vulnerable for significant periods of time. In particular, the pH is at its lowest point, and hence the mucosa is most vulnerable, at the end of the dosing interval (least amount of acid inhibition) and for some time after the subsequent dose of acid inhibitor. In general, it appears that when a short acting acid inhibitor and an NSAID are administered simultaneously, NSAID-related mucosal damage occurs both before the pH of the gastrointestinal tract can be raised and after the acid inhibiting effect of the short acting acid inhibitor dissipates.

[0006] Longer lasting agents, such as proton pump inhibitors (PPIs), usually maintain a consistently higher gastroduodenal pH throughout the day, after several days dosing, their antisecretory effect may be delayed for several hours and may not take full effect for several days. Their effect may be diminished toward the end of the usual dosing interval. Intragastric pH rises particularly slowly with the first does in a course of treatment since this class of drugs is enteric coated to avoid destruction by stomach acid. As a result, absorption is delayed for several hours. Even then, some patients fail to respond consistently to drugs of this type and suffer from "acid breakthrough" which again leaves them vulnerable to NSAID-associated

gastroduodenal damage. Despite a significant reduction in gastroduodenal lesions with the concomitant administration of a proton pump inhibitor during six months of NSAID therapy, some patients still develop ulcers, indicating that there remains substantial room for improvement.

[0007] Overall, it may be concluded that the risk of inducing GI ulcers is a recognized problem associated with the administration of NSAIDs and that, despite considerable effort, an ideal solution has not yet been found. Accordingly, there is still a need in the art for products which contain an NSAID therapeutic benefit, but which cause a reduced incidence of side-effects.

G. Brief summary of the invention

[0008] One embodiment of the present invention provides methods of treating arthritis, inflammation or pain comprising administering a patient naproxen 2(methanesulfonyl)ethyl ester and a proton pump inhibitor.

[0009] A further embodiment of the present invention provides pharmaceutical compositions comprising a therapeutically effective amount of naproxen 2(methanesulfonyl)ethyl ester, a therapeutically effective amount of a proton pump inhibitor and one or more excipients.

[0010] A further embodiment of the present invention provides methods of treating inflammation or pain in a patient who has had a previous ulcer or gastrointestinal bleeding comprising administering said patient naproxen 2(methanesulfonyl)ethyl ester and a proton pump inhibitor.

[0011] Another embodiment o fhte present invention provides methods of treating inflammation or pain in a patient who has a factor for a high risk gastrointestinal complication comprising administering said patient naproxen 2(methanesulfonyl)ethyl ester and a proton pump inhibitor.

[0012] Another embodiment of the present invention provides pharmaceutical formulations comprising naproxen 2(methanesulfonyl)ethyl ester and a proton pump inhibitor, wherein said proton pump inhibitor is separated from the 2(methanesulfonyl)ethyl ester by a layer of one or more excipients and wherein said pharmaceutical formulation is a tablet.

H. Description of Drawings: Not applicable

I. Detailed Description

[0013] Before the present compositions and methods are described, it is to be understood that this invention is not limited to the particular processes, compositions, or methodologies described, as these may vary. It is also to be understood that the terminology used in the description is for the purpose of describing the particular versions or embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims. Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments of the present invention, the preferred methods, devices, and materials are now described. All publications mentioned herein are incorporated by reference in their entirety. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

[0014] It must also be noted that as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to a "cell" is a reference to one or more cells and equivalents thereof known to those skilled in the art, and so forth.

[0015] As used herein, the term "about" means plus or minus 10% of the numerical value of the number with which it is being used. Therefore, about 50% means in the range of 45%-55%.

[0016] A "therapeutically effective amount" or "effective amount" of a composition is a predetermined amount calculated to achieve the desired effect. The activity contemplated by the present methods includes both medical therapeutic and/or prophylactic treatment, as appropriate. The specific dose of a compound administered according to this invention to obtain therapeutic and/or prophylactic effects will, of course, be determined by the particular circumstances surrounding the case, including, for example, the compound administered, the route of administration, and the condition being treated. It will be understood that the effective amount administered will be determined by the physician in the light of the relevant circumstances including the condition to be treated, the choice of compound to be administered, and the chosen route of administration, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. A therapeutically effective amount of compound of this invention is typically an amount such that when it is administered in a physiologically tolerable excipient

composition, it is sufficient to achieve an effective systemic concentration or local concentration in the tissue.

[0017] The terms "treat," "treated," or "treating" as used herein refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) an undesired physiological condition, disorder or disease, or to obtain beneficial or desired clinical results. For the purposes of this invention, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of the condition, disorder or disease; stabilization (*i.e.*, not worsening) of the state of the condition, disorder or disease; delay in onset or slowing of the progression of the condition, disorder or disease; amelioration of the condition, disorder or disease state; and remission (whether partial or total), whether detectable or undetectable, or enhancement or improvement of the condition, disorder or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment.

[0018] Optical Isomers--Diastereomers--Geometric Isomers—Tautomers. Compounds described herein may contain an asymmetric center and may thus exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centers, they may additionally exist as diastereomers. The present invention includes all such possible stereoisomers as substantially pure resolved enantiomers, racemic mixtures thereof, as well as mixtures of diastereomers. The formulas are shown without a definitive stereochemistry at certain positions. The present invention includes all stereoisomers of such formulas and pharmaceutically acceptable salts thereof. Diastereoisomeric pairs of enantiomers may be separated by, for example, fractional crystallization from a suitable solvent, and the pair of enantiomers thus obtained may be separated into individual stereoisomers by conventional means, for example by the use of an optically active acid or base as a resolving agent or on a chiral HPLC column. Further, any enantiomer or diastereomer of a compound of the general formula may be obtained by stereospecific synthesis using optically pure starting materials or reagents of known configuration.

[0019] The present invention is based upon the discovery of improved methods of treatment and pharmaceutical compositions for administering naproxen 2(methanesulfonyl)ethyl ester to patients. In addition to containing naproxen 2(methanesulfonyl)ethyl ester, the

compositions include proton pump inhibitors that are capable of raising the pH of the GI tract of patients. In particular, patients in need of treatment for arthritis, inflammation and pain can benefit from this invention.

[0020] In one embodiment, the invention comprises a method of treating arthritis, inflammation or pain comprising administering a patient naproxen 2(methanesulfonyl)ethyl ester and a proton pump inhibitor. In another embodiment, the invention comprises a method of treating arthritis, inflammation or pain in a patient at risk for having an ulcer a comprising administering naproxen 2(methanesulfonyl)ethyl ester and a proton pump inhibitor. In a further embodiment, the invention comprises a method of treating arthritis, inflammation or pain in a patient who has had a previous ulcer or gastrointestinal bleeding a comprising administering naproxen 2(methanesulfonyl)ethyl ester and a proton pump inhibitor.

[0021] Examples of proton pump inhibitors useful for this invention include, but are not limited to, omeprazole, esomeprazole, lansoprazole, rabeprazole, pantoprazole, tenatoprazole, and ilaprazole.. Included within these examples are salts, isomers, racemic compounds, crystals, polymorphs, amorphous forms and cocrystals of these examples.

[0022] In a still further embodiment, the invention comprises a method of treating arthritis, inflammation or pain in a patient who has a high risk factor for receiving a gastrointestinal disorder comprising administering naproxen 2(methanesulfonyl)ethyl ester and a proton pump inhibitor. Patients who have high risk factors for receiving a gastrointestinal disorder include patients of age over 60 years, patients taking aspirin therapy, patients taking corticosteroids and patients who have had a previous ulcer or gastrointestinal bleeding event.

[0023] In one embodiment, the invention comprises a medicament for the treatment of arthritis, inflammation or pain comprising naproxen 2(methanesulfonyl)ethyl ester and a proton pump inhibitor. In another embodiment, the invention comprises a medicament for treatment of arthritis, inflammation or pain in a patient who has had a previous ulcer or gastrointestinal bleeding comprising naproxen 2(methanesulfonyl)ethyl ester and a proton pump inhibitor . In another embodiment, the invention comprises a medicament for treatment of arthritis, inflammation or pain in a patient who has a high risk factor for receiving a gastrointestinal disorder comprising naproxen 2(methanesulfonyl)ethyl ester and a proton pump inhibitor. Patients who have high risk factors for receiving a gastrointestinal disorder include patients of age over 60 years, patients taking aspirin therapy, and patients taking corticosteroids.

[0024] Included within the definition of arthritis, but not limited to, is rheumatoid arthritis, osteoarthritis, juvenile rheumatoid arthritis, ankylosing spondosis, juvenile arthritis, bursitis, gout, Psoriatic arthritis, and Reactive arthritis as described at http://www.arthritis.org/disease-center.php?disease_id=3.

[0025] In one embodiment, the invention comprises a pharmaceutical composition of naproxen 2(methanesulfonyl)ethyl ester and a proton pump inhibitor. In another embodiment, the invention comprises a pharmaceutical composition of naproxen 2(methanesulfonyl)ethyl ester and omeprazole or a pharmaceutically acceptable salt thereof. In a further embodiment, the invention comprises a pharmaceutical composition of naproxen 2(methanesulfonyl)ethyl ester and esomeprazole or a pharmaceutically acceptable salt thereof. In still further embodiment, the invention comprises a pharmaceutical composition of naproxen 2(methanesulfonyl)ethyl ester and lansoprazole or a pharmaceutically acceptable salt thereof. In another embodiment, the invention comprises a pharmaceutical composition of naproxen 2(methanesulfonyl)ethyl ester and rabeprazole or a pharmaceutically acceptable salt thereof. In one embodiment, the invention comprises a pharmaceutical composition of naproxen 2(methanesulfonyl)ethyl ester and pantoprazole or a pharmaceutically acceptable salt thereof. In one embodiment, the invention comprises a pharmaceutical composition of naproxen 2(methanesulfonyl)ethyl ester and tenatoprazole or a pharmaceutically acceptable salt thereof. In one embodiment, the invention comprises a pharmaceutical composition of naproxen 2(methanesulfonyl)ethyl ester and ilaprazole or a pharmaceutically acceptable salt thereof.

[0026] For some patients the combination of the two drugs might be more useful co-packaged as opposed to combined in the same pill or tablet. In another embodiment, the invention comprises a package comprising naproxen 2(methanesulfonyl)ethyl ester and said proton pump inhibitor . In another embodiment, the invention comprises a package of naproxen 2(methanesulfonyl)ethyl ester and omeprazole or a pharmaceutically acceptable salt thereof. In a further embodiment, the invention comprises a package of naproxen 2(methanesulfonyl)ethyl ester and esomeprazole or a pharmaceutically acceptable salt thereof. In still further embodiment, the invention comprises a package of naproxen 2(methanesulfonyl)ethyl ester and lansoprazole or a pharmaceutically acceptable salt thereof. In another embodiment, the invention comprises a package of naproxen 2(methanesulfonyl)ethyl ester and rabeprazole or a pharmaceutically acceptable salt thereof. In one embodiment, the invention comprises a package

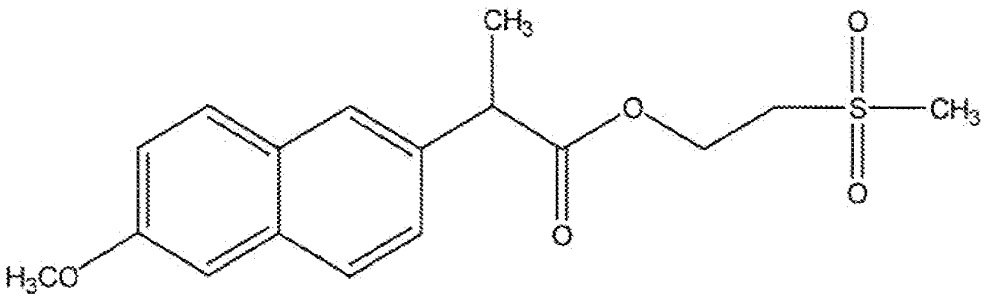
of naproxen 2(methanesulfonyl)ethyl ester and pantopraozle or a pharmaceutically acceptable salt thereof. In one embodiment, the invention comprises a package of naproxen 2(methanesulfonyl)ethyl ester and tenatoprazole or a pharmaceutically acceptable salt thereof. In one embodiment, the invention comprises a package of naproxen 2(methanesulfonyl)ethyl ester and ilaprazole or a pharmaceutically acceptable salt thereof.

[0027] In another embodiment, the invention comprises a pharmaceutical formulation comprising naproxen 2(methanesulfonyl)ethyl ester and a proton pump inhibitor, wherein said proton pump inhibitor is separated from the naproxen 2(methanesulfonyl)ethyl ester by a layer of one or more excipients and wherein said pharmaceutical formulation is a tablet. In a further embodiment, the invention comprises a pharmaceutical formulation comprising naproxen 2(methanesulfonyl)ethyl ester and a proton pump inhibitor, wherein said proton pump inhibitor is separated from the naproxen 2(methanesulfonyl)ethyl ester by a layer of one or more excipients and wherein said pharmaceutical formulation is an enteric coated tablet.

[0028] Compositions of this invention can be used to treat arthritis, pain and inflammation while also reducing the patient's likelihood of having a duodenal ulcer, a gastric ulcer, gastroesophageal reflux disease, gastrointestinal bleeding or erosive esophagitis.

[0029] 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. With respect to a proton pump inhibitors, tablets or capsules may contain anywhere from 1 mg to 100 mg per unit dose. For example, the proton pump inhibitor omeprazole may be present in tablets or capsules in an amount from 5 to 50 mg. Other typical amounts are: esomeprazole, 5-50 mg; lansoprazole, 5-50 mg; pantoprazole, 5-50 mg; rabeprazole 5-50 mg.

[0030] Naproxen 2(methanesulfonyl)ethyl ester is disclosed in U.S. Patent No. 6,355,666 (Application number 09/602,688), herein incorporated by reference in its entirety, as Compound 50 and a method of making Compound 50 is disclosed in Example 17. Naproxen 2(methanesulfonyl)ethyl ester is also called (S)-(+)-2-(6-methoxy-2-naphthyl)propionic acid 2-methanesulfonyl ethyl ester. The structure of naproxen 2(methanesulfonyl)ethyl ester is:



[0031] In certain embodiments, the pharmaceutical compositions of the invention include tablets, dragees, liquids and capsules and can be made in accordance with methods that are standard in the art (see, e.g. Remington's Pharmaceutical Sciences, 16th ea., A Oslo editor, Easton, Pa. (1980)). Drugs and drug combinations will typically be prepared in admixture with conventional excipients.

[0032] Enteric coating layer(s) may be applied onto a tablet using standard coating techniques. The enteric coating materials may be dissolved or dispersed in organic or aqueous solvents and may include one or more of the following materials: methacrylic acid copolymers, shellac, hydroxypropylmethcellulose phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose trimellitate, carboxymethylethyl-cellulose, cellulose acetate phthalate or other suitable enteric coating polymer(s). The pH at which the enteric coat will dissolve can be controlled by the polymer or combination of polymers selected and/or ratio of pendant groups. For example, dissolution characteristics of the polymer film can be altered by the ratio of free carboxyl groups to ester groups. Enteric coating layers also contain pharmaceutically acceptable plasticizers such as triethyl citrate, dibutyl phthalate, triacetin, polyethylene glycols, polysorbates or other plasticizers. Additives such as dispersants, colorants, anti-adhering and anti-foaming agents may also be included.

[0033] In one embodiment, the combination of a proton pump inhibitor and naproxen 2(methanesulfonyl)ethyl ester will be in the form of a bi- or multi-layer tablet. In a bilayer configuration, one portion of the tablet contains the proton pump inhibitor in the required dose along with the appropriate excipients, agents to aid dissolution, lubricants, fillers, etc. The second portion of the tablet will contain naproxen 2(methanesulfonyl)ethyl ester, in the required dose along with other excipients, dissolution agents, lubricants, fillers, etc. In one exemplary embodiment, the naproxen 2(methanesulfonyl)ethyl ester layer is surrounded by a polymeric coating which does not dissolve at a pH of less than 4. The naproxen 2(methanesulfonyl)ethyl

ester may be granulated by methods such as slugging, low- or high- shear granulation, wet granulation, or fluidized-bed granulation. Of these processes, slugging generally produced tablets of less hardness and greater friability. Low-shear granulation, high-shear granulation, wet granulation and fluidized-bed granulation generally produce harder, less friable tablets.

[0034] Specific modes of administration will depend on the indication. The selection of the specific route of administration and the dose regimen is to be adjusted or titrated by the clinician according to methods known to the clinician in order to obtain the optimal clinical response. The amount of compound to be administered is that amount which is therapeutically effective. The dosage to be administered will depend on the characteristics of the subject being treated, *e.g.*, the particular animal treated, age, weight, health, types of concurrent treatment, if any, and frequency of treatments, and can be easily determined by one of skill in the art (*e.g.*, by the clinician).

[0035] Pharmaceutical formulations containing the compounds of the present invention and a suitable carrier can be solid dosage forms which include, but are not limited to, tablets, capsules, cachets, pellets, pills, powders and granules; topical dosage forms which include, but are not limited to, solutions, powders, fluid emulsions, fluid suspensions, semi-solids, ointments, pastes, creams, gels and jellies, and foams; and parenteral dosage forms which include, but are not limited to, solutions, suspensions, emulsions, and dry powder; comprising an effective amount of a polymer or copolymer of the present invention. It is also known in the art that the active ingredients can be contained in such formulations with pharmaceutically acceptable diluents, fillers, disintegrants, binders, lubricants, surfactants, hydrophobic vehicles, water soluble vehicles, emulsifiers, buffers, humectants, moisturizers, solubilizers, preservatives and the like. The means and methods for administration are known in the art and an artisan can refer to various pharmacologic references for guidance. For example, *Modern Pharmaceutics*, Banker & Rhodes, Marcel Dekker, Inc. (1979); and *Goodman & Gilman's The Pharmaceutical Basis of Therapeutics*, 6th Edition, MacMillan Publishing Co., New York (1980) can be consulted.

[0036] The compounds of the present invention can be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. The compounds can be administered by continuous infusion subcutaneously over a period of about 15 minutes to about 24 hours. Formulations for injection can be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions can take

such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

[0037] For oral administration, the compounds can be formulated readily by combining these compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by adding a solid excipient, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include, but are not limited to, fillers such as sugars, including, but not limited to, lactose, sucrose, mannitol, and sorbitol; cellulose preparations such as, but not limited to, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and polyvinylpyrrolidone (PVP). If desired, disintegrating agents can be added, such as, but not limited to, the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[0038] Dragee cores can be provided with suitable coatings. For this purpose, concentrated sugar solutions can be used, which can optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments can be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0039] Pharmaceutical preparations which can be used orally include, but are not limited to, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as, *e.g.*, lactose, binders such as, *e.g.*, starches, and/or lubricants such as, *e.g.*, talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds can be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers can be added. All formulations for oral administration should be in dosages suitable for such administration.

[0040] For buccal administration, the compositions can take the form of, *e.g.*, tablets or lozenges formulated in a conventional manner.

[0041] For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, *e.g.*, gelatin for use in an inhaler or insufflator can be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[0042] The compounds of the present invention can also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

[0043] In addition to the formulations described previously, the compounds of the present invention can also be formulated as a depot preparation. Such long acting formulations can be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection.

[0044] Depot injections can be administered at about 1 to about 6 months or longer intervals. Thus, for example, the compounds can be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0045] In transdermal administration, the compounds of the present invention, for example, can be applied to a plaster, or can be applied by transdermal, therapeutic systems that are consequently supplied to the organism.

[0046] Pharmaceutical compositions of the compounds also can comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as, *e.g.*, polyethylene glycols.

[0047] The compounds of the present invention can also be administered in combination with other active ingredients, such as, for example, adjuvants, protease inhibitors, or other compatible drugs or compounds where such combination is seen to be desirable or advantageous in achieving the desired effects of the methods described herein. It is to be understood that this invention is not limited to the particular processes, compositions, or methodologies described, as

these may vary. It is also to be understood that the terminology used in the description is for the purpose of describing the particular versions or embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims. Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments of the present invention, the preferred methods, devices, and materials are now described. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

[0048] Although the present invention has been described in considerable detail with reference to certain preferred embodiments thereof, other versions are possible. Therefore the spirit and scope of the appended claims should not be limited to the description and the preferred versions contained within this specification.

EXAMPLE 1

[0049] The following compositions are representative compositions which could be made according to embodiments of the present invention.

[0050] A. Naproxen 2(methanesulfonyl)ethyl ester and 10 mg omeprazole

[0051] B. Naproxen 2(methanesulfonyl)ethyl ester and 20 mg omeprazole

[0052] C. Naproxen 2(methanesulfonyl)ethyl ester and 40 mg omeprazole

[0053] D. Naproxen 2(methanesulfonyl)ethyl ester and 20 mg esomeprazole magnesium

[0054] E. Naproxen 2(methanesulfonyl)ethyl ester and 40 mg esomeprazole magnesium

[0055] F. Naproxen 2(methanesulfonyl)ethyl ester and 20 mg esomeprazole sodium

[0056] G. Naproxen 2(methanesulfonyl)ethyl ester and 40 mg esomeprazole sodium

[0057] H. Naproxen 2(methanesulfonyl)ethyl ester and 10 mg lansoprazole

[0058] I. Naproxen 2(methanesulfonyl)ethyl ester and 30 mg lansoprazole

[0059] J. Naproxen 2(methanesulfonyl)ethyl ester and 20 mg pantoprazole sodium

[0060] K. Naproxen 2(methanesulfonyl)ethyl ester and 40 mg pantoprazole sodium

[0061] L. Naproxen 2(methanesulfonyl)ethyl ester and 20 mg rabeprazole sodium

[0062] M. Naproxen 2(methanesulfonyl)ethyl ester and tenatoprazole

[0063] N. Naproxen 2(methanesulfonyl)ethyl ester and ilaprazole

[0064] Any one of the above compositions could be combined with one or more excipients.

J. CLAIMS

What is claimed is:

1. A method of treating arthritis, inflammation or pain comprising administering a patient naproxen 2(methanesulfonyl)ethyl ester and a proton pump inhibitor.

2. The method of claim 1, wherein said proton pump inhibitor is selected from omeprazole, esomeprazole, lansoprazole, rabeprazole, pantoprazole, tenatoprazole, and ilaprazole.

3. The method of claim 1, wherein said patient is a patient at risk for having an ulcer.

4. The method of claim 1, wherein said naproxen 2(methanesulfonyl)ethyl ester and said proton pump inhibitor are co-packaged together.

5. The method of claim 1, wherein said naproxen 2(methanesulfonyl)ethyl ester and said proton pump inhibitor are present in the same pharmaceutical composition.

6. The method of claim 5, wherein said pharmaceutical composition is a tablet.

7. The method of claim 1, wherein said arthritis is selected from the group consisting of rheumatoid arthritis and osteoarthritis.

8. A pharmaceutical composition comprising a therapeutically effective amount of naproxen 2(methanesulfonyl)ethyl ester, a therapeutically effective amount of a proton pump inhibitor and one or more excipients.

9. The pharmaceutical composition of claim 8, wherein said proton pump inhibitor is selected from omeprazole, esomeprazole, lansoprazole, rabeprazole, pantoprazole, tenatoprazole, and ilaprazole.

10. The pharmaceutical composition of claim 8, wherein said pharmaceutical composition is a tablet.

11. A method of treating inflammation or pain in a patient who has had a previous ulcer or gastrointestinal bleeding comprising administering said patient naproxen 2(methanesulfonyl)ethyl ester and a proton pump inhibitor.

12. The method of claim 11, wherein said proton pump inhibitor is selected from omeprazole, esomeprazole, lansoprazole, rabeprazole, pantoprazole, tenatoprazole, and ilaprazole.

13. The method of claim 11, wherein said patient is a patient at risk for having an ulcer.

14. The method of claim 11, wherein said naproxen 2(methanesulfonyl)ethyl ester and said proton pump inhibitor are co-packaged together.

15. The method of claim 11, wherein said naproxen 2(methanesulfonyl)ethyl ester and said proton pump inhibitor are present in the same pharmaceutical composition.

16. The method of claim 15, wherein said pharmaceutical composition is a tablet.

17. A method of treating inflammation or pain in a patient who has a factor for a high risk gastrointestinal complication comprising administering said patient naproxen 2(methanesulfonyl)ethyl ester and a proton pump inhibitor.

18. The method of claim 17, wherein said factor is an age of 60 or more years.

19. The method of claim 17, wherein said factor is concurrent treatment with aspirin or a corticosteroid.

20. A pharmaceutical formulation comprising naproxen 2(methanesulfonyl)ethyl ester and a proton pump inhibitor, wherein said proton pump inhibitor is separated from the 2(methanesulfonyl)ethyl ester by a layer of one or more excipients and wherein said pharmaceutical formulation is a tablet.

21. The tablet of claim 20, wherein said tablet is covered by an enteric coating.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/53932

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 38/00; A61K 39/08 (2008.04)
USPC - 514/12; 424/239.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 38/00; A61K 39/08 (2008.04)
USPC - 514/12; 424/239.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/12, 2; 424/239.1, 469, 451, 465; 435/252.3, 320.1, 325, 68.1

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(USPT,PGPB,EPAB,JPAB); Google Patents; Google Scholar
Search terms: naproxen, proton pump inhibitor, ulcer, arthritis, rheumatoid or osteoarthritis, tablet, layer, NSAID, aspirin, excipient, methanesulfonyl or methanesulfonate, blocking group, ethyl ester

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2005/0249806 A1 (PROEHL et al.) 10 November 2005 (10.11.2005) para [0012], [0016]-[0018], [0040], [0043], [0047]-[0048], [0053] and [0077].	1-7a and 7b-20
Y	LOOKER, Utility of the Methanesulfonyl Blocking Group: II Synthesis of Isovanillic Acid and Methanesulfonyl Derivatives of Phenolic Acids, Journal of Organic Chemistry, August 1959, Vol 24, No 8, pp 1039-1041 (p 1039, para 1-2).	1-7a and 7b-20

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 May 2008 (24.05.2008)	27 JUN 2008
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2007)

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 January 2009 (22.01.2009)

PCT

(10) International Publication Number
WO 2009/012393 A1

(51) International Patent Classification:
A01N 43/40 (2006.01) *A61K 31/44* (2006.01)

(21) International Application Number:
PCT/US2008/070343

(22) International Filing Date: 17 July 2008 (17.07.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/950,549 18 July 2007 (18.07.2007) US

(71) Applicant *(for all designated States except US)*: **THE CURATORS OF THE UNIVERSITY OF MISSOURI** [US/US]; 227 University Hall, Columbia, MO 65211 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **PHILLIPS, Jeffrey, O.** [US/US]; 1250 E. Nashville Church Road, Ashland, MO 65010 (US).

(74) Agent: **MAHONEY, Joseph, A.**; Mayer Brown LLP, P.O. Box 2828, Chicago, IL 60690-2828 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

WO 2009/012393 A1

(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING A PROTON PUMP INHIBITOR AND PROTEIN COMPONENT

(57) Abstract: The present disclosure relates to, *inter alia*, pharmaceutical compositions comprising a H^+,K^+-ATPase proton pump inhibitor and a protein component; to methods for manufacture of such compositions, and to use of such compositions in treating and preventing diseases and/or disorders.

TITLE

PHARMACEUTICAL COMPOSITION COMPRISING A PROTON PUMP INHIBITOR AND PROTEIN COMPONENT

FIELD OF THE INVENTION

The present invention relates to, *inter alia*, pharmaceutical compositions comprising a H^+,K^+-ATPase proton pump inhibitor and a protein component; to methods for manufacture of such compositions, and to use of such compositions in treating and preventing diseases and disorders.

BACKGROUND

Gastrointestinal disorders such as active duodenal ulcers, gastric ulcers, gastroesophageal reflux disease (GERD), severe erosive esophagitis, poorly responsive symptomatic GERD, nocturnal acid breakthrough (NAB), and pathological hypersecretory conditions such as Zollinger Ellison syndrome represent a major health concern impacting millions of people globally. In fact, it is estimated that as many as 60 million Americans alone experience acid reflux at least once a month, while approximately 19 million Americans suffer from GERD.

In the past, the above-described (and other related) gastrointestinal disorders and their associated symptoms have been treated with H_2 histamine antagonists and antacids. Unfortunately, many such available treatments are not very effective in ameliorating the disorders themselves or their symptoms; additionally, many produce adverse side effects including, among others, constipation, diarrhea and thrombocytopenia. Moreover, H_2 antagonists such as ranitidine and cimetidine are relatively costly modes of therapy.

More recently, at least some of the above-described gastrointestinal disorders have been treated with proton pump inhibitors (also called PPIs). PPIs are believed to reduce gastric acid production by inhibiting H^+,K^+-ATPase of the parietal cell—the final common pathway for gastric acid secretion. One particular class of PPIs includes substituted benzimidazole compounds that contain a sulfinyl group bridging substituted benzimidazole and pyridine rings. Another class of PPIs includes imidazopyridine compounds.

At neutral pH, these PPIs are chemically stable, lipid-soluble compounds that have little or no inhibitory activity. It is believed that the neutral PPIs reach parietal cells from the blood and diffuse into the secretory canaliculi where they

become protonated and thereby trapped. The protonated agent is then believed to rearrange to form a sulfenic acid and a sulfenamide. The sulfenamide, in turn, is thought to interact covalently with sulfhydryl groups at critical sites in the extracellular (luminal) domain of the membrane-spanning H^+,K^+-ATPase. *See,* Hardman *et al.*, Goodman & Gilman's The Pharmacological Basis of Therapeutics, p. 907, 9th ed. (1996).

Unfortunately, most commercially available proton pump inhibiting compounds are unstable at neutral or acidic pH and undergo decomposition in gastrointestinal fluid upon oral administration, thereby resulting in loss of therapeutic activity. To overcome this acid instability, such compounds are typically formulated for oral delivery as enteric coated solid dosage forms, for example enteric coated tablets, in which coating protects the drug from contact with acidic stomach secretions. An undesirable consequence of such enteric coating is that therapeutic onset time is significantly delayed by comparison with non-enteric coated dosage forms. Such prolonged time to therapeutic onset is particularly undesirable for patients in need of rapid relief from one or more of the above described disorders or symptoms.

For example, U.S. Patent No. 4,786,505 to Lovgren *et al.* discloses that a pharmaceutical oral solid dosage form of omeprazole must be protected from contact with acidic gastric juice by an enteric coating to maintain its pharmaceutical activity. That patent describes an enteric coated omeprazole preparation containing an alkaline core comprising omeprazole, a subcoating over the core, and an enteric coating over the subcoating.

More recently, a product containing non-enteric coated PPI has become available in the United States. Zegerid® contains, *inter alia*, 20 or 40 mg of omeprazole powder and 1680 mgs of sodium bicarbonate. It would be desirable to have additional formulations of PPI that overcome at least some of the above described drawbacks associated with enteric coated dosage forms.

SUMMARY

In one embodiment, the present disclosure provides a pharmaceutical composition comprising at least one acid labile, H^+,K^+-ATPase proton pump inhibitor and a protein component.

In one embodiment, the present disclosure provides a pharmaceutical composition comprising at least one acid labile, H^+,K^+-ATPase proton pump inhibitor, at least one buffering agent and a protein component.

In another embodiment, the present disclosure provides a pharmaceutical composition comprising at least one acid labile, H^+,K^+-ATPase proton pump inhibitor and L-carnosine.

In yet another embodiment, the present disclosure provides a pharmaceutical composition comprising at least one acid labile, H^+,K^+-ATPase proton pump inhibitor, at least one buffering agent and L-carnosine.

In yet another embodiment, the present disclosure provides a pharmaceutical composition comprising at least one acid labile, H^+,K^+-ATPase proton pump inhibitor, sodium bicarbonate and L-carnosine.

Also disclosed herein are methods of treating acid related gastrointestinal disorders by administering to a subject one or more compositions described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a line graph illustrating the affect on pH of 800 mg of L-carnosine, 800 mg sodium bicarbonate and 40 mg omeprazole (20:1 ratio of L-carnosine to omeprazole and sodium bicarbonate to omeprazole).

Figure 2 is a line graph illustrating the degradation of 40 mg omeprazole when it is administered with 800 mg of L-carnosine and 800 mg sodium bicarbonate (20:1 ratio of L-carnosine to omeprazole and sodium bicarbonate to omeprazole).

Figure 3 is a line graph illustrating the effect on pH of 1600 mg sodium bicarbonate and 40 mg omeprazole (40:1 ratio).

Figure 4 is a line graph illustrating the degradation of 40 mg omeprazole when it is administered with 1600 mg sodium bicarbonate (40:1 ratio).

Figure 5 is a line graph illustrating the affect on pH of 800 mg of aluminum glycinate, 800 mg sodium bicarbonate and 40 mg omeprazole (20:1 ratio of aluminum glycinate to omeprazole and sodium bicarbonate to omeprazole).

Figure 6 is a line graph illustrating the degradation of 40 mg omeprazole when it is administered with 800 mg of aluminum glycinate and 800 mg sodium bicarbonate (20:1 ratio of aluminum glycinate to omeprazole and sodium bicarbonate to omeprazole).

DETAILED DESCRIPTION

While the present invention is capable of being embodied in various forms, the description below of several embodiments is made with the understanding that the present disclosure is to be considered as an exemplification of the invention, and is not intended to limit the invention to the specific embodiments illustrated. Headings are provided for convenience only and are not to be construed to limit the invention in any way. Embodiments illustrated under any heading may be combined with embodiments illustrated under any other heading.

It has been surprisingly found that a pharmaceutical composition comprising at least one acid labile, H^+,K^+-ATPase proton pump inhibitor ("PPI"), at least one buffering agent and a protein component prevents immediate degradation of the PPI by stomach acid. *See* Figures 1 and 2.

It has also been surprisingly found that a pharmaceutical composition comprising at least one acid labile, H^+,K^+-ATPase proton pump inhibitor ("PPI"), L-carnosine and sodium bicarbonate prevents immediate degradation of the PPI by stomach acid. *See* Figures 1 and 2.

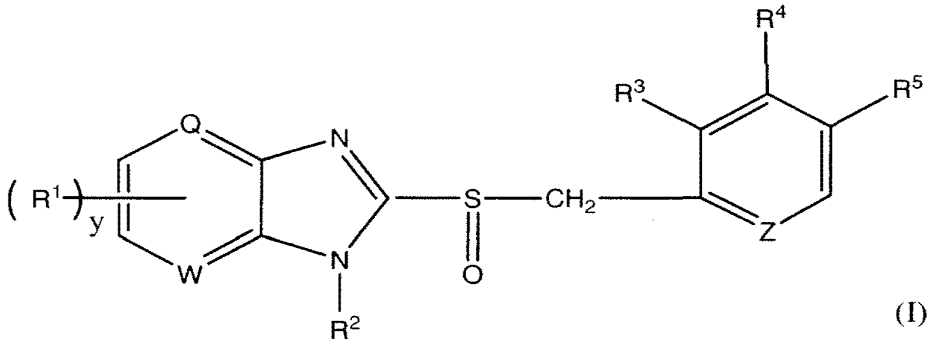
It has further been surprisingly found that a pharmaceutical composition comprising at least one PPI, sodium bicarbonate and L-carnosine, wherein the ratio of sodium bicarbonate to PPI and the ratio of L-carnosine to PPI is about 20 to about 1, prevents immediate degradation of the PPI. *See* Figures 1 and 2.

Proton Pump Inhibitors

Compositions of the disclosure comprise at least one pharmaceutically acceptable acid labile, H^+,K^+-ATPase proton pump inhibitor ("PPI"). The term proton pump inhibitor or PPI means any acid labile pharmaceutical agent possessing pharmacological activity as an inhibitor of H^+,K^+-ATPase. A PPI may, if desired, be in the form of free base, free acid, salt, ester, hydrate, anhydrate, amide, enantiomer, isomer, tautomer, prodrug, polymorph, derivative, or the like, provided that the free base, salt, ester, hydrate, amide, enantiomer, isomer,

tautomer, prodrug, or any other pharmacologically suitable derivative is therapeutically active or undergoes conversion within or outside of the body to a therapeutically active form.

In one embodiment, illustrative PPIs are those compounds of Formula (I):



(I)

wherein

R^1 is hydrogen, alkyl, halogen, cyano, carboxy, carboalkoxy, carboalkoxyalkyl, carbamoyl, carbamoylalkyl, hydroxy, alkoxy which is optionally fluorinated, hydroxyalkyl, trifluoromethyl, acyl, carbamoyloxy, nitro, acyloxy, aryl, aryloxy, alkylthio, or alkylsulfinyl;

R^2 is hydrogen, alkyl, acyl, acyloxy, alkoxy, amino, aralkyl, carboalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, alkylcarbonylmethyl, alkoxycarbonylmethyl, or alkylsulfonyl;

R^3 and R^5 are the same or different and each is hydrogen, alkyl, C_{1-4} lower alkyl (*e.g.* methyl, ethyl, *etc.*), alkoxy, amino, or alkoxyalkoxy;

R^4 is hydrogen, alkyl, C_{1-4} lower alkyl (*e.g.* methyl, ethyl, *etc.*), alkoxy which may optionally be fluorinated, or alkoxyalkoxy;

Q is nitrogen, CH, or CR^1;

W is nitrogen, CH, or CR^1;

y is an integer of 0 through 4; and

Z is nitrogen, CH, or CR^1;

or a free base, salt, ester, hydrate, amide, enantiomer, isomer, tautomer, prodrug, polymorph, or derivative thereof.

Specific examples of suitable PPIs include esomeprazole (also referred to as S-omeprazole), ilaprazole (U.S. Pat. No. 5,703,097), lansoprazole, omeprazole, pantoprazole, pariprazole, rabeprazole, tenatoprazole, leminoprazole and nepaprazole or a free base, a free acid, or a salt, hydrate, ester, amide, enantiomer, isomer, tautomer, polymorph, prodrug, or derivative of such compounds.

Other proton pump inhibitors include but are not limited to: soraprazan (Altana); AZD-0865 (AstraZeneca); YH-1885 (PCT Publication WO 96/05177) (SB-641257) (2-pyrimidinamine, 4-(3,4-dihydro-1-methyl-2(1H)-isoquinolinyl)-N-(4-fluo- rophenyl)-5,6-dimethyl-monohydrochloride) (YuHan); BY-112 (Altana); SPI-447 (Imidazo(1,2-a)thieno(3,2-c)pyridin-3-amine,5-methyl-2-(2-methyl-3-thieny- l) (Shinnippon); 3-hydroxymethyl-2methyl-9-phenyl-7H-8,9-dihydro-pyrano(2,- 3-c)-imidazo(1,2-a)pyridine (PCT Publication WO 95/27714) (AstraZeneca); Pharmaprojects No. 4950 (3-hydroxymethyl-2-methyl-9-phenyl-7H-8,9-dihydro- -pyrano(2,3-c)-imidazo(1,2-a)pyridine) (AstraZeneca, ceased) WO 95/27714; Pharmaprojects No. 4891 (EP 700899) (Aventis); Pharmaprojects No. 4697 (PCT Publication WO 95/32959) (AstraZeneca); H-335/25 (AstraZeneca); T-330 (Saitama 335) (Pharmacological Research Lab); Pharmaprojects No. 3177 (Roche); BY-574 (Altana); Pharmaprojects No. 2870 (Pfizer); AU-1421 (EP 264883) (Merck); AU-2064 (Merck); AY-28200 (Wyeth); Pharmaprojects No. 2126 (Aventis); WY-26769 (Wyeth); pumaprazole (PCT Publication WO 96/05199) (Altana); YH-1238 (YuHan); Pharmaprojects No. 5648 (PCT Publication WO 97/32854) (Dainippon); BY-686 (Altana); YM-020 (Yamanouchi); GYKI-34655 (Ivax); FPL-65372 (Aventis); Pharmaprojects No. 3264 (EP 509974) (AstraZeneca); nepaprazole (To a Eiyo); HN-11203 (Nycomed Pharma); OPC-22575; pumilacidin A (BMS); saviprazole (EP 234485) (Aventis); SKand F-95601 (GSK, discontinued); Pharmaprojects No. 2522 (EP 204215) (Pfizer); S-3337 (Aventis); RS-13232A (Roche); AU-1363 (Merck); SKand F-96067 (EP 259174) (Altana); SUN 8176 (Daiichi Phama); Ro-18-5362 (Roche); ufiprazole (EP 74341) (AstraZeneca); and Bay-p-1455 (Bayer); or a free base, free acid, salt, hydrate, ester, amide, enantiomer, isomer, tautomer, polymorph, prodrug, or derivative of these compounds.

Still other embodiments contemplated by the present disclosure include, but are not limited to those described in the following U.S. Pat. Nos.: 4,628,098; 4,689,333; 4,786,505; 4,853,230; 4,965,269; 5,021,433; 5,026,560; 5,045,321; 5,093,132; 5,430,042; 5,433,959; 5,576,025; 5,639,478; 5,703,110; 5,705,517; 5,708,017; 5,731,006; 5,824,339; 5,840,737; 5,855,914; 5,879,708; 5,948,773; 6,017,560; 6,123,962; 6,187,340; 6,296,875; 6,319,904; 6,328,994; 4,255,431; 4,508,905; 4,636,499; 4,738,974; 5,690,960; 5,714,504; 5,753,265; 5,817,338;

6,093,734; 6,013,281; 6,136,344; 6,183,776; 6,328,994; 6,479,075; 6,489,346; 6,559,167; 6,645,988; 6,699,885; 7,101,573; 7,109,161.

Still other embodiments contemplated by the present disclosure include, but are not limited to those described in the following: EP 0254588; EP 0005129.

Other embodiments contemplated by the present disclosure include, but are not limited to those described in the following PCT Publications: WO 94/27988; WO 05/044223; WO 06/043280.

Still other embodiments contemplated by the present disclosure include, but are not limited to those described in the following U.S. Application Nos.: 20020192299; 20040131675; 20040146554; 20040248939; 20040248942; 20050003005; 20050031700; 20050037070; 20050054682; 20050112193; 20050220870; 20050222210; 20050239845; 20050244517; 20050249806; 20050249811; 20050266071; 20050288334; 20050277672; 20050277673; 20050277671; 20060024238; 20060134210; 20060147522; 20060159760; 20060167262; 20060173045; 20060204585.

The foregoing lists of suitable acid inhibitors are meant to be illustrative and not exhaustive as a person of ordinary skill in the art would recognize that there are many other suitable acid inhibitors which could be created.

Gastric acid inhibitors, including proton pump inhibitors as well as their salts, hydrates, esters, amides, enantiomers, isomers, tautomers, polymorphs, prodrugs, and derivatives may be prepared using standard procedures that a person of ordinary skill in the art of synthetic organic chemistry would recognize. See, *e.g.*, March, Advanced Organic Chemistry: Reactions, Mechanisms and Structure, 4th Ed. (New York: Wiley-Interscience, 1992); Leonard *et al.*, Advanced Practical Organic Chemistry (1992); Howarth et al., Core Organic Chemistry (1998); and Weisermel et al., Industrial Organic Chemistry (2002).

"Pharmaceutically acceptable salts," or "salts," include the salt of a proton pump inhibitor prepared from formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, stearic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic, methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, cyclohexylaminosulfonic, algenic, beta.-hydroxybutyric, galactaric and galacturonic acids.

In one embodiment, acid addition salts are prepared from the free base forms using conventional methodology involving reaction of the free base with a suitable acid. Suitable acids for preparing acid addition salts include both organic acids, *e.g.*, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like, as well as inorganic acids, *e.g.*, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like.

In other embodiments, an acid addition salt is reconverted to the free base by treatment with a suitable base. In a further embodiment, the acid addition salts of the proton pump inhibitors are halide salts, which are prepared using hydrochloric or hydrobromic acids. In still other embodiments, the basic salts are alkali metal salts, *e.g.*, sodium salt.

Salt forms of proton pump inhibitors include, but are not limited to: a sodium salt form such as esomeprazole sodium, omeprazole sodium, rabeprazole sodium, pantoprazole sodium; or a magnesium salt form such as esomeprazole magnesium or omeprazole magnesium, described in U.S. Pat. No. 5,900,424; a calcium salt form; or a potassium salt form such as the potassium salt of esomeprazole, described in U.S. Pat. No. 6,511,996; salt hydrate forms including but not limited to sodium hydrate salt forms, for example tenatoprazole sodium hydrate or omeprazole sodium hydrate. Other salts of esomeprazole are described in U.S. Pat. Nos.: 4,738,974 and 6,369,085. Salt forms of pantoprazole and lansoprazole are discussed in U.S. Pat. Nos. 4,758,579 and 4,628,098, respectively.

The foregoing list of suitable salts of proton pump inhibitors is meant to be illustrative and not exhaustive as a person of ordinary skill in the art would recognize that other pharmaceutically acceptable salts of a proton pump inhibitor could be created.

In one embodiment, preparation of esters involves functionalizing hydroxyl and/or carboxyl groups that may be present within the molecular structure of the drug. In another embodiment, the esters are acyl-substituted derivatives of free alcohol groups, *e.g.*, moieties derived from carboxylic acids of the formula $RCOOR_1$ where$_1$ is a lower alkyl group. Esters can be reconverted to the free acids, if desired, by using conventional procedures such as hydrogenolysis or hydrolysis.

"Amides" may be prepared using techniques known to those skilled in the art or described in the pertinent literature. For example, amides may be prepared from esters, using suitable amine reactants, or they may be prepared from an anhydride or an acid chloride by reaction with an amine group such as ammonia or a lower alkyl amine.

"Tautomers" of substituted bicyclic aryl-imidazoles include, *e.g.*, tautomers of omeprazole such as those described in U.S. Pat. Nos. 6,262,085; 6,262,086; 6,268,385; 6,312,723; 6,316,020; 6,326,384; 6,369,087; and 6,444,689.

An exemplary "isomer" of a substituted bicyclic aryl-imidazole is the isomer of omeprazole including but not limited to isomers described in: Oishi *et al.*, Acta Cryst (1989), C45, 1921-1923; U.S. Pat. No. 6,150,380; U.S. Patent Publication No. 02/0156284; and PCT Publication No. WO 02/085889.

Exemplary "polymorphs" include, but are not limited to, those described in PCT Publication No. WO 92/08716, and U.S. Pat. Nos. 4,045,563; 4,182,766; 4,508,905; 4,628,098; 4,636,499; 4,689,333; 4,758,579; 4,783,974; 4,786,505; 4,808,596; 4,853,230; 5,026,560; 5,013,743; 5,035,899; 5,045,321; 5,045,552; 5,093,132; 5,093,342; 5,433,959; 5,464,632; 5,536,735; 5,576,025; 5,599,794; 5,629,305; 5,639,478; 5,690,960; 5,703,110; 5,705,517; 5,714,504; 5,731,006; 5,879,708; 5,900,424; 5,948,773; 5,997,903; 6,017,560; 6,123,962; 6,147,103; 6,150,380; 6,166,213; 6,191,148; 5,187,340; 6,268,385; 6,262,086; 6,262,085; 6,296,875; 6,316,020; 6,328,994; 6,326,384; 6,369,085; 6,369,087; 6,380,234; 6,428,810; 6,444,689; and 6,462,0577.

In one embodiment, at least one proton pump inhibitor is not enteric coated. In another embodiment, a portion of at least one proton pump inhibitor is optionally enteric coated. In one embodiment, no portion of the proton pump inhibitor is enteric coated. In another embodiment, a therapeutically effective portion of at least one proton pump inhibitor is optionally enteric coated. In another embodiment, about 5%, about 15%, about 20%, about 30%, about 40%, about 50% or about 60% of at least one proton pump inhibitor is optionally enteric coated. In another embodiment, a portion of at least one proton pump inhibitor comprises a "thin enteric coat." The term "thin enteric coat" herein refers to a pH sensitive coating that is applied in a manner or amount such that it delays release of the coated substance in gastrointestinal fluid for a period of time, but ultimately allows release of some of the coated substance prior to passage into the duodenum.

In one embodiment, the proton pump inhibitor has a D_{90}, D_{80}, D_{70} or D_{50} particle size, by weight or by number, of less than about 500 μm, less than about 400 μm , less than about 300 μm, less than about 200 μm, less than about 150 μm, less than about 100 μm, less than about 80 μm, less than about 60 μm, less than about 40 μm, less than about 35 μm, less than about 30 μm, less than about 25 μm, less than about 20 μm, less than about 15 μm, or less than about 10 μm.

In another embodiment, compositions are provided wherein the micronized proton pump inhibitor is of a size which allows greater than about 90% or greater than about 75% of the proton pump inhibitor to be released from the dosage unit within about 1 hour, within about 50 minutes, within about 40 minutes, within about 30 minutes, within about 20 minutes, within about 10 minutes, or within about 5 minutes after placement in a standard dissolution test.

In another embodiment, compositions disclosed herein comprise one or more PPIs in a total amount of about 1 mg to about 3000 mg, about 1 mg to about 2000 mg, about 1 mg to about 1000 mg, about 5 mg to about 750 mg, about 5 mg to about 500 mg, about 5 mg to about 250 mg, about 5 mg to about 100 mg, about 5 mg to about 100 mg, or about 5 mg to about 50 mg, for example about 5 mg, about 7.5 mg, about 10 mg, about 15mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, or about 80 mg.

Compositions of the disclosure can be in the form of an orally deliverable dosage unit. The terms "oral administration" or "orally deliverable" herein include any form of delivery of a therapeutic agent or a composition thereof to a subject wherein the agent or composition is placed in the mouth of the subject, whether or not the agent or composition is swallowed. Thus "oral administration" includes buccal and sublingual as well as esophageal administration.

Protein Component

Compositions disclosed herein comprise a protein component. The term "protein component" as used herein includes protein isolates, hydrolyzed proteins (protein hydrolysates) as well as protein concentrates. Also included within the definition of a protein component are peptone, tryptone, and peptides. A non-limiting example of a protein is lactoferrin. The term "protein component" does

not embrace individual amino acids but can include peptides such as the dipeptide carnosine.

Compositions of the disclosure optionally comprise one or more of a protein isolate, a protein hydrolysate, a protein concentrate, peptone, tryptone, and/or peptides. A suitable protein component can be derived from any origin including plants, animals, or a combination thereof. Non-limiting examples of suitable sources of protein component include soy, corn, whey, egg, casein, fish, meat, poultry *etc*.

Protein isolate typically comprises at least about 85%, for example about 85 – 95% protein on a dry basis. Suitable protein isolates can be prepared using any suitable procedure, for example by using an alcohol wash, water wash or ionization concentration techniques that separate at least a portion of carbohydrates and fats from the protein itself.

Protein concentrate typically comprises about 50% to about 85% protein on a dry basis, for example about 60 to about 85%. Protein concentrate can be prepared using any suitable process, for example by concentrating the desired protein through high heat drying (dehydration), acid extraction or filtration to reduce the original source to a more concentrated protein.

Protein hydrolysates are protein molecules that have been lysed, typically but not exclusively with water, into smaller peptides. Protein isolates suitable for the disclosure include substantially pure protein isolate or protein isolate formulations, for example liquid or powder formulations. Non-limiting examples of powder protein hydrolysate formulations include Alimentum, Nutramigen, and Pregestimil.

In one embodiment, compositions of the disclosure comprise a protein component in a total amount of about 1% to about 95%, about 5% to about 90%, or about 10% to about 85%, or about 15% to about 80%, or about 20% to about 75%, or about 25% to about 70%, or about 30% to about 65%, or about 40% to about 60%, on a dry weight basis in the composition, for example, about 1%, about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%.

In another embodiment, compositions of the disclosure comprise a protein component in a total amount of about 1 mg to about 100 g, about 1 mg to about 20 g, about 1 mg to about 10 g, about 5 mg to about 5 g, about 10 mg to about 2.5 g,

about 10 mg to about 1.0 g, or about 10 mg to about 0.5 g on a dry weight basis, for example, about 1 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1 g, about 1.2 g, about 1.3 g, about 1.4 g, about 1.5 g, about 1.6 g, about 1.7 g, about 1.8 g, about 1.9 g, about 2 g, about 2.1 g, about 2.2 g, about 2.3 g, about 2.4 g, about 2.5 g, about 2.6 g, about 2.7 g, about 2.8 g, about 2.9 g, about 3 g, about 3.5 g, about 4 g, about 4.5 g, about 5 g.

In another embodiment, the weight ratio of PPI to protein component, on a dry basis, is about 0.001 to about 1, about 0.0025 to about 0.5, or about 0.1 to about 0.05.

In another embodiment of the disclosure, the protein component has a Protein Digestibility-Corrected Amino Acid Score (PDCAAS) of at least about 0.68, at least about 0.75, at least about 0.80 at least about 0.85, at least about 0.90, at least about 0.92, at least about 0.95, at least about 0.98, or about 1.

In another embodiment of the disclosure, the protein component has a PDCAAS of about 0.68 to about 1, about 0.75 to about 1, about 0.80 to about 1, about 0.90 to about 1, about 0. 92 to about 1 or about 0.95 to about 1.

Without being bound by theory, it is presently believed that upon administration of a composition of the disclosure to a subject, the protein component sacrificially combines with available hydrogen ion (in the GI tract) thereby preventing, slowing or delaying acid-related degradation of the PPI. In another embodiment, therefore, upon administration of a composition of the disclosure to a human subject, the PPI undergoes reduced gastrointestinal degradation by comparison with administration of PPI alone. This can be

determined by any suitable method, for example by sampling and assaying contents of the subjects stomach at various time points after ingestion of a composition of the disclosure or a comparative PPI composition comprising no protein component (*e.g.* naked PPI).

In one embodiment, a composition of the disclosure comprises L-carnosine. Still another embodiment of the disclosure comprises L-carnosine in a ratio of greater than about 20 parts L-carnosine to about 1 part PPI. Other embodiments comprise L-carnosine and PPI in an amount of about 20:1, about 25:1, about 30:1, about 35:1, about 40:1, about 45:1, or about 50:1.

In another embodiment, a composition of the disclosure does not contain an alkali earth metal buffering agent. In still another embodiment, a composition of the disclosure does not contain an alkaline earth metal buffering agent. In another embodiment, a composition of the disclosure does not contain aluminum and/or aluminum glycinate. As illustrated by Figures 5 and 6, adding aluminum glycinate to a sodium bicarbonate and omeprazole causes immediate degradation of the omeprazole, as opposed to the degradation of omeprazole when sodium bicarbonate and omeprazole are used alone. *See* Figures 3 and 4.

Other embodiments of the disclosure comprises a PPI, at least one buffering agent in an amount of about 20 parts to about 1 part PPI, and a protein component in an amount of about 20 parts to about 1 part PPI. For example, an embodiment of the disclosure comprises tenatoprazole, sodium bicarbonate in an amount of about 20 parts to about 1 part tenatoprazole, and L-carnosine in an amount of about 20 parts to about 1 part tenatoprazole. Another embodiment of the disclosure comprises about 40 mg tenatoprazole, about 1600 mg sodium bicarbonate, and about 1600 mg L-carnosine. Still another embodiment of the disclosure comprises about 40 mg tenatoprazole, about 1600 mg sodium bicarbonate and magnesium hydroxide, and about 1600 mg L-carnosine. Yet another embodiment of the disclosure comprises about 40 mg omeprazole, about 1600 mg sodium bicarbonate and magnesium hydroxide, and about 1600 mg L-carnosine.

Other embodiments of the disclosure comprise omeprazole, sodium bicarbonate in an amount of about 20 parts to about 1 part omeprazole, and L-carnosine in an amount of about 20 parts to about 1 part omeprazole. For example,

an embodiment of the disclosure comprises about 40 mg omeprazole, about 1600 mg sodium bicarbonate, and about 1600 mg L-carnosine.

The foregoing list of suitable protein components is meant to be illustrative and not exhaustive as a person of ordinary skill in the art would recognize that other pharmaceutically acceptable protein components could be created.

Buffering Agent

Compositions of the disclosure comprise one or more pharmaceutically acceptable buffering agents. Buffering agents useful in the present disclosure include agents possessing pharmacological activity as a weak or strong base. In one embodiment, the buffering agent, when formulated with or administered substantially simultaneously with a PPI, functions to raise the pH of gastrointestinal fluid and thereby to substantially prevent or inhibit acid degradation of the PPI by gastrointestinal fluid for a period of time.

In another embodiment, buffering agents useful in accordance with the present disclosure comprise, but are not limited to, a salt of a Group IA metal including, for example, a bicarbonate salt of a Group IA metal, a carbonate salt of a Group IA metal, an alkaline earth metal buffering agent, an aluminum buffering agent, a calcium buffering agent, a sodium buffering agent, or a magnesium buffering agent. Other suitable buffering agents include alkali (sodium and potassium) or alkaline earth (calcium and magnesium) carbonates, phosphates, bicarbonates, citrates, borates, acetates, phthalates, tartrates, succinates and the like, such as sodium or potassium phosphate, citrate, borate, acetate, bicarbonate and carbonate.

Non-limiting examples of suitable buffering agents include aluminum, magnesium hydroxide, aluminum hydroxide/magnesium hydroxide co-precipitate, calcium acetate, calcium bicarbonate, calcium borate, calcium carbonate, calcium bicarbonate, calcium citrate, calcium gluconate, calcium glycerophosphate, calcium hydroxide, calcium lactate, calcium phthalate, calcium phosphate, calcium succinate, calcium tartrate, dibasic sodium phosphate, dipotassium hydrogen phosphate, dipotassium phosphate, disodium hydrogen phosphate, disodium succinate, dry aluminum hydroxide gel, magnesium acetate, magnesium aluminate, magnesium borate, magnesium bicarbonate, magnesium carbonate, magnesium citrate, magnesium gluconate, magnesium hydroxide, magnesium lactate, magnesium metasilicate aluminate, magnesium oxide, magnesium phthalate,

magnesium phosphate, magnesium silicate, magnesium succinate, magnesium tartrate, potassium acetate, potassium carbonate, potassium bicarbonate, potassium borate, potassium citrate, potassium metaphosphate, potassium phthalate, potassium phosphate, potassium polyphosphate, potassium pyrophosphate, potassium succinate, potassium tartrate, sodium acetate, sodium bicarbonate, sodium borate, sodium carbonate, sodium citrate, sodium gluconate, sodium hydrogen phosphate, sodium hydroxide, sodium lactate, sodium phthalate, sodium phosphate, sodium polyphosphate, sodium pyrophosphate, sodium sesquicarbonate, sodium succinate, sodium tartrate, sodium tripolyphosphate, synthetic hydrotalcite, tetrapotassium pyrophosphate, tetrasodium pyrophosphate, tripotassium phosphate, trisodium phosphate, and trometarnol. (Based in part upon the list provided in The Merck Index, Merck & Co. Rahway, N.J. (2001)). In addition, due to the ability of the protein component to react with stomach acids, they too can serve as buffering agents in the present embodiments. Furthermore, combinations or mixtures of the above mentioned buffering agents can be used in the pharmaceutical formulations described herein.

Buffering agents also include buffering agents or combinations of buffering agents that interact with HCl (or other acids in the environment of interest) faster than the proton pump inhibitor interacts with the same acids. When placed in a liquid phase such as water, these buffering agents produce and maintain a pH greater than the pKa of the proton pump inhibitor.

The foregoing list of suitable buffering agents is meant to be illustrative and not exhaustive as a person of ordinary skill in the art would recognize that other pharmaceutically acceptable buffering agents could be created.

In various other embodiments, the buffering agent is present in a total amount of about 0.1 mEq/mg to about 5 mEq/mg of the proton pump inhibitor, about 0.5 mEq/mg to about 3 mEq/mg of the proton pump inhibitor, about 0.6 mEq/mg to about 2.5 mEq/mg of the proton pump inhibitor, about 0.7 mEq/mg to about 2.0 mEq/mg of the proton pump inhibitor, about 0.8 mEq/mg to about 1.8 mEq/mg of the proton pump inhibitor, about 1.0 mEq/mg to about 1.5 mEq/mg of the proton pump inhibitor. In another embodiment, the buffering agent is present in an amount of about 0.5 mEq/mg of the proton pump inhibitor, about 0.75 mEq/mg of the proton pump inhibitor, or about 1 mEq/mg of the proton pump inhibitor on a dry weight basis.

In still another embodiment, one or more buffering agents are present in a total amount of about 0.5 mEq to about 160 mEq, about 1 mEq to about 150 mEq, about 10 mEq to about 150 mEq, about 10 mEq to about 75 mEq, about 10 mEq to about 60 mEq, or about 10 mEq to about 50 mEq. Illustratively, a composition of the disclosure can comprise about 1 mEq, about 5 mEq, about 10 mEq, about 15 mEq, about 20 mEq, about 25 mEq, about 30 mEq, about 35 mEq, about 40 mEq, about 45 mEq, about 50 mEq, about 60 mEq, about 70 mEq, about 80 mEq, about 90 mEq, about 100 mEq, about 110 mEq, about 120 mEq, about 130 mEq, about 140 mEq, about 150 mEq, or about 160 mEq of buffering agent.

In yet another embodiment, one or more buffering agents are present in a total amount of about 10 mEq, about 11 mEq, about 12 mEq, about 13 mEq, about 14 mEq, about 15 mEq, or at least about 16 mEq.

In another embodiment, one or more buffering agents and the mixture of the first and subsequent proton pump inhibitors or the salt form of a proton pump inhibitor and the free base form of a proton pump inhibitor are present in a weight ratio of about 5:1, about 7:1, about 10:1, about 20:1, greater than about 20:1, about 21:1, about 22:1, about 23:1, about 25:1, about 30:1, about 35:1, about 40:1, greater than about 40:1, about 45:1, about 53:3; about 11:1, about 28:3, about 28:5, about 23:3, about 26:1, about 27:2, or about 31:1.

In still another embodiment, a first PPI ("PPI1"), a second PPI ("PPI2"), and one or more buffering agents are present in a weight ratio of about 2:1:50, about 3:2:50, about 2:1:25, about 2:1:60, about 3:2:25, about 2:1:20, about 1:1:50, about 1:2:50, about 1:1:25, about 1:1:60, about 1:2:25, or about 1:1:20.

In yet another embodiment, the salt form of a proton pump inhibitor ("PPI-salt"), the free base form of a proton pump inhibitor ("PPI-base"), and one or more buffering agents are present in a weight ratio of about 2:1:50, about 3:2:50, about 2:1:25, about 2:1:60, about 3:2:25, about 2:1:20, about 1:1:50, about 1:2:50, about 1:1:25, about 1:1:60, about 1:2:25, or about 1:1:20.

In another embodiment, the amount of buffering agent present in a composition of the disclosure ranges from about 200 to about 3500 mg, about 300 to about 3000 mg, about 400 to about 2500 mg, or about 500 to about 2200 mg, about 600 to about 2000, or about 700 to about 1800 mg. In other embodiments, the amount of buffering agent present in a composition of the disclosure is about 200 mgs, or about 300 mgs, or about 400 mgs, or about 500 mgs, or about 600

mgs, or about 700 mgs, or about 800 mgs, or about 900 mgs, or about 1000 mgs, or about 1100 mgs, or about 1200 mgs, or about 1300 mgs, or about 1400 mgs, or about 1500 mgs, or about 1600 mgs, or about 1700 mgs, or about 1800 mgs, or about 1900 mgs, or about 2000 mgs, or about 2100 mgs, or about 2200 mgs, or about 2300 mgs, or about 2400 mgs, or about 2500 mgs, or about 2600 mgs, or about 2700 mgs, or about 2800 mgs, or about 2900 mgs, or about 3000 mgs, or about 3200 mgs, or about 3500 mgs.

In another embodiment, one or more buffering agents are present in a composition of the disclosure in a total amount that is greater than 800 mg, for example about 920 mg or at least about 1000 mg.

In still another embodiment, the buffering agent and the mixture of PPI1 and PPI2 or PPI-salt and PPI-base (hereinafter "proton pump inhibitor mixture") are present in a weight ratio greater than 20:1, not less than about 21:1, not less than about 22:1, not less than about 23:1, not less than about 24:1, not less than about 25:1, not less than about 26:1, not less than about 27:1, not less than about 28:1, not less than about 29:1, not less than about 30:1, not less than about 31:1, not less than about 32:1, not less than about 33:1, not less than about 34:1, not less than about 35:1, not less than about 36:1, not less than about 37:1, not less than about 38:1, not less than about 39:1, not less than about 40:1, not less than about 41:1, not less than about 42:1, not less than about 43:1, not less than about 44:1, not less than about 45:1, not less than about 46:1, not less than about 47:1, not less than about 48:1, not less than about 49:1, not less than about 50:1, not less than about 53:3; not less than about 11:1, not less than about 28:3, not less than about 21:1, not less than about 28:5, not less than about 23:3, not less than about 26:1, not less than about 53:3, not less than about 27:2, or not less than about 31:1.

In yet another embodiment, PPI1, PPI2, and the one or more buffering agents are present in a weight ratio of about 2:1:50, about 3:2:50, about 2:1:25, about 2:1:60, about 3:2:25, about 2:1:20, about 1:1:50, about 1:2:50, about 1:1:25, about 1:1:60, about 1:2:25, or about 1:1:20.

In another embodiment, PPI-salt, PPI-base, and one or more buffering agents are present in a weight ratio of about 2:1:50, about 3:2:50, about 2:1:25, about 2:1:60, about 3:2:25, about 2:1:20, about 1:1:50, about 1:2:50, about 1:1:25, about 1:1:60, about 1:2:25, or about 1:1:20.

In yet another embodiment, a composition is provided that comprises a combination of at least two non-amino acid buffering agents, wherein the combination of at least two non-amino acid buffering agents comprises substantially no aluminum hydroxide-sodium bicarbonate co-precipitate. In a related embodiment, if such a composition comprises a poly[phosphoryl/sulfon]-ated carbohydrate, the weight ratio of poly[phosphoryl/sulfon]-ated carbohydrate to buffering agent is less than 1:5 (0.2), less than 1:10 (0.1) or less than 1:20 (0.05). Alternatively, the poly[phosphoryl/sulfon]-ated carbohydrate is present in the composition, if at all, in an amount less than 50 mg, less than 25 mg, less than 10 mg or less than 5 mg. In another embodiment, the composition contains no poly[phosphoryl/sulfon]-ated carbohydrate.

In another embodiment, a composition of the disclosure comprises at least one non-amino acid buffering agent wherein the non-amino acid buffering agent is present in the composition in a total amount greater than 800 mg. In a related embodiment, if such a composition comprises a poly[phosphoryl/sulfon]-ated carbohydrate, the weight ratio of poly[phosphoryl/sulfon]-ated carbohydrate to buffering agent is less than 1:5 (0.2), less than 1:10 (0.1) or less than 1:20 (0.05). Alternatively, the poly[phosphoryl/sulfon]-ated carbohydrate is present in the composition, if at all, in an amount less than 50 mg, less than 25 mg, less than 10 mg or less than 5 mg.

In other embodiments, where two or more buffering agents are present, the two or more buffering agents comprise at least two non-amino acid buffering agents, wherein the combination of at least two non-amino acid buffering agents comprises substantially no aluminum hydroxide-sodium bicarbonate co-precipitate.

In still another embodiment, the buffering agent comprises a mixture of sodium bicarbonate, calcium carbonate, and magnesium hydroxide, wherein the sodium bicarbonate, calcium carbonate, and magnesium hydroxide are each present in an amount of about 0.1 mEq/mg proton pump inhibitor mixture to about 5 mEq/mg of the proton pump inhibitor mixture.

In another embodiment, the buffering agent comprises a mixture of sodium bicarbonate, calcium carbonate, and magnesium hydroxide, wherein the sodium bicarbonate, calcium carbonate, and magnesium hydroxide are each present in an amount of about 0.1 mEq/mg proton pump inhibitor to about 5 mEq/mg of the either proton pump inhibitor.

Also provided herein are pharmaceutical compositions comprising at least one soluble buffering agent. The term "soluble buffering agent" as used herein refers to an antacid that has a solubility of at least about 500 mg/mL, or at least about 300 mg/mL, or at least about 200 mg/mL, or at least about 100 mg/mL in gastrointestinal fluid or simulated gastrointestinal fluid.

In some embodiments, the buffering agent has a defined particle size distribution. For example, in one embodiment, the D_{50}, D_{70}, D_{80}, or D_{90} particle size of the buffering agent, by weight or by number, is no greater than about 10 μm, is no greater than about 20 μm, no greater than about 30 μm, no greater than about 40 μm, no greater than about 50 μm, no greater than about 60 μm, no greater than about 70 μm, no greater than about 80 μm, no greater than about 90 μm, no greater than about 100 μm in diameter, no greater than about 200 μm in diameter, no greater than about 300 μm in diameter, no greater than about 400 μm in diameter, no greater than about 1000 μm in diameter, no greater than about 2000 μm in diameter, no greater than about 3000 μm in diameter, no greater than about 4000 μm in diameter, no greater than about 6000 μm in diameter, or no greater than about 9000 μm in diameter.

The foregoing list of suitable buffering agents is meant to be illustrative and not exhaustive as a person of ordinary skill in the art would recognize that other pharmaceutically acceptable buffering agents could be created.

Pharmaceutical Excipients

Various embodiments can, if desired, include one or more pharmaceutically acceptable excipients. The term "excipient" herein means any substance, not itself a therapeutic agent, used as a carrier or vehicle for delivery of a therapeutic agent to a subject or added to a pharmaceutical composition to improve its handling or storage properties or to permit or facilitate formation of a dose unit of the composition. Excipients include, by way of illustration and not limitation, diluents, disintegrants, binding agents, adhesives, wetting agents, lubricants, glidants, surface modifying agents, substances added to mask or counteract a disagreeable taste or odor, flavors, dyes, fragrances, and substances added to improve appearance of the composition. Any such excipients can be used in any dosage forms of according to the present disclosure, including liquid, solid or semi-solid dosage forms.

Excipients optionally employed in compositions disclosed herein can be solids, semi-solids, liquids or combinations thereof. Compositions of the disclosure containing excipients can be prepared by any known technique of pharmacy that comprises admixing an excipient with a drug or therapeutic agent.

In various embodiments, compositions optionally comprise one or more pharmaceutically acceptable diluents as excipients. Suitable diluents illustratively include, either individually or in combination, lactose, including anhydrous lactose and lactose monohydrate; starches, including directly compressible starch and hydrolyzed starches (*e.g.*, Celutab™ and Emdex™); mannitol; sorbitol; xylitol; dextrose (*e.g.*, Cerelose™ 2000) and dextrose monohydrate; dibasic calcium phosphate dihydrate; sucrose-based diluents; confectioner's sugar; monobasic calcium sulfate monohydrate; calcium sulfate dihydrate; granular calcium lactate trihydrate; dextrates; inositol; hydrolyzed cereal solids; amylose; celluloses including microcrystalline cellulose, food grade sources of α- and amorphous cellulose (*e.g.*, Rexcel™) and powdered cellulose; calcium carbonate; glycine; bentonite; polyvinylpyrrolidone; and the like. Such diluents, if present, constitute in total about 5% to about 99%, about 10% to about 85%, or about 20% to about 80%, of the total weight of the composition. The diluent or diluents selected may exhibit suitable flow properties and, where tablets are desired, compressibility.

The use of extragranular microcrystalline cellulose (that is, microcrystalline cellulose added to a wet granulated composition after a drying step) can be used to improve hardness (for tablets) and/or disintegration time.

In various embodiments, compositions optionally comprise one or more pharmaceutically acceptable disintegrants as excipients, particularly for tablet formulations. Suitable disintegrants include, either individually or in combination, starches, including sodium starch glycolate (*e.g.*, Explotab™ of PenWest) and pregelatinized corn starches (*e.g.*, National™ 1551, National™ 1550, and Colocorn™ 1500), clays (*e.g.*, Veegum™ HV), celluloses such as purified cellulose, microcrystalline cellulose, methylcellulose, carboxymethylcellulose and sodium carboxymethylcellulose, croscarmellose sodium (*e.g.*, Ac-Di-Sol™ of FMC), alginates, crospovidone, and gums such as agar, guar, locust bean, karaya, pectin and tragacanth gums.

Disintegrants may be added at any suitable step during the preparation of the composition, particularly prior to a granulation step or during a lubrication step

prior to compression. Such disintegrants, if present, constitute in total about 0.2% to about 30%, about 0.2% to about 10%, or about 0.2% to about 5%, of the total weight of the composition.

Croscarmellose sodium is one example of a disintegrant for tablet or capsule disintegration, and, if present, typically constitutes about 0.2% to about 10%, about 0.2% to about 7%, or about 0.2% to about 5%, of the total weight of the composition.

Various embodiments described herein optionally comprise one or more pharmaceutically acceptable binding agents or adhesives as excipients, particularly for tablet formulations. Such binding agents and adhesives may impart sufficient cohesion to the powder being tableted to allow for normal processing operations such as sizing, lubrication, compression and packaging, but still allow the tablet to disintegrate and the composition to be absorbed upon ingestion. Suitable binding agents and adhesives include, either individually or in combination, acacia; tragacanth; sucrose; gelatin; glucose; starches such as, but not limited to, pregelatinized starches (*e.g.*, National™ 1511 and National™ 1500); celluloses such as, but not limited to, methylcellulose and carmellose sodium (*e.g.*, Tylose™); alginic acid and salts of alginic acid; magnesium aluminum silicate; PEG; guar gum; polysaccharide acids; bentonites; povidone, for example povidone K-15, K-30 and K-29/32; polymethacrylates; HPMC; hydroxypropylcellulose (*e.g.*, Klucel™); and ethylcellulose (*e.g.*, Ethocel™). Such binding agents and/or adhesives, if present, constitute in total about 0.5% to about 25%, about 0.75% to about 15%, or about 1% to about 10%, of the total weight of the composition.

Compositions described herein optionally comprise one or more pharmaceutically acceptable wetting agents as excipients. Non-limiting examples of surfactants that can be used as wetting agents in compositions of the disclosure include quaternary ammonium compounds, for example benzalkonium chloride, benzethonium chloride and cetylpyridinium chloride, dioctyl sodium sulfosuccinate, polyoxyethylene alkylphenyl ethers, for example nonoxynol 9, nonoxynol 10, and octoxynol 9, poloxamers (polyoxyethylene and polyoxypropylene block copolymers), polyoxyethylene fatty acid glycerides and oils, for example polyoxyethylene (8) caprylic/capric mono- and diglycerides (*e.g.*, Labrasol™ of Gattefossé), polyoxyethylene (35) castor oil and polyoxyethylene (40) hydrogenated castor oil; polyoxyethylene alkyl ethers, for example

polyoxyethylene (20) cetostearyl ether, polyoxyethylene fatty acid esters, for example polyoxyethylene (40) stearate, polyoxyethylene sorbitan esters, for example polysorbate 20 and polysorbate 80 (*e.g.*, Tween™ 80 of ICI), propylene glycol fatty acid esters, for example propylene glycol laurate (*e.g.*, Lauroglycol™ of Gattefossé), sodium lauryl sulfate, fatty acids and salts thereof, for example oleic acid, sodium oleate and triethanolamine oleate, glyceryl fatty acid esters, for example glyceryl monostearate, sorbitan esters, for example sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate and sorbitan monostearate, tyloxapol, and mixtures thereof. Such wetting agents, if present, constitute in total about 0.25% to about 15%, about 0.4% to about 10%, or about 0.5% to about 5%, of the total weight of the composition.

Compositions described herein optionally comprise one or more pharmaceutically acceptable lubricants (including anti-adherents and/or glidants) as excipients. Suitable lubricants include, either individually or in combination, glyceryl behapate (*e.g.*, Compritol™ 888); stearic acid and salts thereof, including magnesium (magnesium stearate), calcium and sodium stearates; hydrogenated vegetable oils (*e.g.*, Sterotex™); colloidal silica; talc; waxes; boric acid; sodium benzoate; sodium acetate; sodium fumarate; sodium chloride; DL-leucine; PEG (*e.g.*, Carbowax™ 4000 and Carbowax™ 6000); sodium oleate; sodium lauryl sulfate; and magnesium lauryl sulfate. Such lubricants, if present, constitute in total about 0.1% to about 10%, about 0.2% to about 8%, or about 0.25% to about 5%, of the total weight of the composition.

Suitable anti-adherents include talc, cornstarch, DL-leucine, sodium lauryl sulfate and metallic stearates. Talc is a anti-adherent or glidant used, for example, to reduce formulation sticking to equipment surfaces and also to reduce static in the blend. Talc, if present, constitutes about 0.1% to about 10%, about 0.25% to about 5%, or about 0.5% to about 2%, of the total weight of the composition.

Glidants can be used to promote powder flow of a solid formulation. Suitable glidants include colloidal silicon dioxide, starch, talc, tribasic calcium phosphate, powdered cellulose and magnesium trisilicate.

Compositions described herein can comprise one or more anti-foaming agents. Simethicone is an illustrative anti-foaming agent.

Compositions described herein can comprise one or more flavoring agents, sweetening agents, and/or colorants. Flavoring agents useful in the present

embodiments include, without limitation, acacia syrup, alitame, anise, apple, aspartame, banana, Bavarian cream, berry, black currant, butter, butter pecan, butterscotch, calcium citrate, camphor, caramel, cherry, cherry cream, chocolate, cinnamon, citrus, citrus punch, citrus cream, cocoa, coffee, cola, cool cherry, cool citrus, cyclamate, cylamate, dextrose, eucalyptus, eugenol, fructose, fruit punch, ginger, glycyrrhetinate, glycyrrhiza (licorice) syrup, grape, grapefruit, honey, isomalt, lemon, lime, lemon cream, MagnaSweet®, maltol, mannitol, maple, menthol, mint, mint cream, mixed berry, nut, orange, peanut butter, pear, peppermint, peppermint cream, Prosweet® Powder, raspberry, root beer, rum, saccharin, safrole, sorbitol, spearmint, spearmint cream, strawberry, strawberry cream, stevia, sucralose, sucrose, Swiss cream, tagatose, tangerine, thaumatin, tutti fruitti, vanilla, walnut, watermelon, wild cherry, wintergreen, xylitol, and combinations thereof, for example, anise-menthol, cherry-anise, cinnamon-orange, cherry-cinnamon, chocolate-mint, honey-lemon, lemon-lime, lemon-mint, menthol-eucalyptus, orange-cream, vanilla-mint, *etc.*

Sweetening agents that can be used in the present embodiments include, by way of example and not limitation, acesulfame potassium (acesulfame K), alitame, aspartame, cyclamate, cylamate, dextrose, isomalt, MagnaSweet®, maltitol, mannitol, neohesperidine DC, neotame, Prosweet® Powder, saccharin, sorbitol, stevia, sucralose, sucrose, tagatose, thaumatin, xylitol, and the like.

The foregoing excipients can have multiple roles. For example, starch can serve as a filler as well as a disintegrant. The classification of excipients listed herein is not to be construed as limiting in any manner.

Pharmaceutical Dosage Forms

In various embodiments, compositions can be formulated as solid, liquid or semi-solid dosage forms. In one embodiment, such compositions are in the form of discrete dose units or dosage units. The terms "dose unit" and/or "dosage unit" herein refer to a portion of a pharmaceutical composition that contains an amount of a therapeutic agent suitable for a single administration to provide a therapeutic effect. Such dosage units may be administered one to a small plurality (*i.e.* 1 to about 4) of times per day, or as many times as needed to elicit a therapeutic response. A particular dosage form can be selected to accommodate any desired frequency of administration to achieve a specified daily dose. Typically one dose

unit, or a small plurality (*i.e.* up to about 4) of dose units, provides a sufficient amount of the active drug (*e.g.* benzimidazole or imidazopyridine moiety) to result in the desired response or effect.

Non-limiting examples of suitable solid dosage forms include tablets (*e.g.* suspension tablets, bite suspension tablets, rapid dispersion tablets, chewable tablets, effervescent tablets, bilayer tablets, *etc*), caplets, capsules (*e.g.* a soft or a hard gelatin capsule), powder (*e.g.* a packaged powder, a dispensable powder or an effervescent powder), lozenges, sachets, cachets, troches, pellets, granules, microgranules, encapsulated microgranules, powder aerosol formulations, or any other solid dosage form reasonably adapted for oral administration.

In one embodiment, a composition disclosed herein comprises a multi-layer tablet having a core comprising a proton pump inhibitor; the core is substantially or completely surrounded by the protein component. In one embodiment, the protein component layer completely surrounds the core. In another embodiment, the protein component layer partially surrounds the core. In yet another embodiment, the protein component layer is in contact with a portion of or with all of the surface area of the core.

In still another embodiment, there is one or more intermediate layers in between the core and the protein component. The intermediate layers can comprise any pharmaceutically acceptable material, such as inert and non-pH sensitive coating materials such as polymer based coatings.

In another embodiment, a composition of the disclosure comprises a proton pump inhibitor and a protein component mixed together in powder form and optionally filled into a capsule, for example a hard or soft gelatin or HPMC capsule.

Non-limiting examples of suitable liquid dosage forms include solutions, suspension, elixirs, syrups, liquid aerosol formulations, *etc*. Alternatively, compositions of the disclosure can also be formulated for rectal, topical, or parenteral (*e.g.* subcutaneous, intramuscular, intravenous and intradermal or infusion) delivery.

In one embodiment, a liquid composition of the disclosure can be prepared comprising water, PPI and a protein component. In another embodiment, a composition of the disclosure can be prepared as two separate liquids that can be mixed together prior to administration to a subject. In this embodiment, the first

liquid comprises de-ionized water and PPI. The second liquid comprises a protein component in water. Alternatively, instead of a second liquid comprising the protein component, a dry protein component could be added to the PPI/de-ionized water mixture prior to administration to a subject.

In another embodiment, a single dosage unit comprises a therapeutically effective amount or a therapeutically and/or prophylactically effective amount of PPI. The term "therapeutically effective amount" or "therapeutically and/or prophylactically effective amount" as used herein refers to an amount of compound or agent that is sufficient to elicit the required or desired therapeutic and/or prophylactic response, as the particular treatment context may require.

It will be understood that a therapeutically and/or prophylactically effective amount of a drug for a subject is dependent *inter alia* on the body weight of the subject. A "subject" herein to which a therapeutic agent or composition thereof can be administered includes a human subject of either sex and of any age, and also includes any nonhuman animal, particularly a domestic or companion animal, illustratively a cat, dog or a horse.

Tablets are an illustrative dosage form for compositions disclosed herein. Tablets can be prepared according to any of the many relevant, well known pharmacy techniques. In one embodiment, tablets or other solid dosage forms can be prepared by processes that employ one or a combination of methods including, without limitation, (1) dry mixing, (2) direct compression, (3) milling, (4) dry or non-aqueous granulation, (5) wet granulation, or (6) fusion.

The individual steps in the wet granulation process of tablet preparation typically include milling and sieving of the ingredients, dry powder mixing, wet massing, granulation and final grinding. Dry granulation involves compressing a powder mixture into a rough tablet or "slug" on a heavy-duty rotary tablet press. The slugs are then broken up into granular particles by a grinding operation, usually by passage through an oscillation granulator. The individual steps include mixing of the powders, compressing (slugging) and grinding (slug reduction or granulation). Typically, no wet binder or moisture is involved in any of the steps.

In another embodiment, solid dosage forms such as tablets can be prepared by mixing a PPI with at least one protein component as described herein above and, if desired, with one or more optional pharmaceutical excipient to form a substantially homogeneous preformulation blend. The preformulation blend can

then be subdivided and optionally further processed (*e.g.* compressed, encapsulated, packaged, dispersed, *etc.*) into any desired dosage forms.

Compressed tablets can be prepared by compacting a powder or granulation composition of the disclosure. The term "compressed tablet" generally refers to a plain, uncoated tablet suitable for oral ingestion, prepared by a single compression or by pre-compaction tapping followed by a final compression. Tablets of the present disclosure may be coated or otherwise compounded to provide a dosage form affording the advantage of improved handling or storage characteristics. Any such coating may be selected so as to not substantially delay onset of therapeutic effect of a composition of the disclosure upon administration to a subject. The term "suspension tablet" as used herein refers to a compressed tablet that rapidly disintegrates after placement in water.

In one embodiment, compositions of the disclosure are suitable for rapid onset of therapeutic effect, particularly with respect to the PPI component. In another embodiment, upon oral administration of a composition of the disclosure to a subject, at least a therapeutically effective amount of the PPI is available for absorption in the stomach of the subject. As discussed above, most commercially available PPIs require enteric coating to prevent exposure of the PPI to gastrointestinal fluids (and consequent drug degradation) by way of pH dependent coatings. Such coating, in turn, prevents rapid PPI absorption and therapeutic onset of action. Compositions of the present disclosure, by contrast, do not require enteric coating to maintain drug stability in gastrointestinal fluids and thereby provide for rapid absorption and onset of therapeutic effect. In fact, in one embodiment, a composition comprises at least a therapeutically effective amount of PPI that is not enteric coated.

In another embodiment, upon oral administration of a composition of the disclosure to a plurality of fasted adult human subjects, the subjects exhibit an average T_{max} of active ingredient, (*e.g.* PPI) within about 30 seconds to about 90 minutes, within about 1 minute to about 80 minutes, within about 5 minutes to about 60 minutes, within about 10 minutes to about 50 minutes, or within about 15 minutes to about 45 minutes.

In still another embodiment, upon administration of a composition of the disclosure to a plurality of fasted adult human subjects, the subjects exhibit an

average plasma concentration of the PPI of at least about 0.1 μg/ml, at least about 0.15 μg/ml, at least about 0.2 μg/ml, at least about 0.3 μg/ml, at least about 0.4 μg/ml, at least about 0.5 μg/ml, at least about 0.6 μg/ml, at least about 0.7 μg/ml, at least about 0.8 μg/ml, at least about 0.9 μg/ml, at least about 1 μg/ml, at least about 1.5 μg/ml, or at least about 2.0 μg/ml at any time within about 90 minutes, within about 75 minutes, within about 60 minutes, within about 55 minutes, within about 50 minutes, within about 45 minutes, within about 40 minutes, within about 35 minutes, within about 30 minutes, within about 25 minutes, within about 20 minutes, within about 17 minutes, within about 15 minutes, within about 12 minutes, or within about 10 minutes after administration.

In yet another embodiment, upon administration of a composition of the disclosure to a plurality of fasted adult human subjects, the subjects exhibit a plasma concentration of active ingredient (*e.g.* PPI) of at least about 0.1 μg/ml, at least about 0.15 μg/ml, at least about 0.2 μg/ml, at least about 0.3 μg/ml, at least about 0.4 μg/ml, at least about 0.5 μg/ml, at least about 0.6 μg/ml, at least about 0.7 μg/ml, at least about 0.8 μg/ml, at least about 0.9 μg/ml, at least about 1.0 μg/ml, at least about 1.5 μg/ml or at least about 2.0 μg/ml, maintained from about 15 minutes to about 60 minutes after administration, from about 15 minutes to about 90 minutes after administration, from about 15 minutes to about 120 minutes after administration, or from about 15 minutes to about 180 minutes after administration.

In another embodiment, upon administration of a composition of the disclosure to a plurality of fasted adult human subjects, the subjects exhibit at least one of: a mean C_{max} of PPI of about 500 μg/ml to about 2000 μg/ml, about 600 μg/ml to about 1900 μg/ml, or about 700 ng/ml to about 1800 μg/ml; a mean T_{max} of PPI of about 0.15 to about 2 hours, about 0.25 to about 1.75 hours, or about 0.3 hours to about 1 hour; and/or a mean $AUC_{(0\text{-}inf)}$ of PPI of about 1000 to about 3000 μg*hr/ml, about 1500 to about 2700 μg*hr/ml, or about 1700 to about 2500 μg*hr/ml.

In another embodiment, upon administration of a composition of the disclosure to a plurality of fasted adult human subjects, the subjects exhibit: a mean C_{max} of PPI of about 500 μg/ml to about 2000 μg/ml, about 600 μg/ml to about 1900 μg/ml, or about 700 μg/ml to about 1800 μg/ml; a mean T_{max} of PPI of

about 0.15 to about 2 hours, about 0.25 to about 1.75 hours, or about 0.3 hours to about 1 hour; and a mean $AUC_{(0\text{-}inf)}$ of PPI of about 1000 to about 3000 ng*hr/ml, about 1500 to about 2700 ng*hr/ml, or about 1700 to about 2500 ng*hr/ml.

Storage Stability

In one embodiment, compositions disclosed herein are in the form of a powder for suspension that can be suspended in a liquid vehicle prior to administration to a subject. Liquid compositions comprising an acid labile PPI and a protein component dissolved and/or suspended in a liquid vehicle comprise another embodiment of the disclosure. Generally, a liquid composition of PPI (without a protein component) would exhibit very short period of stability, even when maintained under refrigerated conditions. This is particularly inconvenient in the hospital setting as fresh batches of suspension are continually required. .

Suspension compositions of the disclosure comprise at least one PPI, a protein component, a liquid media (*e.g.* water, de-ionized water, etc) and one or more optional pharmaceutical excipients. Such compositions, upon storage in a closed container maintained at either room temperature, refrigerated (*e.g.* about 5 - 10 °C) temperature, or freezing temperature for a period of about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months, exhibit at least about 90%, at least about 92.5%, at least about 95%, or at least about 97.5% of the original PPI present therein.

Gastrointestinal Disorders

Compositions of the present disclosure are useful for treating and/or preventing gastrointestinal disorders and acid related gastrointestinal disorders. The phrase "acid related gastrointestinal disorder" or "acid related gastrointestinal disease" refers generally to a disorder or disease that occurs due an imbalance between acid and pepsin production on the one hand, so-called aggressive factors, and mucous, bicarbonate, and prostaglandin production on the other hand, so-called defensive factors. In mammals such disorders include, but are not limited to, duodenal ulcer, gastric ulcer, stress erosions and ulceration, stress-related mucosal damage, gastric and duodenal erosions and ulceration, acid dyspepsia, gastroesophageal reflux disease (GERD), nocturnal acid breakthrough (NAB), severe erosive esophagitis, poorly responsive symptomatic gastroesophageal reflux disease, acid reflux, heartburn, nighttime heartburn symptoms, esophageal ulcers

and erosions, Barrett's esophagus, precancerous and cancerous lesions of the esophagus induced by acid exposure, acid hypersecretory conditions, gastrointestinal pathological hypersecretory conditions (such as Zollinger Ellison Syndrome), gastrointestinal bleeding, acute upper gastrointestinal bleeding, non-ulcer dyspepsia, heartburn, ulcers induced by NSAIDs, atypical reflux conditions, laryngitis, chronic cough, otitis media, sinusitis, eye pain, globus sensation, esophagitis, erosive esophagitis, esophageal squamous cell reversion, gastrinoma, *Helicobacter pylori* (*H. pylori*) infection, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), ulcerative colitis, pre- and post-operative acid aspiration, Crohn's disease, asthma, laryngitis, sleep apnea, sleep disturbance, psoriasis, intensive care therapy, and diseases related to any of the above-mentioned conditions are also provided.

Where the disorder is heartburn, the heartburn can be meal-related or induced, sleep-related or induced, and/or nighttime-related or induced heartburn. Sleep-related heartburn and/or nighttime-related heartburn can be caused, for example, by breakthrough gastritis between conventional doses of a therapeutic agent, such as while sleeping or in the early morning hours after a night's sleep. Treatment of these conditions is accomplished by administering to a subject a gastrointestinal-disorder-effective amount (or a therapeutically-effective amount) of a pharmaceutical composition according to the present disclosure. A subject may be experiencing one or more of these conditions or disorders.

Compositions of the disclosure can be administered to a subject at any suitable time, for example upon waking, prior to a meal, during the day, or at night time (*e.g.* before bed).

The term "treat" or "treatment" as used herein refers to any treatment of a disorder or disease associated with a gastrointestinal disorder, and includes, but is not limited to, preventing the disorder or disease from occurring in a subject that may be predisposed to the disorder or disease but has not yet been diagnosed as having the disorder or disease; inhibiting the disorder or disease, for example, arresting the development of the disorder or disease; relieving the disorder or disease, for example, causing regression of the disorder or disease; or relieving the condition caused by the disease or disorder, for example, stopping the symptoms of the disease or disorder.

The term "prevent" or "prevention," in relation to a gastrointestinal disorder or disease, means preventing the onset of gastrointestinal disorder or disease development if none had occurred, or preventing further gastrointestinal disorder or disease development if the gastrointestinal disorder or disease was already present.

In one embodiment of the disclosure, a composition of the present disclosure can further include one or more parietal cell activators (in addition to the protein component which may also be a parietal cell activator). Parietal cell activators may be used where the benzimidazole or imidazopyridine moiety is a PPI. Parietal cell activators stimulate the parietal cells and enhance the pharmacologic activity of the PPI administered. For the purposes of this application, "parietal cell activator" or "activator" shall mean any compound or mixture of compounds possessing such stimulatory effect including, but not limited to, chocolate, peppermint oil, spearmint oil, coffee, tea and colas (even if decaffeinated), caffeine, theophylline, theobromine, and combinations thereof.

Parietal cell activators, if desired, are typically present in a composition of the disclosure in an amount sufficient to produce the desired stimulatory effect without causing untoward side effects to patients. For example, chocolate, as raw cocoa, is administered in an amount of about 5 mg to 2.5 g per 20 mg dose of omeprazole (or equivalent pharmacologic dose of another proton pump inhibiting agent). The dose of activator administered to a subject, for example, a human, in the context of the present disclosure should be sufficient to result in enhanced effect of a PPI over a desired time frame.

Illustratively, the approximate effective ranges for various parietal cell activators per 20 mg dose of omeprazole (or equivalent dose of other PPI) include, Chocolate (raw cocoa) – 5 mg to 2.5 g; Peppermint oil – (powdered form) 1 mg to 1 g; Spearmint oil – (powdered form) 1 mg to 1 g; Coffee – 20 ml to 240 ml; Tea – 20 ml to 240 ml; Cola – 20 ml to 240 ml; Caffeine – 0.5 mg to 1.5 g; Theophylline – 0.5 mg to 1.5 g; Theobromine – 0.5 mg to 1.5g; Phenylalanine – 0.5 mg to 1.5 g; and Tryptophan – 0.5 mg to 1.5 g.

EXAMPLES

The following examples illustrate various embodiments of the present disclosure and are not to be construed as limiting the invention in any way.

Example 1

Formulation 1 as shown in the following table is prepared as described below.

Formulation 1

Component	Amount
Casein hydrolysate	4000 mg (10 mg to 20 g range)
Sucrose	2400 mg
Sucralose	10 mg
Lactoferrin	100 mg
Neotame	3 mg
Omeprazole, Tenatoprazole, Esomeprazole, Pantoprazole or Lanzoprazole	20 mg
Total	**6533 mg**

The formulation can be suitable for administration in a liquid vehicle or infant formula or as a standalone feeding/medication regime. The formulation can be heat stable such that warming to body temperature (as is normal practice for feeding to infants) has no effect on stability of medication or other additives. When added to infant formula, the entire dry contents may be added without prior reconstitution with water. When used as a stand alone feeding/medication regime, a quantity of water sufficient to bring the total volume to 100mL can be added.

Alternatively, the formulation can be encapsulated, tableted, or otherwise formed into one or more suitable solid finished dosage form(s). For example, the formulation may further comprise a disintegrant such as starch or croscarmellose sodium in an amount of about 1% to about 6%.

Example 2

Formulation 2 as shown in the following table is prepared as described below.

Formulation 2

Component	Amount
Casein hydrolysate	2000 mg (10 mg to 20 g range)
Demineralized whey hydrolysate	2000 mg

Sucrose	2400 mg
Sucralose	10 mg
Neotame	3 mg
Omeprazole, Tenatoprazole, Esomeprazole, Pantoprazole or Lanzoprazole	10 mg (1 mg to 4 g range)
Total	**6423 mg**

The formulation can be suitable for administration in a liquid vehicle or infant formula or as a standalone feeding/medication regime. The formulation can be heat stable such that warming to body temperature (as is normal practice for feeding to infants) has no effect on stability of medication or other additives. When added to infant formula, the entire dry contents may be added without prior reconstitution with water. When used as a stand alone feeding/medication regime, a quantity of water sufficient to bring the total volume to 100mL can be added.

Alternatively, the formulation can be encapsulated, tableted, or otherwise formed into one or more suitable solid finished dosage form(s). For example, the formulation may further comprise a disintegrant such as starch or croscarmellose sodium in an amount of about 1% to about 10%.

Example 3

Formulation 3 as shown in the following table is prepared as described below.

Formulation 3

Component	**Amount**
Soy hydrolysate	4000 mg (10 mg to 20 g range)
Demineralized whey hydrolysate	2000 mg
Sucrose	2400 mg
Lactoferrin	100 mg
Neotame	3 mg
Omeprazole, Tenatoprazole, Esomeprazole, Pantoprazole or Lanzoprazole	10 mg (1 mg to 5 g range)
Total	**8513**

The formulation can be suitable for administration in a liquid vehicle or infant formula or as a standalone feeding/medication regime. The formulation can

be heat stable such that warming to body temperature (as is normal practice for feeding to infants) has no effect on stability of medication or other additives. When added to infant formula, the entire dry contents may be added without prior reconstitution with water. When used as a stand alone feeding/medication regime, a quantity of water sufficient to bring the total volume to 100 mL can be added.

Alternatively, the formulation can be encapsulated, tableted, or otherwise formed into one or more suitable solid finished dosage form(s). For example, the formulation may further comprise a disintegrant such as starch or croscarmellose sodium in an amount of about 1% to about 8%.

Example 4

Formulations 4-10 as shown in the following table are prepared as described below.

Formulations 4-10

Component	F4	F5	F6	F7	F8	F9	F10
L-carnosine	4000 mg	4000 mg	4000 mg	4000 mg	4000 mg	4000 mg	4000 mg
Demineralized whey hydrolysate	2000 mg	2000 mg	2000 mg	2000 mg	2000 mg	2000 mg	2000 mg
Sucrose	2400 mg	2400 mg	2400 mg	2400 mg	2400 mg	2400 mg	2400 mg
Lactoferrin	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg
Neotame	3 mg	3 mg	3 mg	3 mg	3 mg	3 mg	3 mg
Omeprazole, Tenatoprazole, Esomeprazole, Pantoprazole or Lanzoprazole	10 mg	20 mg	40 mg	60 mg	80 mg	90 mg	100 mg
Total	**8513 mg**	**8523 mg**	**8543 mg**	**8563 mg**	**8583 mg**	**8593 mg**	**8603 mg**

The formulation can be suitable for administration in a liquid vehicle or infant formula or as a standalone feeding/medication regime. The formulation can be heat stable such that warming to body temperature (as is normal practice for feeding to infants) has no effect on stability of medication or other additives. When added to infant formula, the entire dry contents may be added without prior reconstitution with water. When used as a stand alone feeding/medication regime, a quantity of water sufficient to bring the total volume to 100 mL can be added.

Alternatively, the formulation can be encapsulated, tableted, or otherwise formed into one or more suitable solid finished dosage form(s). For example, the formulation may further comprise a disintegrant such as starch or croscarmellose sodium in an amount of about 2% to about 10%.

Example 5

Formulation 11 as shown in the following table is prepared as described below.

Formulation 11

Component	Amount
Whey hydrolysate	4000 mg (10 mg to 20 g range)
Hydrolyzed guar gum	1000 mg(1 mg to 20 g range)
Sucrose	2000 mg
Thaumatin	3 mg
Neotame	2 mg
Omeprazole, Tenatoprazole, Esomeprazole, Pantoprazole or Lanzoprazole	10 mg (1 mg to 5 g range)
Total	**7015 mg**

The formulation can be suitable for administration in a liquid vehicle or infant formula or as a standalone feeding/medication regime. The formulation can be heat stable such that warming to body temperature (as is normal practice for feeding to infants) has no effect on stability of medication or other additives. When added to infant formula, the entire dry contents may be added without prior reconstitution with water. When used as a stand alone feeding/medication regime, a quantity of water sufficient to bring the total volume to 100 mL can be added.

Alternatively, the formulation can be encapsulated, tableted, or otherwise formed into one or more suitable solid finished dosage form(s). For example, the formulation may further comprise a disintegrant such as starch or croscarmellose sodium in an amount of about 2% to about 10%.

Example 6

Formulations 5-11 as shown in the following table are prepared as described below.

Formulations 5-11

Component	F5	F6	F7	F8	F9	F10	F11
L-carnosine	4000	4000	4000	4000	4000	4000	4000

	mg	mg	mg	mg	mg	mg	mg
Hydrolyzed guar gum	1000 mg	1000 mg	1000 mg	1000 mg	1000 mg	1000 mg	1000 mg
Sucrose	2000 mg	2000 mg	2000 mg	2000 mg	2000 mg	2000 mg	2000 mg
Thaumatin	3 mg	3 mg	3 mg	3 mg	3 mg	3 mg	3 mg
Neotame	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg
Omeprazole, Tenatoprazole, Esomeprazole, Pantoprazole or Lanzoprazole	10 mg	20 mg	40 mg	60 mg	80 mg	90 mg	100 mg
Total	**7015 mg**	**7025 mg**	**7045 mg**	**7065 mg**	**7085 mg**	**7095 mg**	**7100 mg**

The formulation can be suitable for administration in a liquid vehicle or infant formula or as a standalone feeding/medication regime. The formulation can be heat stable such that warming to body temperature (as is normal practice for feeding to infants) has no effect on stability of medication or other additives. When added to infant formula, the entire dry contents may be added without prior reconstitution with water. When used as a stand alone feeding/medication regime, a quantity of water sufficient to bring the total volume to 100 mL can be added.

Alternatively, the formulation can be encapsulated, tableted, or otherwise formed into one or more suitable solid finished dosage form(s). For example, the formulation may further comprise a disintegrant such as starch or croscarmellose sodium in an amount of about 1% to about 10%.

Example 7

Formulation 12 as shown in the following table is prepared as described below.

Formulation 12

Component	Amount
Sodium Caseinate	3000 mg (10 mg to 20 g range)
Sucralose	600 mg
Dextrose	400 mg
Omeprazole, Tenatoprazole, Esomeprazole, Pantoprazole or Lanzoprazole	30 mg (1 mg to 5 g range)
Total	**4030 mg**

The formulation can be packaged as a dosage packet for addition to coffee or other beverage or food where a creamer is desired. The formulation may also be formed into a square (such as a typical "sugar cube") or into a rapidly dissolvable tablet or square (with the addition of hydroxypropyl cellulose, hypromellose or other disintegrants as known by those skilled in the art). Alternatively, the formulation can be encapsulated, tableted, or otherwise formed into one or more suitable solid finished dosage form(s). For example, the formulation may further comprise a disintegrant such as starch or croscarmellose sodium in an amount of about 1% to about 10%.

Example 8

Formulation 13 as shown in the following table is prepared as described below.

Formulation 13

Component	Amount
Calcium Caseinate	3000 mg (10 mg to 20 g range)
Sucralose	200 mg
Dextrose	200 mg
Aspartame	200 mg
Omeprazole, Tenatoprazole, Esomeprazole, Pantoprazole or Lanzoprazole	20 mg (1 mg to 5 g range)
Total	**3620 mg**

The formulation can be packaged as a dosage packet for addition to coffee or other beverage or food where a creamer is desired. The formulation may also be formed into a square (such as a typical "sugar cube") or into a rapidly dissolvable tablet or square (with the addition of hydroxypropyl cellulose, hypromellose or other disintegrants as known by those skilled in the art).

Alternatively, the formulation can be encapsulated, tableted, or otherwise formed into one or more suitable solid finished dosage form(s). For example, the formulation may further comprise a disintegrant such as starch or croscarmellose sodium in an amount of about 1% to about 10%.

Example 9

Formulations 14-20 as shown in the following table are prepared as described below.

Formulations 14-20

Component	F14	F15	F16	F17	F18	F19	F20
L-carnosine	3000 mg	3000 mg	3000 mg	3000 mg	3000 mg	3000 mg	2800 mg
Sucralose	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg
Dextrose	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg
Aspartame	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg
Omeprazole, Tenatoprazole, Esomeprazole, Pantoprazole or Lanzoprazole	10 mg	20 mg	40 mg	60 mg	80 mg	90 mg	100 mg
Total	**3610 mg**	**3620 mg**	**3640 mg**	**3660 mg**	**3680 mg**	**3690 mg**	**3500 mg**

The formulation can be packaged as a dosage packet for addition to coffee or other beverage or food where a creamer is desired. The formulation may also be formed into a square (such as a typical "sugar cube") or into a rapidly dissolvable tablet or square (with the addition of hydroxypropyl cellulose, hypromellose or other disintegrants as known by those skilled in the art).

Alternatively, the formulation can be encapsulated, tableted, or otherwise formed into one or more suitable solid finished dosage form(s). For example, the formulation may further comprise a disintegrant such as starch or croscarmellose sodium in an amount of about 1 to 10%.

Example 10

Formulation 21 as shown in the following table is prepared as described below.

Formulation 21

Component	Amount
Hydrolyzed Whey isolate	3000 mg (10 mg to 20 g range)
Sucralose	200 mg
Dextrose	200 mg
Aspartame	200 mg
Neotame	3 mg
Omeprazole, Tenatoprazole, Esomeprazole, Pantoprazole or Lanzoprazole	40 mg (1 mg to 5 g range)
Total	**3643 mg**

The formulation can be packaged as a dosage packet for addition to coffee or other beverage or food where a creamer is desired. The formulation may also be formed into a square (such as a typical "sugar cube") or into a rapidly dissolvable tablet or square (with the addition of hydroxypropyl cellulose, hypromellose or other disintegrants as known by those skilled in the art).

Alternatively, the formulation can be encapsulated, tableted, or otherwise formed into one or more suitable solid finished dosage form(s). For example, the formulation may further comprise a disintegrant such as starch or croscarmellose sodium in an amount of about 1% to about 10%.

Example 11

Formulations 22-28 as shown in the following table are prepared as described below.

Formulations 22-28

Component	F22	F23	F24	F25	F26	F27	F28
L-carnosine	800 mg	800 mg	800 mg	1200 mg	1600 mg	1800 mg	2000 mg
Sucralose	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg
Dextrose	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg
Aspartame	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg
Neotame	2 g	2 g	2 g	2 g	1.5 g	1000 mg	1000 mg
Omeprazole, Tenatoprazole, Esomeprazole, Pantoprazole or Lanzoprazole	10 mg	20 mg	40 mg	60 mg	80 mg	90 mg	100 mg
Total	**3410 mg**	**3420 mg**	**3440 mg**	**3860 mg**	**3780 mg**	**3490 mg**	**3700 mg**

The formulation can be packaged as a dosage packet for addition to coffee or other beverage or food where a creamer is desired. The formulation may also be formed into a square (such as a typical "sugar cube") or into a rapidly dissolvable tablet or square (with the addition of hydroxypropyl cellulose, hypromellose or other disintegrants as known by those skilled in the art).

Alternatively, the formulation can be encapsulated, tableted, or otherwise formed into one or more suitable solid finished dosage form(s). For example, the formulation may further comprise a disintegrant such as starch or croscarmellose sodium in an amount of about 1% to about 10%.

Example 12

The following Formulations 29-35 are prepared as described below.

Formulations 29-35

Component	F29	F30	F31	F32	F33	F34	F35
L-carnosine	800 mg	800 mg	800 mg	1200 mg	1600 mg	1800 mg	2000 mg
Sodium Bicarbonate	800 mg	800 mg	800 mg	1200 mg	1600 mg	1800 mg	2000 mg
Omeprazole, Tenatoprazole, Esomeprazole, Pantoprazole or Lanzoprazole	10 mg	20 mg	40 mg	60 mg	80 mg	90 mg	100 mg
Total	**1610 mg**	**1620 mg**	**1640 mg**	**2460 mg**	**3280 mg**	**3690 mg**	**4100 mg**

The formulation may be prepared as solid, liquid or semi-solid dosage forms as described hereinabove. For example, the formulation may be tableted or encapsulated or prepared as other dosage forms (with optional excipients). The formulation may further include disintegrants such as crosslinked polyvinylpyrrolidone (Crospovidone USP/NF) in an amount, for example, of about 1% to about 10% weight to weight.

Alternatively, other disintegrants include sodium CMC (carboxymethyl cellulose), chitin, or chitosan. The formulation may further include one or more flavoring agents as described hereinabove, for example, sucralose, dextrose, aspartame, thaumatin or neotame.

All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference there individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

The use of the terms "a" and "an" and "the" and similar referents in the context of this disclosure (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary

language (e.g., such as, preferred, preferably, particularly) provided herein, is intended merely to further illustrate the content of the disclosure and does not pose a limitation on the scope of the claims. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the claimed invention.

Alternative embodiments of the claimed invention are described herein, including the best mode known to the inventors for carrying out the claimed invention. Of these, variations of the disclosed embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing disclosure. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the claimed invention to be practiced otherwise than as specifically described herein.

Accordingly, the claimed invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the claimed invention unless otherwise indicated herein or otherwise clearly contradicted by context.

The use of individual numerical values are stated as approximations as though the values were preceded by the word "about" or "approximately." Similarly, the numerical values in the various ranges specified in this application, unless expressly indicated otherwise, are stated as approximations as though the minimum and maximum values within the stated ranges were both preceded by the word "about" or "approximately." In this manner, variations above and below the stated ranges can be used to achieve substantially the same results as values within the ranges. As used herein, the terms "about" and "approximately" when referring to a numerical value shall have their plain and ordinary meanings to a person of ordinary skill in the art to which the disclosed subject matter is most closely related or the art relevant to the range or element at issue. The amount of broadening from the strict numerical boundary depends upon many factors. For example, some of the factors which may be considered include the criticality of the element and/or the effect a given amount of variation will have on the performance of the claimed subject matter, as well as other considerations known to those of skill in the art. As used herein, the use of differing amounts of significant digits for different numerical values is not meant to limit how the use of the words "about" or

"approximately" will serve to broaden a particular numerical value. Thus, as a general matter, "about" or "approximately" broaden the numerical value. Also, the disclosure of ranges is intended as a continuous range including every value between the minimum and maximum values plus the broadening of the range afforded by the use of the term "about" or "approximately." Thus, recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it there individually recited herein.

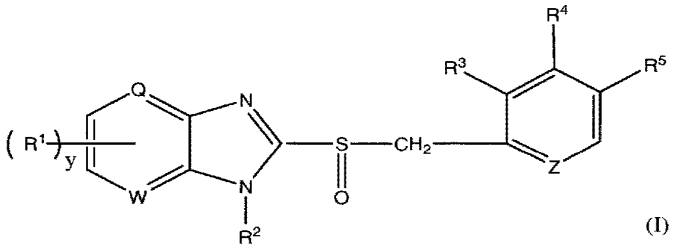
It is to be understood that any ranges, ratios and ranges of ratios that can be formed by, or derived from, any of the data disclosed herein represent further embodiments of the present disclosure and are included as part of the disclosure as though they were explicitly set forth. This includes ranges that can be formed that do or do not include a finite upper and/or lower boundary. Accordingly, a person of ordinary skill in the art most closely related to a particular range, ratio or range of ratios will appreciate that such values are unambiguously derivable from the data presented herein.

CLAIMS

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising an acid labile proton pump inhibitor and a protein component.

2. The composition of Claim 1 wherein the proton pump inhibitor is of Formula (I):



(I)

wherein

R^1 is hydrogen, alkyl, halogen, cyano, carboxy, carboalkoxy, carboalkoxyalkyl, carbamoyl, carbamoylalkyl, hydroxy, alkoxy which is optionally fluorinated, hydroxyalkyl, trifluoromethyl, acyl, carbamoyloxy, nitro, acyloxy, aryl, aryloxy, alkylthio, or alkylsulfinyl;

R^2 is hydrogen, alkyl, acyl, acyloxy, alkoxy, amino, aralkyl, carboalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, alkylcarbonylmethyl, alkoxycarbonylmethyl, or alkylsulfonyl;

R^3 and R^5 are the same or different and each is hydrogen, alkyl, alkoxy, amino, or alkoxyalkoxy;

R^4 is hydrogen, alkyl, alkoxy which may optionally be fluorinated, or alkoxyalkoxy;

Q is nitrogen, CH, or CR^1;

W is nitrogen, CH, or CR^1;

y is an integer of 0 through 4; and

Z is nitrogen, CH, or CR^1;

or a free base, salt, ester, hydrate, amide, enantiomer, isomer, tautomer, prodrug, polymorph, or derivative thereof.

3. The composition of claim 1 wherein the proton pump inhibitor is omeprazole, tenatoprazole, lansoprazole, rabeprazole, esomeprazole (also

referred to as S-omeprazole), pantoprazole, pariprazole, leminoprazole and nepaprazole or a free base, a free acid, or a salt, hydrate, ester, amide, enantiomer, isomer, tautomer, polymorph, prodrug, or derivative of such compounds.

4. The composition of claim 1 wherein the proton pump inhibitor is omeprazole or a free base, a free acid, or a salt, hydrate, ester, amide, enantiomer, isomer, tautomer, polymorph, prodrug, or derivative of such compounds.

5. The composition of claim 1 wherein the proton pump inhibitor is tenatoprazole or a free base, a free acid, or a salt, hydrate, ester, amide, enantiomer, isomer, tautomer, polymorph, prodrug, or derivative of such compounds.

6. The composition of claim 1 wherein the proton pump inhibitor is present in an amount of about 1 mg to about 1000 mg.

7. The composition of claim 1 wherein the proton pump inhibitor is present in an amount of about 15 mg to about 50 mg.

8. The composition of claim 1 wherein the protein component is present in an amount of about 1 mg to about 100 g on a dry weight basis.

9. The composition of claim 1 wherein the protein component is present in an amount of about 10 mg to about 500 mg on a dry weight basis.

10. The composition of claim 1 wherein the proton pump inhibitor and the protein component are present in the composition in a dry weight ratio of about 0.001:1.

11. The composition of claim 1 wherein the proton pump inhibitor and the protein component are present in the composition in a dry weight ratio of about 0.1:0.5.

12. The composition of claim 1 wherein the proton component comprises protein concentrate, protein isolate and/or protein hydrolysate.

13. The composition of claim 1 wherein the protein component is L-carnosine.

14. The composition of claim 1 further comprising at least one

pharmaceutically acceptable excipient.

15. The composition of claim 1 wherein the composition comprises a solid dosage forms selected from a tablet, a suspension tablet, a bite suspension tablet, a rapid dispersion tablet, a chewable tablet, an effervescent tablet, a bilayer tablet, a caplet, a capsule, a powder, a lozenge, a sachet, a cachet, a troche, a pellet, a granule and a microgranule.

16. The composition of claim 1 wherein the composition comprises a bi-layer tablet having a core comprising said proton pump inhibitor and a outer layer comprising the protein component, wherein said outer layer substantially completely surrounds the core.

17. A method of treating or preventing an acid related gastrointestinal disorder, the method comprising administering to a subject in need thereof a therapeutically effective amount of a composition of Claim 1.

18. A pharmaceutical composition comprising an acid labile proton pump inhibitor and a protein component, wherein: upon administration the composition to a plurality of fasted adult human subjects, the subjects exhibit an average plasma concentration of the PPI of at least about 0.1 μg/ml at any time within about 90 minutes.

Figure 1: 20:1 L-carnosine + 20:1 sodium bicarbonate

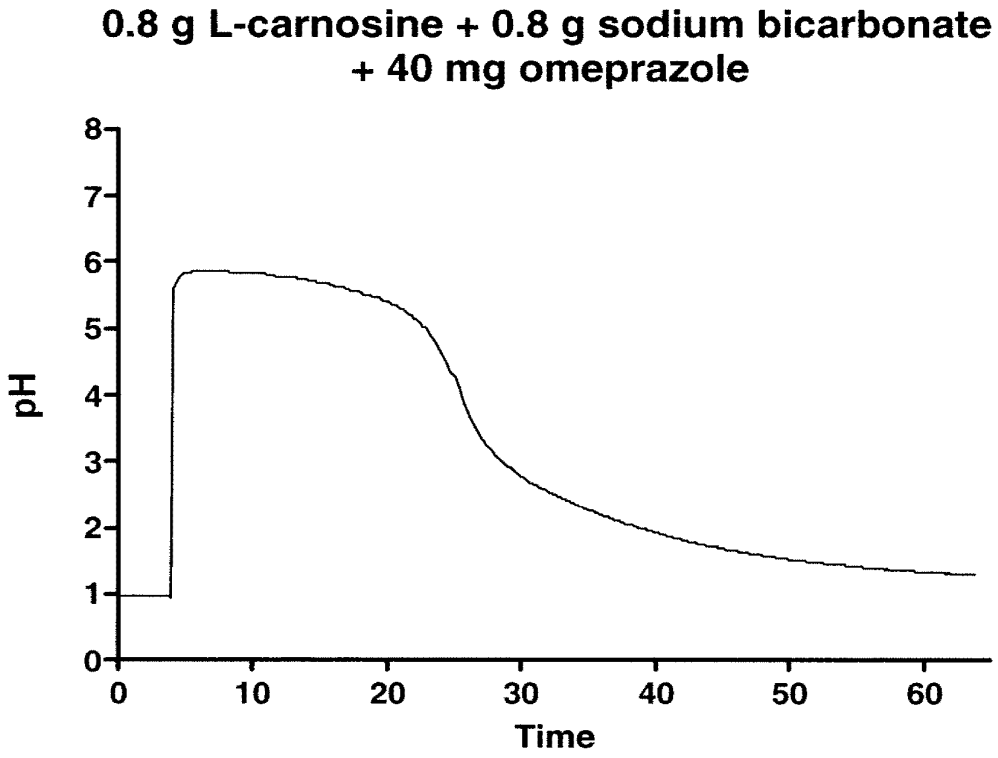


Figure 2: 20:1 L-carnosine + 20:1 sodium bicarbonate

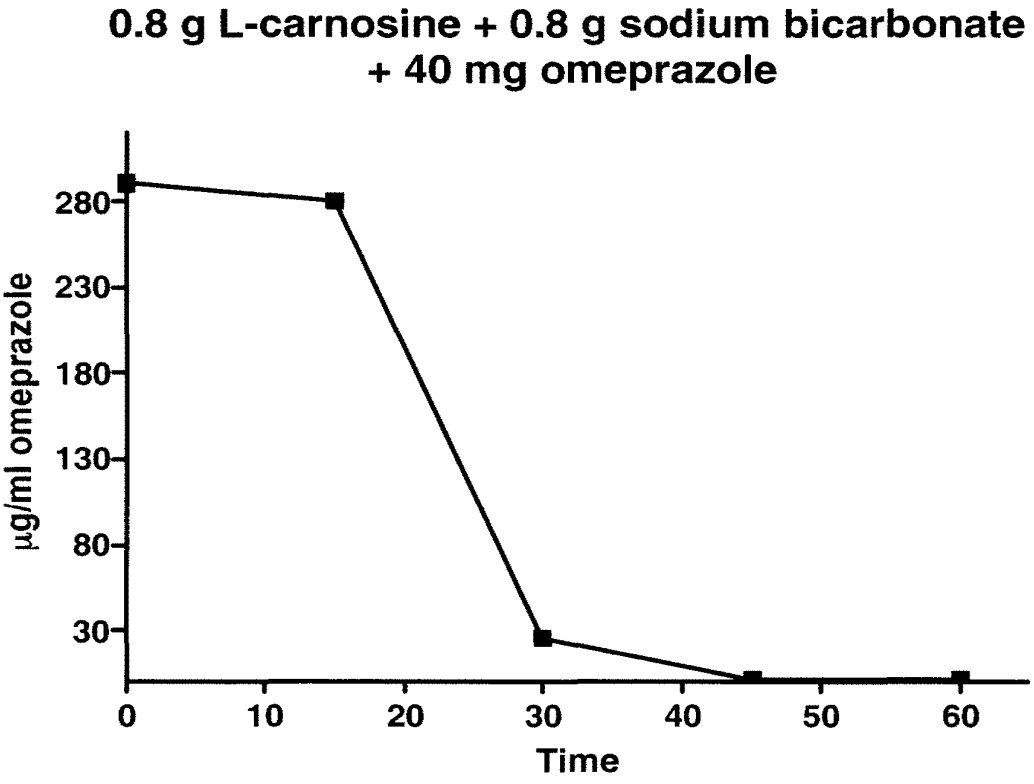


Figure 3: 40:1

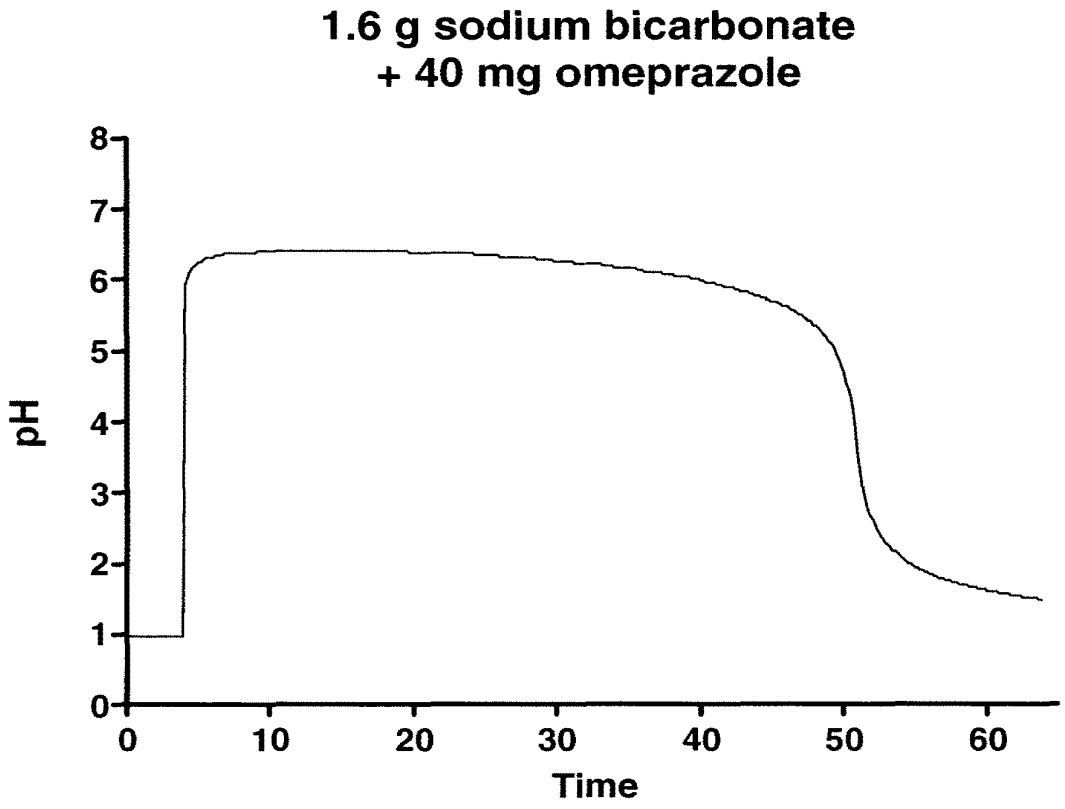

1.6 g sodium bicarbonate
+ 40 mg omeprazole
pH
8
7
6
5
4
3
2
1
0
0
10
20
30
40
50
60
Time

Figure 4: 40:1

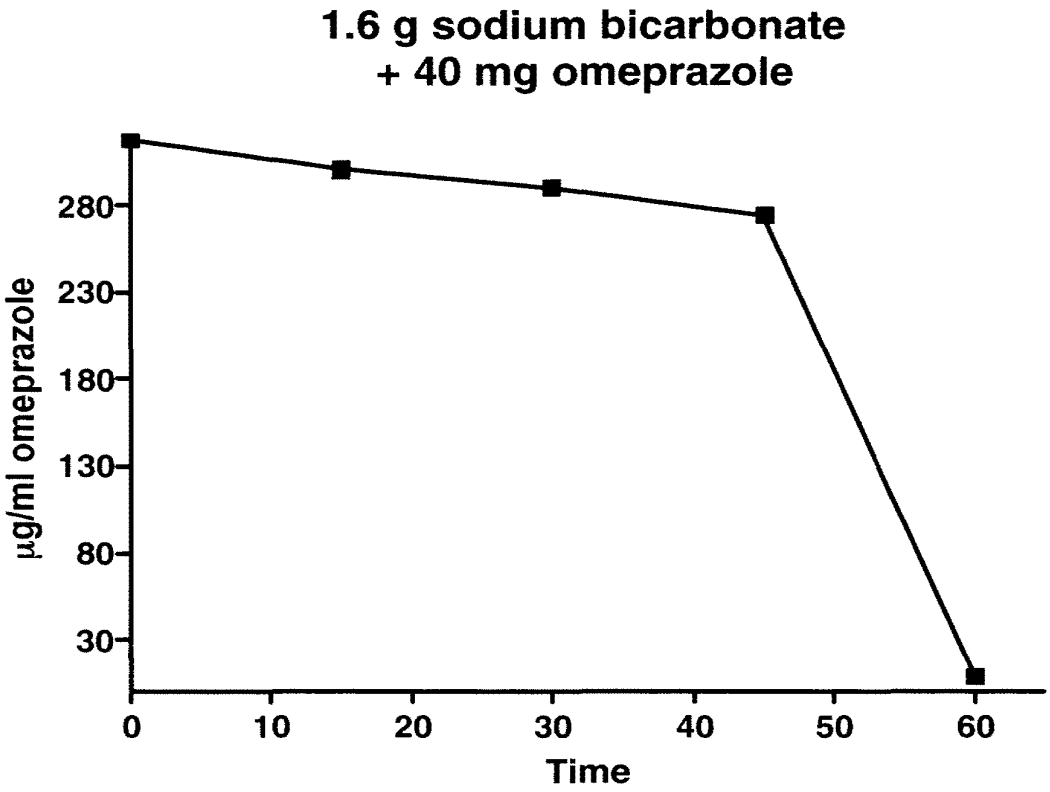

1.6 g sodium bicarbonate
+ 40 mg omeprazole
μg/ml omeprazole
280
230
180
130
80
30
0
10
20
30
40
50
60
Time

Figure 5: 20:1 aluminum glycinate + 20:1 sodium bicarbonate

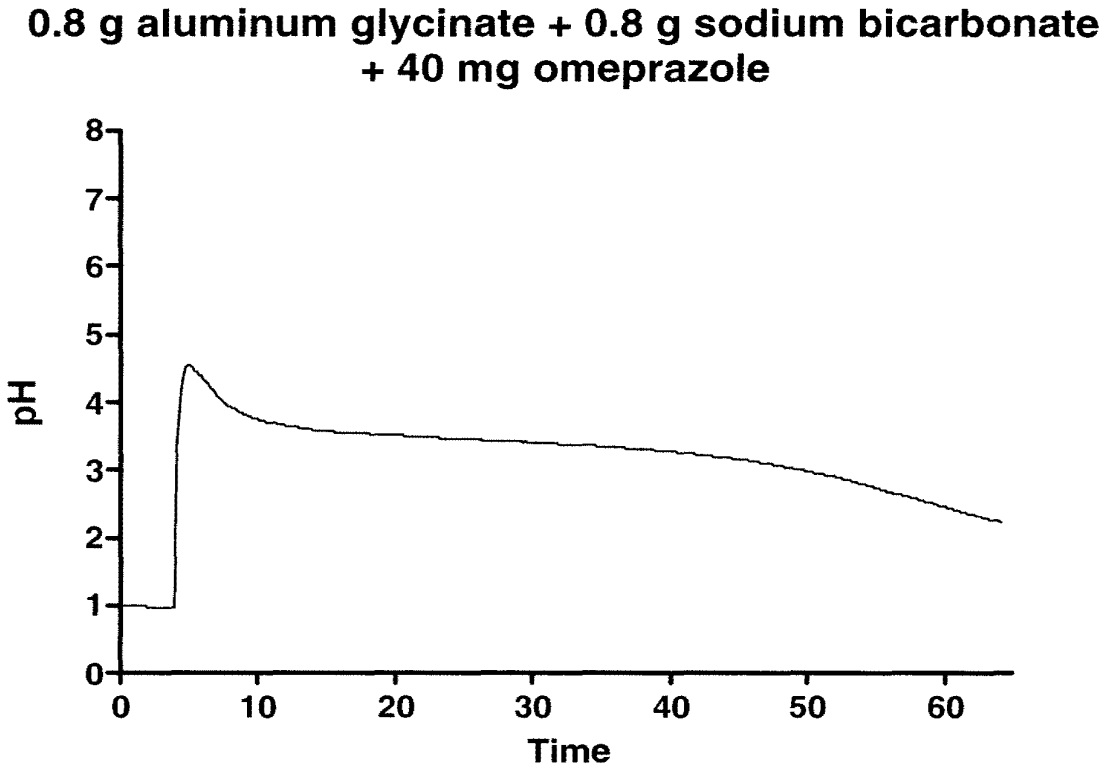
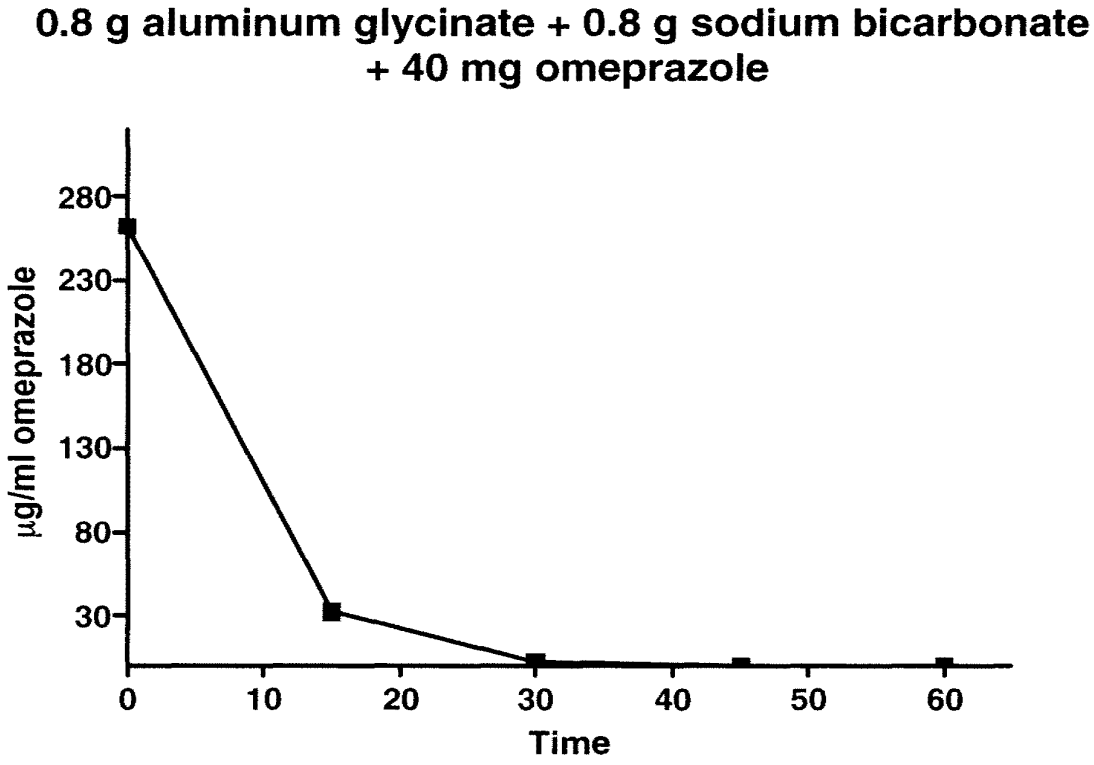


Figure 6: 20:1 aluminum glycinate + 20:1 sodium bicarbonate



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/70343

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/40; A61K 31/44 (2008.04)
USPC - 514/338
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
514/338

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
514/256 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PGPB,USPT,EPAB,JPAB; Google, PubMed
proton pump inhibitor, formulation or composition stabilization, protein or polypeptide or dipeptide or carnosine, gastric acid reduction degradation, omeprazole, tenatoprazole

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6,780,882 B2 (PHILLIPS) 24 August 2004 (24.08.2004) col 6, ln 30-65; col 9, ln 21-25; col 12, ln 55-62; col 13, ln 44-45; col 22, ln 51-55	1-18
Y	US 4,637,996 A (KONISHI) 20 January 1987 (20.01.1987) col 1, ln 20-25	1-18

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
02 October 2008 (02.10.2008)	08 OCT 2008
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2007)

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 December 2009 (03.12.2009)

PCT

(10) International Publication Number
WO 2009/145905 A1

(51) International Patent Classification:
A61K 9/48 (2006.01) *A01N 43/40* (2006.01)

(21) International Application Number:
PCT/US2009/003281

(22) International Filing Date:
29 May 2009 (29.05.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/129,029 30 May 2008 (30.05.2008) US

(71) Applicant *(for all designated States except US)*: **POZEN INC.** [US/US]; 1414 Raleigh Road, Suite 400, Chapel Hille, NC 27517 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **PLACHETKA, John, R.** [US/US]; 321 Silver Creek Trail, Chapel Hill, NC 27517 (US).

(74) Agents: **ANDREW, Mcaleavey** et al.; Law Office Of Michael A. Sanzo, Llc, 15400 Calhoun Drive, Suite 125, Rockville, MD 20855 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

(54) **Title**: DOSAGE FORMS FOR THE RAPID AND SUSTAINED ELEVATION OF GASTRIC PH

(57) **Abstract**: The present invention is directed to pharmaceutical compositions and dosage forms that can be used to treat diseases characterized by abnormal gastric acid secretion. The dosage forms are designed to immediately release both a proton pump inhibitor (ppi) and an H2 blocker.

WO 2009/145905 A1

Dosage Forms for the Rapid and Sustained Elevation of Gastric pH

Cross Reference to Related Applications

The present application claims priority to, and the benefit of, United States provisional application 61/129,029 filed on May 30, 2008, the contents of which is hereby incorporated by reference in its entirety.

Field of the Invention

The present invention is directed to orally administered pharmaceutical compositions that rapidly elevate the gastric pH of a patient. The pharmaceutical compositions include at least one H2 blocker and at least one proton pump inhibitor, both of which are released immediately after ingestion. The compositions may be used in the treatment of gastrointestinal disorders, and particularly for the treatment of gastroesophageal reflux disease.

Background of the Invention

The ability to regulate gastric pH is important in the treatment of gastroesophogeal reflux disease (GERD), in maintaining the integrity of acid labile drugs and in preventing the development of gastrointestinal lesions associated with the administration of certain drugs, particularly NSAIDs (see U.S. 6,926,907 and WO 2004/060372). Two types of agents frequently prescribed for regulating gastric pH are H2 blockers and proton pump inhibitors. H2 blockers have a relatively rapid onset of action but a short duration of effectiveness (typically 8-12 hours). As a result, these agents provide rapid relief but may not provide sufficient protection for patients with more severe forms of GERD or for patients chronically taking NSAIDs. Examples of H2 blockers currently on the market are: cimetidine (Tagamet®); famotidine (Pepcid®); nizatidine (Axid®); and ranitidine (Zantac®)

Proton pump inhibitors (PPIs) inhibit the enzyme responsible for secreting acid into the stomach and typically have a duration of action long enough that they only need to be taken once a day. However, most proton pump inhibitors are acid labile. As a result, they are usually enterically coated and this contributes to a very slow onset of effectiveness (see U.S. 4,853,230; 4,786,505; EP 0277,741; and EP 0342,522). Patients taking PPIs usually

do not get substantial relief from their symptoms for at least 24 hours after ingestion and several days may be required (*Clin. Pharmakinet 20*:38-49(1991)). Recently, attempts have been made to reduce the time needed for achieving a therapeutic effect by using dosage forms that release PPIs immediately after ingestion along with an antacid buffer to raise gastric pH (U.S. 5,840,737; 6,489,346; 6,645,988; 6,780,882; 4,786,505; and 6,183,776). Examples of proton pump inhibitors are: omeprazole (Prilosec®); esomeprazole (Nexium®); lansoprazole (Prevacid®); pantoprazole (Protonix®); rabeprazole (Aciphex®), tenatoprazole and s-tenatoprazole. "Reversible proton pump inhibitors" and "acid pump antagonists" that are less susceptible to acid degradation include AZD-0865, AR-H047108, CS-526, pumaprazole, revaprazan and soraprazan (see WO9605177 and WO9605199).

Although the PPIs are most commonly used in the treatment of severe GERD, they have also been used to reduce the risk of gastrointestinal lesions in patients taking NSAIDs (U.S. 5,204,118; U.S. 5,417,980; U.S. 5,466,436; U.S. 5,037,815; and 6,365,184). However, the slow onset of effectiveness associated with these drugs is a serious disadvantage in a medication designed to relieve acute symptoms. In addition, attempts to reduce the risk of gastrointestinal ulcers using PPIs alone appears not to have been met with complete success. Despite a significant reduction in gastroduodenal lesions with the concomitant administration of a proton pump inhibitor during six months of NSAID therapy, up to 16% of patients still develop ulcers (*N. Eng. J. Med. 338*:727-734 (1998)).

Summary of the Invention

The present invention is based upon the development of dosage forms for oral administration that provide for both the rapid and long term elevation of gastric pH. This is accomplished by releasing both a PPI and an H2 blocker from the dosage forms immediately after ingestion. The dosage forms may be used to treat patients for diseases characterized by abnormal gastric acid secretion, especially gastric esophageal reflux disease.

In its first aspect, the invention is directed to a pharmaceutical composition in unit dosage form for oral administration to a patient which contains both a therapeutically effective amount of a proton pump inhibitor (ppi), and a therapeutically effective amount of an H2 blocker. The term "therapeutically effective amount" means that, upon ingestion of

one or more unit dosage forms by a patient, sufficient drug is present to achieve the desired therapeutic effect. For example a "therapeutically effective amount" of a ppi means that there is a sufficient amount of drug to produce an increase in the median of gastric pH measurements taken at regular intervals over a 24 hour period. Therapeutically effective dosages for the PPIs and H2 blockers specifically recited herein are well known in the art.

The dosage forms are designed so that at least 10%, and preferably at least 20% or 50%, of both the ppi and the H2 blocker are released into the stomach of a patient within fifteen minutes, and preferably within ten, five or three minutes, after ingestion as determined using standard *in vivo* or *in vitro* methods. Unless otherwise indicated, all percentages herein are weight percentages. For example, in a tablet with 10 mg of a ppi, 10 mg of an H2 blocker and 80 mg of other components, the ppi and H2 blocker would each be present at 10%. Ten percent of both the ppi and the H2 blocker in this tablet would be released when 1 mg of ppi and 1 mg of H2 blocker were released. In other dosage forms of the invention, at least 1 mg (and preferably 5 or 10 mg) of a ppi and at least 1 mg (and preferably 5 or 10 mg) of an H2 blocker are released within fifteen minutes and preferably within ten, five or three minutes after ingestion, regardless of the percentage of total drug this represents. Again, the amount released may be determined using either standard *in vivo* or *in vitro* methods.

In order to allow for immediate release, at least a portion (and preferably all) of the ppi and the H2 blocker must be free of agents or barriers that retard dissolution, *e.g.*, at least a portion (and optionally all) of these drugs must not be surrounded by an enteric coating. Small amounts of buffer may be present in dosage forms to stabilize the drugs but the total amount of buffer should not exceed 15 mg, and preferably should not exceed 5 mg or 1 mg. After administration, the pH in the stomach of a patient with a gastric pH of 2.5 or less should rise to 3.5 or higher within 45 minutes, and preferably within 30 or 20 minutes. pH should remain elevated at or above 3.5 for at least 2 hours, and preferably for at least 6, 8, 10, 12 or 16 hours.

The PPIs used in dosage forms should typically be present at 1-200 mg and are preferably selected from the group consisting of: omeprazole, esomeprazole, lansoprazole, pantoprazole, tenatoprazole, S-tenatoprazole and rabeprazole. Particularly preferred are

dosage forms having a ppi selected from the group consisting of: omeprazole, present at between 5 mg and 50 mg; esomeprazole, present at 5-100 mg; lansoprazole, present at 15-150 mg; pantoprazole, present at between 10 mg and 200 mg; and rabeprazole, present at between 5 mg and 100 mg.

Preferably, H2 blockers are present in dosage forms at 1-300 mg and are selected from the group consisting of: cimetidine; ranitidine; famotidine; ebrotidine; pabutidine; lafutidine; and nizatidine. Especially preferred are dosage forms having: cimetidine at 100 to 800 mg; ranitidine at 50-300 mg; famotidine at 5-100 mg; ebrotidine at 400–800 mg/unit dose; pabutidine at 40 mg/unit dose; lafutidine at 5–20 mg; and nizatidine at 50-600 mg.

The dosage forms may be tablets, capsules or powders and have the ppi and the H2 blocker in admixture. Alternatively, the dosage forms may be multilayer tablets in which essentially all of the ppi is in one layer and essentially all of the H2 blocker is in a separate layer. The term "essentially all" refers to greater than 90% (and preferably greater than 95% or 99%) of the total amount of a drug present. Optionally, the layer containing the ppi and/or the layer containing said H2 blocker also includes at least one disintegrant and/or a compound that causes effervescence. Disintegrants that may be used include: croscarmellose sodium, crospovidone, sodium starch glycolate, povidone, crosslinked polyvinylpyrrolidone, starch, low substituted hydroxymethylcellulose, methylcellulose, microcrystalline cellulose.

In another aspect, the invention is directed to method of treating a patient for a disease or condition characterized by abnormal gastric acid production, especially gastric acid reflux disease. Treatment involves administering to the patient any of the dosage forms above. The invention also includes a method of treating a patient for pain or inflammation, by administering one of the NSAID-containing dosage forms described above.

Definitions

A. “Unit dose” or “unit dosage form” refers to a single drug administration entity. By way of example, a single tablet or capsule would be a unit dosage form.

B. "Proton pump inhibitors" are drugs (usually benzimidazole derivatives) that block gastric acid secretion by irreversibly inhibiting H^+/K^+ ATPase. Examples include omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole.

C. "H2 blockers" as used herein is synonymous with "H_2-receptor antagonist" or "H_2 antagonist." These drugs block the action of histamine on parietal cells in the stomach, thereby decreasing acid production by these cells. Examples include: cimetidine; ranitidine; famotidine; ebrotidine; pabutidine; lafutidine; and nizatidine.

D. A "disease or condition characterized by abnormal gastric acid production" includes all diseases and conditions in which acid secretion: a) is abnormally elevated; b) occurs at inappropriate times; or c) results in the irritation of the esophagus or other organs. The term includes: dyspepsia, peptic ulcers, Zollinger-Ellison syndrome, and gastroesophageal reflux disease (GORD/GERD).

E. "Therapeutically effective amount" as to drug dosage shall mean a dosage that provides the specific pharmacological response for which the drug is administered in a significant number of subjects in need of such treatment. For drugs already on the market, a therapeutically effective amount shall include dosages that have been determined as safe and effective for any indication. Nevertheless, this does not necessarily exclude substantially lesser (or greater) dosages than established minimum (or maximum) dosages in particular cases.

F. "Onset of action" refers to the interval that begins when a drug is first ingested by a patient and that ends when a therapeutic effect is first observed.

G. "Co-timely" with respect to drug administration refers to the administration of a second drug for the treatment of a condition while a first drug is still present in a therapeutically effective amount.

H. "Multilayer tablet" refers to a tablet dosage form in which components are found in two or more distinct regions. For example, a multilayer tablet may contain an outer layer

in which an H2 blocker is essentially the only active agent and an inner layer in which essentially the only active agent is a PPI antagonist.

I. "Pharmaceutical composition" refers to a composition containing the drug combinations described herein together with one or more pharmaceutically acceptable carriers or excipients. Typical excipients would include buffering agents (*e.g.*, phosphate or bicarbonate buffers); binders (*e.g.*, polyvinyl pyrrolidone (PVP), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC)); plasticizers (*e.g.*, polysorbates; dimethyl phthalate, diethyl phthalate, triacetin, triethyl citrate, and polyethylene glycol (PEG)); lubricants (*e.g.*, magnesium stearate); disintegrants (*e.g.*, croscarmellose salts) etc. Flavoring agents, coloring agents and coatings may also be present.

Detailed Description of the Invention

The present invention is directed to dosage forms that provide for the quick release of both a ppi and an H2 blocker and which may be used to elevate the gastric pH of a patient. These drugs are well known in the art and the preferred agents described herein are commercially available. If desired, drugs can also be manufactured using methodology well known in the art.

It will be understood that the drugs used in dosage forms, *i.e.*, PPIs, H2 blockers and NSAIDs, may be used in any pharmaceutically acceptable form, *e.g.* they may be in the form of an acid, base or salt. Unless otherwise indicated the recitation of any drug herein encompasses all these different forms of the drug. However, the weights and percentages recited refer to the free form of the drug. Thus, a composition having 10 mg of naproxen would have the same amount of this drug even though different salt forms may be used.

Making of Pharmaceutical Preparations

The pharmaceutical compositions and dosage forms of the present invention can be made in accordance with methods that are standard in the art (see *e.g.*, Remington's Pharmaceutical Sciences, 16th edition, A. Oslow, editor, Easton, PA (1980)). Drugs may be prepared in admixture with conventional excipients, carriers, buffers, flavoring agents, etc. Typical 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. Pharmaceutical preparations can be sterilized and, if desired, mixed with auxiliary agents such as: lubricants; preservatives; disintegrants; stabilizers such as cyclodextrans; wetting agents; emulsifiers; salts; buffers; coloring agents; flavoring agents; or aromatic substances. Tablets can be made using standard technology well known in the art. Drugs may be granulated by methods such as slugging, low-shear or high-shear granulation, wet granulation, or fluidized bed granulation. Outer coatings may be formed by preparing a mixture containing appropriate polymers.

It is expected that a skilled pharmacologist will adjust the amount of drug in a pharmaceutical composition or administered to a patient based upon standard techniques well known in the art. Nevertheless, the following general guidelines are provided:

With respect to H2 blockers and PPIs, unit dosage forms may contain anywhere from 1 mg to as much as 1g. Typical amounts for H2 blockers are: cimetidine, 100 to 800 mg/unit dose; ranitidine, 50-300 mg/unit dose; famotidine, 5-100 mg/unit dose; ebrotidine 400 – 800 mg/unit dose; pabutidine 40 mg/unit dose; lafutidine 5–20 mg/unit dose; and nizatidine, 50-600 mg/unit dose. Proton pump inhibitors will typically be present at about 5 mg to 600 mg per unit dose. For example, the proton pump inhibitor omeprazole should be present in an amount from 5 to 50 mg, with about 10 or 20 mg being preferred. Other typical amounts are: esomeprazole, 5–100 mg, with about 40 mg being preferred; lansoprazole, 5-150 mg (preferably 5-50 mg), with about 7.5, 15 or 30 mg being most preferred; pantoprazole, 10-200 mg, with about 40 mg being preferred; and rabeprazole, 5-100 mg, with about 20 mg being preferred.

Treatment of Patients

The pharmaceutical compositions described above can be used to treat a patient for any disease or condition in which proton pump inhibitors are indicated. Common conditions will include GERD, duodenal ulcers, gastric ulcers, severe erosive esophagitis, and Zollinger Ellison syndrome In all cases, a patient should be administered a sufficient daily dosage to eliminate the symptoms associated with excess gastric acid production. Typical

daily dosages of all of the preferred agents are well known in the art. As a general rule, drugs will be designed to be taken once a day but other dosing regimens may also be used.

All references cited herein are fully incorporated herein by reference. Having now fully described the invention, it will be understood by those of skill in the art that the invention may be performed within a wide and equivalent range of conditions, parameters and the like, without affecting the spirit or scope of the invention or any embodiment thereof.

What is Claimed is:

1. A pharmaceutical composition in unit dosage form for oral administration to a patient comprising: a therapeutically effective amount of a proton pump inhibitor (ppi), and a therapeutically effective amount of an H2 blocker, wherein:
   a) at least 10% of both said ppi and said H2 blocker are released from said dosage form into the stomach of said patient within fifteen minutes after ingestion and/or at least 1 mg of said ppi and said H2 blocker are released from said dosage form into the stomach of said patient within fifteen minutes after ingestion;
   b) at least a portion of both said ppi and said H2 blocker are not surrounded by an enteric coating;
   c) said dosage form contains no more than 15 mg of buffer.

2. The pharmaceutical composition of claim 1, wherein, after ingestion by a patient with a gastric pH of 2.5 or less, said gastric pH rises to at least 3.5 within 45 minutes and remains at or above 3.5 for at least 6 hours.

3. The pharmaceutical composition of claim 2, wherein said gastric pH rises to at least 3.5 within 30 minutes after ingestion and remains at or above 3.5 for at least 24 hours.

4. The pharmaceutical composition form of claim 1, wherein none of the ppi and none of the H2 blocker in said dosage form are surrounded by an enteric coating.

5. The pharmaceutical composition of claim 4, wherein:
   a) at least 20% of both said ppi and said H2 blocker are released from said dosage form into the stomach of said patient within ten minutes after ingestion; and
   b) after ingestion by a patient with a gastric pH of 2.5 or less, said gastric pH rises to at least 3.5 within 45 minutes and remains at or above 3.5 for at least 12 hours.

6. The pharmaceutical composition of claim 5, wherein said gastric pH rises to at least 3.5 within 30 minutes after ingestion and remains at or above 3.5 for at least 24 hours.

7. The pharmaceutical composition of claim 1, wherein:
   a) at least 5 mg of both said ppi and said H2 blocker are released from said dosage form into the stomach of said patient within five minutes after ingestion; and
   b) after ingestion by a patient with a gastric pH of 2.5 or less, said gastric pH rises to at least 3.5 within 45 minutes and remains at or above 3.5 for at least 16 hours.

8. The pharmaceutical composition of claim 7, wherein said gastric pH rises to at least 3.5 within 30 minutes after ingestion and remains at or above 3.5 for at least 24 hours.

9. The pharmaceutical composition of claim 1, wherein said ppi is present in said dosage form at 1-200 mg and is selected from the group consisting of: omeprazole, esomeprazole, lansoprazole, pantoprazole, tenatoprazole and rabeprazole.

10. The pharmaceutical composition of claim 1, wherein said ppi is selected from the group consisting of: omeprazole, present in said dosage form at between 5 mg and 50 mg; esomeprazole, present in said dosage form at 5-100 mg; lansoprazole, present in said dosage form at 15-150 mg; pantoprazole, present in said dosage form at between 10 mg and 200 mg; and rabeprazole, present in said dosage form at between 5 mg and 100 mg.

11. The pharmaceutical composition form of claim 1, wherein said H2 blocker is present in said dosage form at 1-300 mg and is selected from the group consisting of: cimetidine; ranitidine; famotidine; ebrotidine; pabutidine; lafutidine; and nizatidine.

12. The pharmaceutical composition form of claim 11, wherein said ppi is present in said dosage form at 1-200 mg and is selected from the group consisting of:

omeprazole, esomeprazole, lansoprazole, pantoprazole, tenatoprazole and rabeprazole.

13. The pharmaceutical composition of claim 12, wherein said ppi is selected from the group consisting of: omeprazole, present in said dosage form at between 5 mg and 50 mg; esomeprazole, present in said dosage form at 5-100 mg; lansoprazole, present in said dosage form at 15-150 mg; pantoprazole, present in said dosage form at between 10 mg and 200 mg; and rabeprazole, present in said dosage form at between 5 mg and 100 mg.

14. The pharmaceutical composition of claim 5, wherein:

a) said ppi is selected from the group consisting of: omeprazole, present in said dosage form at between 5 mg and 50 mg; esomeprazole, present in said dosage form at 5-100 mg; lansoprazole, present in said dosage form at 15-150 mg; pantoprazole, present in said dosage form at between 10 mg and 200 mg; and rabeprazole, present in said dosage form at between 5 mg and 100 mg; and

b) said H2 blocker is selected from the group consisting of: cimetidine present in said dosage form at 100 to 800 mg; ranitidine present in said dosage form at 50-300 mg; famotidine present in said dosage form at 5-100 mg; ebrotidine present in said dosage form at 400 – 800 mg; pabutidine present in said dosage form at 40 mg; lafutidine present in said dosage form at 5–20 mg; and nizatidine present in said dosage form at 50-600 mg.

15. The pharmaceutical composition of claim 14, wherein said gastric pH rises to at least 3.5 within 30 minutes after ingestion and remains at or above 3.5 for at least 24 hours.

16. The pharmaceutical composition of claim 1, wherein said dosage form is a tablet, capsule or powder and wherein said ppi and said H2 blocker are in admixture.

17. The pharmaceutical composition of claim 1, wherein said dosage form is a tablet and wherein essentially all of said ppi is in one layer and essentially all of said H2 blocker is in a separate layer.

18. The pharmaceutical composition of claim 17, wherein the layer containing said ppi and/or the layer containing said H2 blocker also comprise at least one disintegrant and/or a compound that causes effervescence.

19. The pharmaceutical composition form of claim 17, wherein said dosage form comprises a disintegrant selected from the group consisting of: croscarmellose sodium, crospovidone, sodium starch glycolate, povidone, crosslinked polyvinylpyrrolidone, starch, low substituted hydroxymethylcellulose, methylcellulose, microcrystalline cellulose.

20. A method of treating a patient for a disease or condition characterized by abnormal gastric acid production comprising administering to said patient the pharmaceutical composition of any one of claims 1-19.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 09/03281

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 9/48; A01N 43/40 (2009.01)
USPC - 514/452; 514/338
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC - 514/452; 514/338

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 424/400; 514/338 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB,USPT,USOC,EPAB,JPAB); Google
Search Terms Used: omeprazole, cimetidine, pH, 24 hour, non-enteric, separate layer

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — Y	US 2008/0103169 A1 (Phillips) 01 May 2008 (01.05.2008) para [0018]-[0030], [0057]-[0074], [0122]-[0133], [0181]-[0187], [0212], [0230]-[0238], [0275]-[0276], [0350], [0435]-[0438]; Fig 3-4	1-16, 20 --- 17-19
Y	US 2008/0031941 A1 (Pettersson) 07 February 2008 (07.02.2008) para [0021], [0034]-[0037], [0069]	17-19
A	US 2007/0243251 A1 (Taneja et al.) 18 October 2007 (18.10.2007) entire document	1-20
A	US 2006/0165797 A1 (Plachetka) 27 July 2006 (27.07.2006) entire document	1-20

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 July 2009 (06.07.2009)	14 JUL 2009
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2007)

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 December 2010 (29.12.2010)

PCT

(10) International Publication Number
WO 2010/151697 A1

(51) International Patent Classification:
A01N 43/40 (2006.01) *A61K 31/44* (2006.01)

(21) International Application Number:
PCT/US2010/039864

(22) International Filing Date:
24 June 2010 (24.06.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/220,483 25 June 2009 (25.06.2009) US
61/248,755 5 October 2009 (05.10.2009) US

(71) Applicant *(for all designated States except US)*: **POZEN INC.** [US/US]; 1414 Raleigh Road, Suite 400, Chapel Hill, NC 27517 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **PLACHETKA, John, R.** [US/US]; 321 Silver Creek Trail, Chapel Hill, NC 27514 (US).

(74) Agents: **SANZO, Michael, A.** et al.; Law Office of Michael A. Sanzo, LLC, 15400 Calhoun Drive, Suite 125, Rockville, MD 20855 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

(54) **Title**: METHOD FOR TREATING A PATIENT IN NEED OF ASPIRIN THERAPY

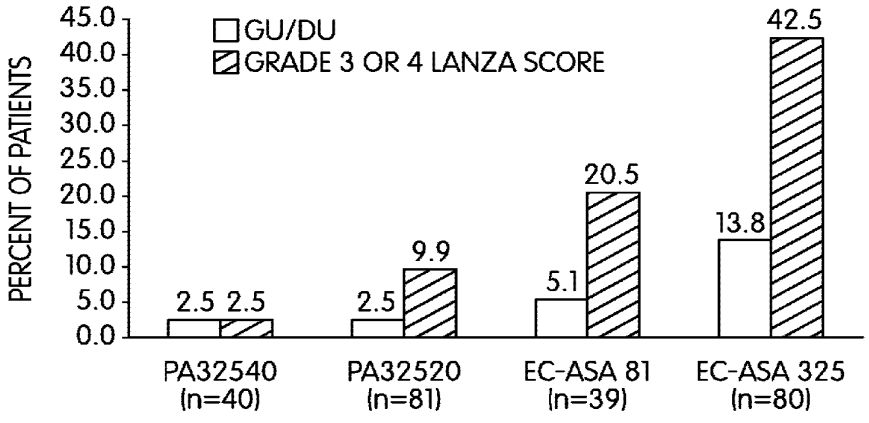


FIG. 1

(57) **Abstract**: The present disclosure is directed to a method for treating a disease or disorder in a patient at risk of developing an NSAID-associated ulcer by administering to the patient in need thereof a pharmaceutical composition in unit dosage form comprising aspirin, or a pharmaceutically acceptable salt thereof, and an acid inhibitor to the at risk patient and thereby decreasing the patient's risk of developing an ulcer.

WO 2010/151697 A1

Method for Treating a Patient in Need of Aspirin Therapy

Cross Reference to Related Applications

[0001] The present application claims the benefit of United States provisional application 61/220,483, filed on June 25, 2009 and of United States provisional application 61/248,755, filed on October 5, 2009, both of which are incorporated herein by reference in their entirety.

Field of the Invention

[0002] The present disclosure is directed to a method for treating a disease or disorder in a patient at risk of developing a non-steroidal anti inflammatory drug ("NSAID") -associated ulcer by administering to the patient in need thereof a pharmaceutical composition in unit dosage form comprising aspirin, or a pharmaceutically acceptable salt thereof, and an acid inhibitor to the at risk patient and thereby decreasing the patient's risk of developing an ulcer.

Background of the Invention

[0003] Aspirin is an NSAID, and is the general name for acetylsalicylic acid. Aspirin is used to reduce fever and provide pain relief from conditions such as muscle aches, toothaches, common colds, and headaches. It may also be used to reduce pain and inflammation in conditions such as arthritis, rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis. Aspirin is also an anti-coagulant, and low-dose aspirin is often used to reduce blood clots that may lead to cardiovascular disease, including heart attack and stroke. In addition to its preventative use, it is also used in treatment of cardiovascular diseases. Low-dose aspirin is recommended for the prevention of cardiovascular and cerebrovascular events, and an estimated 50 million people in the United States take aspirin for cardioprotection.

[0004] Aspirin is a potent inhibitor of thromboxane A2 ("TxA2") synthesis by platelets, reducing their aggregation and adhesion and thus reducing the risk of arterial thrombosis (Awtry, *et al.*, *Circulation 101*:1206-1218 (2000); Gengo, *et al.*, *J. Clin. Pharmacol. 48*:335-343 (2008)). This cardioprotective benefit of aspirin is not realized with antiplatelet drugs until platelet TxA2 generation is reduced by more than 95% in serum (Patrono, *et al.*, *New Eng. J. Med. 353*:2373-2382 (2005); Grosser, *et al.* "Thromboxane Generation," in Platelets, 2nd ed., Michelson ed., Elseiver (2007)). For example, 95% inhibition of

TxA2 in plasma corresponds to only a 50-75% reduction in the urinary excretion rates of the TxA2 metabolite, 11-dh-TXB_2, due to the extraplatelet sources of this urinary metabolite (Hart, *et al.*, *Pharmacotherapy 23(5)*:579-584 (2003)).

[0005] While aspirin and other NSAIDs remain a key therapy for pain, inflammation, and cardiovascular disease, there is a substantial risk of upper gastrointestinal ("UGI") ulcerations and ulcer complications, such as, for example, bleedings and perforations, with chronic NSAID therapy. This risk increases with use over time. The cumulative incidence of gastroduodenal ulcers ("GDUs") with conventional NSAID use has been reported to be as high as 25-30% at 3 months and 45% at 6 months versus 3-7% for placebo. At any given time, the incidence of UGI ulcers in NSAID users has been estimated to be as high as 30%. Certain risk factors associated with an NSAID user developing UGI ulcers are: age $\geq$ 50 years and history of UGI ulcer or bleeding. The mechanism associated with the increased incidence of ulcers in chronic NSAID users may be complex, but it is thought that gastric acid, combined with a reduction in protective mechanisms of the UGI mucosa, contribute to this pathology. UGI mucosal injury includes petechia, erosions and ulcers. In addition, once mucosal injury occurs, acid has the ability to impair normal hemostasis and healing. These factors, coupled with the known anti-platelet effect of some NSAIDs, may increase the risk for gastrointestinal ("GI") injury and bleeding. UGI effects of NSAIDs also include: dyspepsia (experienced by up to 40% of patients on NSAID therapy), erosive esophagitis ("EE") (experienced by 21% of regular NSAID users), and an increase in gastroesophageal reflux disease symptoms.

[0006] Because of these risks, physicians generally prefer to prescribe low-dose aspirin for preventing cardiovascular disease or stroke, even though low-dose aspirin does not have the same beneficial therapeutic effects as high-dose aspirin. Instead, physicians generally only prescribe high-dose aspirin if the therapeutic benefits outweigh the risks associated with aspirin therapy, for example if the patient has existing cardiovascular disease. Thus, if a formulation of aspirin reduces the risks associated with aspirin therapy, it would be preferable to have patients on high-dose aspirin therapy, for example for preventative treatment of cardiovascular disease or stroke. Thus, there is a need in the art for a formulation of aspirin that reduces the risks associated with aspirin therapy, particularly during chronic treatment.

Summary of the Invention

[0007] The present disclosure is based upon the discovery of an aspirin combination treatment that reduces the risks associated with aspirin therapy, for example undesirable gastrointestinal side effects and other safety concerns, particularly during chronic treatment. In certain embodiments, the treatment involves the administration of a single, coordinated, unit dosage form that combines: a) an acid inhibitor that raises intragastric pH levels; and b) aspirin that is specially formulated to be released in a coordinated way with the acid inhibitor, such that administration of the unit dosage form reduces the risks associated with aspirin therapy, for example any adverse effects the aspirin may have on gastroduodenal mucosa. Either short- or long-acting acid inhibitors can be effectively used in the unit dosage forms disclosed herein. In certain embodiments, this treatment has the added benefit of being able to protect patients from other gastrointestinal ulcerogens whose effect may otherwise be enhanced by the disruption of gastroprotective prostaglandins due to aspirin therapy.

[0008] In one aspect, the disclosure is directed to preventing or treating a disease or disorder in a patient at risk of developing an NSAID-associated ulcer by administration of the pharmaceutical compositions in unit dosage form disclosed herein. In another embodiment, administration of the pharmaceutical compositions in unit dosage form disclosed herein to treat a disease or disorder in a patient at risk of developing an NSAID-associated ulcer decreases the risk of the patient developing an ulcer, including but not limited to decreasing the risk of the occurrence of a gastroduodenal ulcer or a duodenal ulcer. In yet another embodiment, administration of the pharmaceutical compositions in unit dosage form disclosed herein to treat a disease or disorder in a patient at risk of developing an NSAID-associated ulcer reduces the patient's heartburn associated symptoms. In still another embodiment, administration of the pharmaceutical compositions in unit dosage form disclosed herein to treat a disease or disorder in a patient at risk of developing an NSAID-associated ulcer reduces the patient's dyspepsia associated symptoms. In yet another embodiment, administration of the pharmaceutical compositions in unit dosage form disclosed herein to treat a disease or disorder in a patient at risk of developing an NSAID-associated ulcer reduces the patient's level of urinary 11-dehydrothromboxane. In another aspect, the disclosure is directed to preventing or treating a disease or disorder in a patient in need thereof wherein the disease or disorder is

pain, inflammation, arthritis osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, headache, toothache, common cold, muscle ache, cardiovascular disease, cancer, cerebrovascular disease, or combinations thereof

[0009] In each of the embodiments disclosed herein the pharmaceutical composition in unit dosage form administered to the patient comprises: a) a therapeutically effective amount of an acid inhibitor in an amount sufficient to raise the gastric pH of the patient to at least about 3.5, 4.0, 4.5, 5.0, 5.5, or higher upon administration of one or more of the unit dosage forms, and b) a therapeutically effective amount of aspirin, or a pharmaceutically acceptable salt thereof; wherein the aspirin, or a pharmaceutically acceptable salt thereof, is released from the unit dosage form only when the pH of the surrounding medium or environment is about 3.5, 4.0, 4.5, 5.0, 5.5 or higher. In some embodiments, the pharmaceutical composition in unit dosage form comprises a) a therapeutically effective amount of an acid inhibitor that is immediately soluble when the dosage form is place in an aqueous medium, independent of pH, for example in an amount effective to raise the gastric pH of the patient to at least about 3.5, 4.0, 4.5, 5.0, 5.5, or higher upon administration of one or more of the unit dosage forms. In other embodiments, the pharmaceutical composition in unit dosage form comprises a) an acid inhibitor in an amount effective to raise the gastric pH of the patient to at least 3.5, 4.0, 4.5, 5.0, 5.5, or higher upon administration of one or more of the unit dosage forms. In certain embodiments, the pharmaceutical composition in unit dosage form comprises b) a therapeutically effective amount of aspirin, or a pharmaceutically acceptable salt thereof; wherein the aspirin or a pharmaceutically acceptable salt thereof is surrounded by a coating that is substantially insoluble in an aqueous medium at a pH below about 3.5, 3.0, 2.5, 2.0, 1.5, or lower. In other embodiments, the pharmaceutical composition in unit dosage form comprises b) aspirin or a pharmaceutically acceptable salt thereof, wherein the aspirin or a pharmaceutically acceptable salt thereof is released from the unit dosage form only when the pH of the surrounding medium or environment is about 3.5, 4.0, 4.5, 5.0, 5.5, or higher. In certain embodiments, the aqueous medium is also at a temperature of about 37°C.

[0010] In still other embodiments, a therapeutically effective amount of an acid inhibitor is an amount sufficient to raise the gastric pH of the patient to at least about 3.5, 4.0, 4.5, 5.0, 5.5, or higher upon administration of one or more of the unit dosage forms wherein the unit dosage form provides for coordinated release of the acid inhibitor and the

aspirin such that: i) at least a portion of the acid inhibitor is released independent of the pH of the surrounding medium or environment; and ii) the aspirin, or a pharmaceutically acceptable salt thereof, is not released from the unit dosage form until the pH of the surrounding medium is 3.5, 4.0, 4.5, 5.0, 5.5, or higher. Such pharmaceutical compositions have been described in U.S. Patent No. 6,926,907, which is incorporated herein by reference in its entirety. In still other embodiments, the pharmaceutical composition in unit dosage form comprises any mixture of the above described acid inhibitor and aspirin, or a pharmaceutically acceptable salt thereof.

[0011] In certain embodiments of the present disclosure, the risk of NSAID-associated gastrointestinal ulcer in a patient may be associated with short-term or chronic NSAID treatment, age of the patient (for example if the patient is 50 years of age or older), or a combination thereof. In the embodiments disclosed herein, a pharmaceutical composition in unit dosage form is administered to the patient for 7 days, 10 days, 14 days, 15 days, 16 days, 17 days, 18 days, 19 days, 20 days, 21 days, 22 days, 23 days, 24 days, 25 days, 26 days, 27 days, 28 days, 29 days, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 12 months, 18 months, or longer. In other embodiments, a pharmaceutical composition in unit dosage form is administered to the patient frequently or chronically.

[0012] In another aspect, the pharmaceutical composition in unit dose form disclosed herein decreases the risk of the patient developing a gastric ulcer, duodenal ulcer, or both. In yet another aspect, the disease or disorder treated by the pharmaceutical compositions disclosed herein include but are not limited to pain, inflammation, arthritis, osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, headache, toothache, common cold, muscle ache, cardiovascular disease, cancer (e.g., colon cancer) or any combination thereof. In other embodiments, the pharmaceutical composition in unit dose form disclosed herein may be administered to prevent or treat cardiovascular disease or cerebrovascular disease.

[0013] Numerous studies have provided evidence that NSAIDs, including aspirin, may prevent cancer. Experimental and epidemiologic (nonrandomized) studies, along with randomized clinical trials, have shown that NSAIDs may have a prophylactic effect against certain cancers. These results have been confirmed in certain colorectal cancers and suggested for other cancer sites. In other embodiments, the pharmaceutical composition in unit dose form disclosed herein may be administered to prevent or treat cancer, including but not limited to biliary tract cancer; brain cancer; breast cancer; cervical cancer;

choriocarcinoma; colon cancer; endometrial cancer; esophageal cancer; fibrosarcoma, gastric cancer; hepatoma, intraepithelial neoplasms; lymphomas; liver cancer; lung cancer (*e.g.*, small cell and non-small cell); melanoma; neuroblastomas; oral cancer; ovarian cancer; pancreatic cancer; prostate cancer; rectal cancer; sarcomas; skin cancer; testicular cancer; thyroid cancer; renal cancer, glioblastoma, adenocarcinoma, adenoma, astrocytoma, bladder tumor, bone carcinoma, brain carcinoma, Burkitt lymphoma, Kaposi Sarcoma, non-Hodgkins lymphoma, Hodgkins lymphoma, gastric tumor, breast carcinoma, cervical carcinoma, colon carcinoma, kidney carcinoma, liver carcinoma, lung carcinoma, ovarian carcinoma, pancreatic carcinoma, prostate carcinoma, rectal carcinoma, skin carcinoma, stomach carcinoma, testis carcinoma, thyroid carcinoma, chondrosarcoma, choriocarcinoma, fibroma, fibrosarcoma, glioblastoma, glioma, hepatoma, histiocytoma, leiomyoblastoma, leiomyosarcoma, leukemia, lymphoma, liposarcoma cell, mammary carcinoma, medulloblastoma, melanoma, metastases, muscle tumor, myeloma, ovarian carcinoma, plasmacytoma, neuroblastoma, neuroglioma, osteogenic sarcoma, pancreatic tumor, pituitary carcinoma, renal tumors, retinoblastoma, rhabdomyosarcoma, sarcoma, testicular tumor, thymoma, uterine carcinoma, Wilms' tumor, as well as other carcinomas and sarcomas. In particular embodiments, the pharmaceutical compositions disclosed herein are administered to a patient to prevent or treat colon cancer or colorectal cancer.

[0014] In a further aspect, the pharmaceutical compositions in unit dosage form disclosed herein may comprise an acid inhibitor in an amount effective to raise the pH of the gastric fluid of a patient to at least 3.5, at least 4.0, at least 4.5, at least 5.0, at least 5.5 or greater when the dosage form is administered to the patient, for example orally administered. The acid inhibitor may be present in the unit dosage form in an amount of from about 5 mg to about 1000 mg. In certain embodiments, the acid inhibitor is omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole, dexlansoprazole, and tenatoprazole, or pharmaceutically acceptable salts thereof. In particular embodiments, the pharmaceutical compositions in unit dosage forms disclosed herein comprise omeprazole, or a pharmaceutically acceptable salt thereof, in an amount of, for example, about 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, or 100 mg. In other embodiments, the pharmaceutical compositions in unit dosage forms disclosed herein comprise aspirin, or a pharmaceutically acceptable salt thereof, in an amount of, for example, from about 30 mg to about 1300 mg, or at an amount of about 75 mg, 81 mg, 100 mg, 150 mg, 162 mg, 300 mg, 325 mg, 500 mg, or 650 mg.

[0015] In a still further aspect, the pharmaceutical composition is formulated for administration to a patient one or more times daily. In one embodiment, the unit dosage form is suitable for oral administration. In certain embodiments, the unit dosage form may be a tablet, a sequential-delivery tablet formulation, a capsule, a capsule containing beads or minitablets. In one aspect, the unit dosage form is a tablet comprising a core and two or more layers, in which i) the core comprises aspirin or a pharmaceutically acceptable salt thereof; ii) a first layer surrounds the core and the layer is a coating that is substantially insoluble in aqueous medium at a pH below 3.5, for example below 3.0, 2.5, 2.0, 1.5, 1.0, or lower and/or at a temperature of about 37°C; and iii) at least one second layer surrounds the first layer and comprises the acid inhibitor. In some embodiments, the first layer may be, for example, an enteric coating ("EC") or a time-release coating. In other embodiments, the unit dosage form may be further surrounded by a pharmacologically inert, water soluble coating or film. In another embodiment, the administration of the unit dosage form disclosed herein improves compliance in a patient who requires short-term or chronic daily dosages of aspirin or a pharmaceutically acceptable salt thereof.

[0016] In one aspect, administering a pharmaceutical composition in unit dosage form to a patient is more effective at decreasing the risk of developing an ulcer than treatment with only aspirin, for example enteric-coated or non-enteric-coated aspirin, or a pharmaceutically acceptable salt thereof. In another aspect, administering a pharmaceutical composition in unit dosage form disclosed herein to a patient reduces the patient's heartburn associated symptoms more than treating the patient in need thereof with only aspirin, for example enteric coated or non-enteric coated aspirin, or a pharmaceutically acceptable salt thereof. In still another aspect, administering a pharmaceutical composition in unit dosage form disclosed herein to a patient reduces the patient's dyspepsia more than treating the patient in need thereof with only aspirin, for example enteric coated or non-enteric coated aspirin, or a pharmaceutically acceptable salt thereof. In yet another aspect, administering a pharmaceutical composition in unit dosage form disclosed herein to a patient reduces the patient's level of urinary 11-dehydrothromboxane more than treating the patient in need thereof with only aspirin, for example enteric coated or non-enteric coated aspirin, or a pharmaceutically acceptable salt thereof.

[0017] Another embodiment of the present disclosure is a solid pharmaceutical composition in unit dosage form suitable for oral administration to a mammal, comprising: a) omeprazole or pharmaceutically acceptable salt thereof that is immediately soluble when the dosage form is placed in an aqueous medium, independent of pH; and b) aspirin or a pharmaceutically acceptable salt thereof, surrounded by a coating that is substantially insoluble in an aqueous medium at a pH below 3.5 and/or at a temperature of about 37°C. In one embodiment, the omeprazole or pharmaceutically acceptable salt thereof is present in the composition in an amount effective to raise the pH of the gastric fluid of a mammal to at least about 3.5, 4.0, 4.5, 5.0, 5.5 or higher when the dosage form is administered orally to the mammal. In another embodiment, the amount of aspirin, or a pharmaceutically acceptable salt thereof, is about 75 mg, 81 mg, 100 mg, 150 mg, 162 mg, 300 mg, 325 mg, 500 mg, or 650 mg. In yet another embodiment, the amount of omeprazole, or a pharmaceutically acceptable salt thereof, is about 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, or 100 mg. The solid pharmaceutical composition in unit dosage form may be formulated to be administered to a patient one or more times daily. In certain embodiments, the solid pharmaceutical composition in unit dosage form is suitable for oral administration. In other embodiments, the solid pharmaceutical composition in unit dosage form may be a tablet, a sequential-delivery tablet formulation, a capsule, a capsule containing beads or minitablets. In another aspect, the solid pharmaceutical composition in unit dosage form is a tablet comprising a core and two or more layers, in which i) the core comprises aspirin or a pharmaceutically acceptable salt thereof; ii) a first layer surrounds the core and the layer is a coating that is substantially insoluble in aqueous medium at a pH below 3.5, for example below 3.0, 2.5, 2.0, 1.5, 1.0, or lower and/or at a temperature of about 37°C; and iii) at least one second layer surrounds the first layer and comprises omeprazole or pharmaceutically acceptable salt. In some embodiments, the first layer may be, for example, an enteric coating ("EC") or a time-release coating. In other embodiments, the solid pharmaceutical composition in unit dosage form may be further surrounded by a pharmacologically inert, water soluble coating or film.

Brief Description of the Drawings

[0018] The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be

better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

[0019] Figure 1 illustrates pooled gastroduodenal data from three Phase I studies on PA32520 and PA32540. Further information regarding Figure 1 may be found below in Example 1.

[0020] Figure 2 illustrates the change in urinary 11-dh-TXB_2 at Day 28 in a Phase I study on PA32520. Further information regarding Figure 2 may be found below in Example 2.

[0021] Figure 3 shows a release profile of PA32540 and is described more fully below in Example 3.

Detailed Description of the Invention

[0022] The term "acid inhibitor" includes without limitation proton pump inhibitors and histamine H_2 receptor antagonists. Examples of proton pump inhibitors include but are not limited to omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole, dexlansoprazole, and tenatoprazole. Examples of histamine H_2 receptor antagonists include but are not limited to cimetidine, ranitidine, ebrotidine, pabutidine, lafutidine, loxtidine, nizatidine, and famotidine.

[0023] The term "at risk patient" refers to patient(s) at risk for NSAID associated ulcer due to age $\geq$ 50 years, or a patient who has a history of UGI ulcer or bleeding. In one embodiment, the at risk patient is a patient at risk for NSAID associated ulcer due to age greater than or equal to 50 years. In yet another embodiment, the at risk patient is a patient at risk for NSAID associated ulcer due to history of UGI ulcer or bleeding.

[0024] The term "enantiomerically pure" refers to a compound containing at least about 75% of the named enantiomer out of the total amount of the two possible enantiomers contained therein. In various embodiments, "enantiomerically pure" refers to a compound containing at least about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 99.9% of the named enantiomer out of the total amount of the two possible enantiomers contained therein.

[0025] The term "pharmaceutically acceptable," as employed herein, indicates the subject matter being identified as "pharmaceutically acceptable" is suitable and physiologically acceptable for administration to a patient/subject. For example, the term

"pharmaceutically acceptable salt(s)" denotes suitable and physiologically acceptable salt(s).

[0026] The phrase "aspirin or pharmaceutically acceptable salt thereof" refers to the free base of aspirin, pharmaceutically acceptable salt(s) of aspirin, and/or mixtures of the free base of aspirin and at least one pharmaceutically acceptable salt of aspirin.

[0027] The phrase "omeprazole, or pharmaceutically acceptable salt thereof" refers to the free base of omeprazole, pharmaceutically acceptable salt(s) of omeprazole, and/or mixtures of the free base of omeprazole and at least one pharmaceutically acceptable salt of omeprazole.

[0028] The term "unit dosage form" or "unit dose form" as used herein refers to a single entity for drug administration. For example, a single tablet or capsule containing both an acid inhibitor and aspirin or a pharmaceutically acceptable salt thereof is a unit dosage form. Unit dosage forms of the present disclosure can provide for sequential drug release in a way that elevates gastric pH and reduces the deleterious effects of aspirin on the gastroduodenal mucosa, *e.g.*, the acid inhibitor is released first and the release of aspirin is delayed until after the pH in the GI tract has risen to at least 3.5, 4.0, 4.5, 5.0, 5.5, or greater. A "unit dosage form" may also be referred to as a "fixed dosage form" or a "fixed dosage combination" and are otherwise interchangeable.

[0029] With regard to the dosages of aspirin or a pharmaceutically acceptable salt thereof and/or an acid inhibitor, the term "about" is intended to reflect variations from the specifically identified dosages that are acceptable within the art. With regard to the pH values and/or ranges recited herein, the term "about" is intended to capture variations above and below the stated number that may achieve substantially the same results as the stated number.

[0030] With regard to the term numerical values used in conjunction with the phrase "substantially free," the term is intended to capture variations above and below the stated number that may achieve substantially the same results as the stated number. The phrase "substantially free" means from about 95% to about 99.99% free. For example, substantially free may mean about 95% free, about 96% free, about 97% free, about 98% free, about 99% free, or about 99.99% free. In the present disclosure, each of the variously stated ranges is intended to be continuous so as to include each numerical parameter

between the stated minimum and maximum value of each range. For example, a range of about 1 to about 4 includes about 1, 1, about 2, 2, about 3, 3, about 4, and 4.

[0031] One embodiment is directed to a method comprising: treating a disease or disorder in a patient at risk of developing an NSAID-associated ulcer by administering to the patient in need thereof a pharmaceutical composition in unit dosage form comprising a) an acid inhibitor in an amount sufficient to raise the gastric pH of the patient to at least about 3.5, 4.0, 4.5, 5.0, 5.5, or greater upon administration of one or more of the unit dosage forms, and b) a therapeutically effective amount of aspirin, or a pharmaceutically acceptable salt thereof; wherein the unit dosage form provides for coordinated release of the acid inhibitor and the aspirin such that: i) at least a portion of the acid inhibitor is released independent of the pH of the surrounding medium; and ii) the aspirin, or a pharmaceutically acceptable salt thereof, is not released from the unit dosage form until the pH of the surrounding medium is at least about 3.5, 4.0, 4.5, 5.0, 5.5, or higher; and wherein the pharmaceutical composition in unit dosage form decreases the risk of the patient developing an ulcer.

[0032] Another embodiment is directed to a method comprising: treating a disease or disorder in a patient in need of chronic NSAID treatment and at risk of developing an NSAID-associated ulcer by administering to the patient in need thereof a pharmaceutical composition in unit dosage form comprising a) an acid inhibitor in an amount sufficient to raise the gastric pH of the patient to at least about 3.5, 4.0, 4.5, 5.0, 5.5 or higher upon administration of one or more of the unit dosage forms, and b) a therapeutically effective amount of aspirin, or a pharmaceutically acceptable salt thereof; wherein the unit dosage form provides for coordinated release of the acid inhibitor and the aspirin such that: i) at least a portion of the acid inhibitor is released independent of the pH of the surrounding medium; and ii) the aspirin, or a pharmaceutically acceptable salt thereof, is not released from the unit dosage form until the pH of the surrounding medium is at least about 3.5, 4.0, 4.5, 5.0, 5.5 or higher; and wherein the pharmaceutical composition in unit dosage form decreases the risk of the patient developing an ulcer.

[0033] Still another embodiment is directed to a method comprising: treating signs and symptoms of pain, inflammation, osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, headache, toothache, common cold, muscle ache, cardiovascular disease, cancer, or any combination thereof in a patient at risk of developing an NSAID-associated

ulcer by administering to the patient in need thereof a pharmaceutical composition in unit dosage form comprising a) an acid inhibitor in an amount sufficient to raise the gastric pH of the patient to at least about 3.5, 4.0, 4.5, 5.0, 5.5 or higher upon administration of one or more of the unit dosage forms, and b) a therapeutically effective amount of aspirin, or a pharmaceutically acceptable salt thereof; wherein the unit dosage form provides for coordinated release of the acid inhibitor and the aspirin such that: i) at least a portion of the acid inhibitor is released independent of the pH of the surrounding medium; and ii) the aspirin, or a pharmaceutically acceptable salt thereof, is not released from the unit dosage form until the pH of the surrounding medium is at least about 3.5, 4.0, 4.5, 5.0, 5.5 or higher; and wherein the pharmaceutical composition in unit dosage form decreases the risk of the patient developing an ulcer.

[0034] Still yet another embodiment is directed to a method comprising: treating signs and symptoms of pain, inflammation, osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, headache, toothache, common cold, muscle ache, cardiovascular disease, cancer, or any combination thereof in a patient in need of chronic NSAID treatment and at risk of developing an NSAID-associated ulcer by administering to the patient in need thereof a pharmaceutical composition in unit dosage form comprising a) an acid inhibitor in an amount sufficient to raise the gastric pH of the patient to at least about 3.5, 4.0, 4.5, 5.0, 5.5 or higher upon administration of one or more of the unit dosage forms, and b) a therapeutically effective amount of aspirin, or a pharmaceutically acceptable salt thereof; wherein the unit dosage form provides for coordinated release of the acid inhibitor and the aspirin such that: i) at least a portion of the acid inhibitor is released independent of the pH of the surrounding medium; and ii) the aspirin, or a pharmaceutically acceptable salt thereof, is not released from the unit dosage form until the pH of the surrounding medium is at least about 3.5, 4.0, 4.5, 5.0, 5.5 or higher; and wherein the pharmaceutical composition in unit dosage form decreases the risk of the patient developing an ulcer.

[0035] In a further embodiment, the disease or disorder treated by the pharmaceutical compositions disclosed herein is selected from pain and inflammation. In yet another embodiment, the disease or disorder treated by the pharmaceutical compositions disclosed herein is osteoarthritis, rheumatoid arthritis, or ankylosing spondylitis. A still another embodiment, the disease or disorder treated by the pharmaceutical compositions disclosed herein is headache, toothache, common cold, muscle ache, cardiovascular disease, or any

combination thereof. In another embodiment, the disease or disorder treated by the pharmaceutical compositions disclosed herein is cancer. In yet a further embodiment, the patient at risk of developing an NSAID associated ulcer is $\geq$ 50 years old. In still yet another embodiment, the patient at risk of developing an NSAID associated ulcer has a history of UGI ulcer or bleeding.

[0036] In a further embodiment, the pharmaceutical composition in unit dosage form decreases the risk of the patient developing a gastroduodenal ulcer. In yet a further embodiment, the pharmaceutical composition in unit dosage form decreases the risk of the patient developing a duodenal ulcer. In a further embodiment, the pharmaceutical composition in unit dosage form decreases the risk of the patient developing a gastric ulcer.

[0037] In another embodiment, administering the pharmaceutical composition in unit dosage form of the present disclosure to patients in need of NSAID treatment results in fewer patients developing a gastric ulcer than patients in need of NSAID treatment who are administered aspirin, whether enteric coated or non-enteric coated aspirin. In yet another embodiment, administering the pharmaceutical composition in unit dosage form of the present disclosure to patients in need of NSAID treatment results in fewer patients developing a duodenal ulcer than patients in need of NSAID treatment who are administered aspirin, whether enteric coated or non-enteric coated aspirin. In still another embodiment, administering the pharmaceutical composition in unit dosage form of the present disclosure to patients in need of NSAID treatment results in fewer patients developing heartburn associated symptoms than patients in need of NSAID treatment who are administered aspirin, whether enteric coated or non-enteric coated aspirin. In another embodiment, administering the pharmaceutical composition in unit dosage form of the present disclosure to patients in need of NSAID treatment results in fewer patients developing dyspepsia than patients in need of NSAID treatment who are administered aspirin, whether enteric coated or non-enteric coated aspirin. In yet another embodiment, administering the pharmaceutical composition in unit dosage form of the present disclosure to patients in need of NSAID treatment reduces the patents' level of urinary 11-dehydrothromboxane compared to patients in need of NSAID treatment who are administered aspirin, whether enteric coated or non-enteric coated aspirin. In a yet still further embodiment, the patient is treated longer with the pharmaceutical composition in unit dosage form of the present disclosure than with aspirin, whether enteric coated or non-

enteric coated aspirin. In yet another embodiment, patient compliance with long-term treatment is improved with the pharmaceutical compositions disclosed herein as compared to aspirin, whether enteric coated or non-enteric coated aspirin.

[0038] In a yet even further embodiment, the pharmaceutical composition in unit dosage form is a multilayer tablet comprising at least one core and at least a first layer and a second layer, wherein:

i) the core comprises aspirin, or a pharmaceutically acceptable salt thereof;
ii) the first layer is a coating that at least begins to release the aspirin, or a pharmaceutically acceptable salt thereof, when the pH of the surrounding medium is about 3.5, 4.0, 4.5, 5.0, 5.5 or greater; and
iii) the second layer comprises an acid inhibitor, wherein at least some of the acid inhibitor is released at a pH of from about 0 or greater, for example 0.5, 1.0, 1.5, 2.0, 2.5, or 3.0.

[0039] In a further embodiment, the acid inhibitor is released from the multilayer tablet at a pH of from about 1.0 or greater. In a yet further embodiment, the acid inhibitor is released from the multilayer tablet at a pH of from about 0 to about 2.0. In a still further embodiment, at least a portion of the acid inhibitor contained in the multilayer tablet is not coated with an enteric coating. In a yet still further embodiment, the first layer of the multilayer tablet is an enteric coating or a time-release coating. In a yet even still further embodiment, the multi-layer tablet is substantially free of sodium bicarbonate. In a still further embodiment, the acid inhibitor is enantiomerically pure.

[0040] In another embodiment, the therapeutically effective amount of aspirin, or a pharmaceutically acceptable salt thereof, in the pharmaceutical compositions disclosed herein is selected from 30 mg and 1300 mg. In a still yet further embodiment, the therapeutically effective amount of aspirin, or a pharmaceutically acceptable salt thereof, is 81 mg. In a still yet further embodiment, the therapeutically effective amount of aspirin, or a pharmaceutically acceptable salt thereof, is 325 mg. In an even still further embodiment, the therapeutically effective amount of aspirin, or a pharmaceutically acceptable salt thereof, is 650 mg. In another embodiment, the therapeutically effective amount of aspirin, or a pharmaceutically acceptable salt thereof, is 75 mg, 100 mg, 150 mg, 162 mg, 300 mg, or 500 mg. In another embodiment, aspirin can be present as the free base. In yet another

embodiment, aspirin can be present in equivalent amounts of pharmaceutically acceptable salts of aspirin.

[0041] In one embodiment, the pharmaceutical composition in unit dosage form comprises about 30-1300 mg of the aspirin, or a pharmaceutically acceptable salt thereof, and about 1-1000 mg of the acid inhibitor. In another embodiment, the pharmaceutical composition in unit dosage form comprises about 30-1300 mg of the aspirin, or a pharmaceutically acceptable salt thereof, and about 5-650 mg of a proton pump inhibitor. In another embodiment, the pharmaceutical composition in unit dosage form comprises about 30-1300 mg of the aspirin, or a pharmaceutically acceptable salt thereof, and about 5-50 mg omeprazole, or a pharmaceutically acceptable salt thereof, or about 15, 20, 30, or 40 mg omeprazole, or a pharmaceutically acceptable salt thereof. In yet another embodiment, the pharmaceutical composition in unit dosage form comprises about 30-1300 mg of the aspirin, or a pharmaceutically acceptable salt thereof, and about 5-100 mg esomeprazole, or a pharmaceutically acceptable salt thereof, or about 20, 30, or 40 mg esomeprazole, or a pharmaceutically acceptable salt thereof. In yet another embodiment, the pharmaceutical composition in unit dosage form comprises about 30-1300 mg of the aspirin, or a pharmaceutically acceptable salt thereof, and about 10-150 lansoprazole, or a pharmaceutically acceptable salt thereof. In still another embodiment, the pharmaceutical composition in unit dosage form comprises about 30-1300 mg of the aspirin, or a pharmaceutically acceptable salt thereof, and about 10-200 pantoprazole, or a pharmaceutically acceptable salt thereof. In another embodiment, the pharmaceutical composition in unit dosage form comprises about 30-1300 mg of the aspirin, or a pharmaceutically acceptable salt thereof, and about 15-100 mg dexlansoprazole, or a pharmaceutically acceptable salt thereof. In yet another embodiment, the pharmaceutical composition in unit dosage form comprises about 30-1300 mg of the aspirin, or a pharmaceutically acceptable salt thereof, and about 10-150 mg tenatoprazole, or a pharmaceutically acceptable salt thereof. In another embodiment, the pharmaceutical composition in unit dosage form comprises about 30-1300 mg of the aspirin, or a pharmaceutically acceptable salt thereof, and about 5-100 mg rabeprazole, or a pharmaceutically acceptable salt thereof, or about 20 mg rabeprazole, or a pharmaceutically acceptable salt thereof.

[0042] In one embodiment, the pharmaceutical composition in unit dosage form comprises about 81 mg of the aspirin, or a pharmaceutically acceptable salt thereof, and about 20 mg omeprazole, or a pharmaceutically acceptable salt thereof. In another embodiment, the pharmaceutical composition in unit dosage form comprises about 325 mg of the aspirin, or a pharmaceutically acceptable salt thereof, and about 20 mg omeprazole, or a pharmaceutically acceptable salt thereof. In still another embodiment, the pharmaceutical composition in unit dosage form comprises about 81 mg of the aspirin, or a pharmaceutically acceptable salt thereof, and about 40 mg omeprazole, or a pharmaceutically acceptable salt thereof. In yet another embodiment, the pharmaceutical composition in unit dosage form comprises about 325 mg of the aspirin, or a pharmaceutically acceptable salt thereof, and about 40 mg omeprazole, or a pharmaceutically acceptable salt thereof. In one embodiment, the pharmaceutical composition in unit dosage form comprises about 650 mg of the aspirin, or a pharmaceutically acceptable salt thereof, and about 15 mg omeprazole, or a pharmaceutically acceptable salt thereof. In another embodiment, the pharmaceutical composition in unit dosage form comprises about 650 mg of the aspirin, or a pharmaceutically acceptable salt thereof, and about 20 mg omeprazole, or a pharmaceutically acceptable salt thereof. In yet another embodiment, the pharmaceutical composition in unit dosage form comprises about 650 mg of the aspirin, or a pharmaceutically acceptable salt thereof, and about 40 mg omeprazole, or a pharmaceutically acceptable salt thereof.

[0043] In certain embodiments, the duration of treatment may be approximately 1 week, 10 days, 2 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months or longer, and may be chronic treatment.

[0044] In an even further embodiment, the pharmaceutical composition in unit dosage form is a multilayer tablet comprising a core comprising aspirin, or a pharmaceutically acceptable salt thereof, and a first layer comprising a coating that at least begins releasing the aspirin when the pH of the surrounding medium is about 3.5, 4.0, 4.5, 5.0, 5.5 or greater and a second layer comprising an acid inhibitor, wherein at least a portion of the acid inhibitor is not surrounded by an enteric coating. In one embodiment, at least about 95%, at least about 99%, or at least about 99.5% of the acid inhibitor is not surrounded by an enteric coating. In yet another embodiment, the multilayer tablet is substantially free of

sodium bicarbonate. In still another embodiment, the multilayer tablet is completely (i.e., 100%) free of sodium bicarbonate.

[0045] In one embodiment, the dosing regimen of the pharmaceutical compositions disclosed herein is one or more times daily. In another embodiment, the dosages are separated by a period of at least about 10 hours. In another embodiment, the pharmaceutical composition in unit dosage form is given before a patient ingests a meal, for example about 30-60 minutes prior to ingesting a meal. In another embodiment, the pharmaceutical compositions of the present disclosure may be administered therapeutically to patients either short term or over a longer period of time, for example chronically.

[0046] The pharmaceutical compositions disclosed herein include, but are not limited to, for example, tablets and capsules that can be made in accordance with methods that are standard in the art (see, *e.g.*, Remington's Pharmaceutical Sciences, 16th ed., A Oslo editor, Easton, Pa. (1980)). 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; carnauba wax, colloidal silicon dioxide, croscarmellose sodium, glyceryl monostearate, hypromellose, methacrylic acid copolymer dispersion, methylparaben, polysorbate 80, polydextrose, povidone, propylene glycol, propylparaben, titanium dioxide, and triethyl citrate.

[0047] In one embodiment, at least one of the layers comprising the pharmaceutical compositions disclosed herein may be applied using standard coating techniques. The layer materials may be dissolved or dispersed in organic or aqueous solvents. The layer materials may include, but are not limited to, for example, one or more of the following materials: methacrylic acid copolymers, shellac, hydroxypropylmethcellulose phthalate, polyvinyl acetate phthalate, hydroxypropylmethyl-cellulose trimellitate, carboxymethyl-ethyl-cellulose, cellulose acetate phthalate, and/or other suitable polymer(s). The pH at which the first layer dissolves can be controlled by the polymer or combination of polymers selected and/or ratio of pendant groups. For example, dissolution characteristics of the polymer film can be altered by the ratio of free carboxyl groups to ester groups. The layers may also contain pharmaceutically acceptable plasticizers, such as, for example, triethyl citrate, dibutyl phthalate, triacetin, polyethylene glycols, polysorbates or other

plasticizers. Additives may also be used in the pharmaceutical compositions disclosed herein, such as, for example, dispersants, colorants, anti-adhering, and anti-foaming agents.

[0048] In one embodiment, the pharmaceutical compositions disclosed herein can be in the form of a bi- or multi-layer tablet. In a bi-layer tablet, one portion/layer of the tablet contains the acid inhibitor, or a pharmaceutically acceptable salt thereof, in the required dosage along with any appropriate excipients, agents to aid dissolution, lubricants, fillers, and the like; and a second portion/layer of the tablet contains the aspirin or a pharmaceutically acceptable carrier thereof in the required dosage along with any excipients, dissolution agents, lubricants, fillers, and the like. In another embodiment, the aspirin or a pharmaceutically acceptable carrier portion/layer is surrounded by a polymeric coating that dissolves at a pH of at least about 3.5, 4.0, 4.5, 5.0, 5.5 or greater. In still another embodiment, the aspirin or a pharmaceutically acceptable carrier portion/layer is surrounded by a coating that delays release until the pH of the surrounding environment is at least about 3.5, 4.0, 4.5, 5.0, 5.5 or greater.

[0049] The aspirin, or a pharmaceutically acceptable salt thereof, may be granulated by methods such as slugging, low- or high- shear granulation, wet granulation, or fluidized-bed granulation. Of these processes, slugging generally produces tablets of less hardness and greater friability. Low-shear granulation, high-shear granulation, wet granulation and fluidized-bed granulation generally produce harder, less friable tablets.

Examples

[0050] The invention is further defined in the following Examples. It should be understood the Examples are given by way of illustration only. From the above discussion and the Examples, one skilled in the art can ascertain the essential characteristics of the invention, and without departing from the spirit and scope thereof, can make various changes and modifications to adapt the invention to various uses and conditions. As a result, the invention is not limited by the illustrative Examples set forth herein, but rather defined by the claims appended hereto.

Example 1

Three Phase I, 4-Week Endoscopic Studies on PA32520 (Single-Tablet of EC-ASA 325 mg + IR Omeprazole 20 mg) and PA32540 (Single-Tablet of EC-ASA 325 mg + IR Omeprazole 40 mg), Showing a Decreased Risk of Gastroduodenal Mucosal Injury

[0051] A total of 240 healthy volunteers with normal baseline endoscopy (Lanza score 0) participated in three Phase I, single-blind, randomized, controlled studies to evaluate via endoscopy the gastroduodenal effects of a fixed combination tablet of delayed release ("DR") aspirin ("ASA") 325 mg and immediate release ("IR") omeprozole (20 or 40 mg). Two studies evaluated PA32520 (DR ASA 325 mg + IR omeprazole 20 mg) vs. either EC-ASA 81 mg or 325 mg. The third study compared PA32540 (DR ASA 325 mg + IR omeprazole 40 mg) with EC-ASA 325 mg. All medications were dosed once daily for 4 weeks. Endoscopy results were evaluated using 1988 Lanza scoring, which is a system that scores the severity of NSAID-induced GI tract ulcers on a scale of 0 = no visible lesions, 1 = 1 hemorrhage or erosion, 2 = 2-10 hemorrhages or erosions, 3 = 11-25 hemorrhages or erosions, 4 = more than 25 hemorrhages or erosions or any ulcer. The primary endpoint was the proportion of subjects with Grade 3 or Grade 4 Lanza scores at week 4; additional assessments included incidence of gastric or duodenal ulcers ("GU/DU") at 4 weeks and pharmacokinetics. Data were pooled across the 3 studies.

[0052] As shown in Figure 1, Grade 3 or 4 Lanza scores and the incidences of GU/DU for the PA products were lower than for EC-ASA. With regard to Grade 3 or 4 Lanza scores, the results showed the following: PA32520 vs. EC-ASA 81 mg (9.9 vs. 20.5%, $p=0.151$); PA32520 vs. EC-ASA 325 mg (9.9% vs. 42.5%, $p<0.001$); PA32540 vs. EC-ASA 81 mg (2.5% vs. 20.5%, $p=0.014$); PA32540 vs. EC-ASA 325 mg (2.5% vs. 42.5%, $p<0.001$). With regard to the incidence of GU/DU, the results showed the following: PA32520 vs. EC-ASA 81 mg (2.5% vs. 5.1%, $p=0.595$); PA32520 vs. EC-ASA 325 mg (2.5% vs.13.8%, $p=0.009$); PA32540 vs. EC-ASA 81 mg (2.5% vs. 5.1%, $p=0.615$); PA32540 vs. EC-ASA 325 mg (2.5% vs. 13.8%, $p=0.059$). As shown in Table 1, Day 14 and Day 28 mean gastric pH values were higher with PA32520 than with EC-ASA, and a greater percent of PA32520 subjects had a pH of >3. Plasma salicylic acid pharmacokinetics were similar following dosing with PA32520 or PA32540 and EC-ASA 325 mg following both single-dose and repeat-dose administration. PA32520 was well tolerated and resulted in a similar frequency of GI adverse events as EC-ASA 325 mg. There was no statistically significant difference in gastroduodenal mucosal damage caused

by 27 days of treatment with once daily PA32520 or EC-ASA 81 mg, although there was a trend to less damage with PA32520. PA32520 induced less GI mucosal damage than EC-ASA 81 mg based on Grade 3 or 4 Lanza scores for the duodenum at Day 14 and duodenal erosion counts at Day 14. PA32520 was statistically significantly better than EC-ASA aspirin 81 mg in increasing mean gastric pH at Day 14 and Day 28, and increasing the proportion of subjects with gastric pH >3 at Day 14.

	Day 14			Day 28		
	PA32520 N=40 (%)	EC ASA N=40 (%)	p-value[1]	PA32520 N=40 (%)	EC ASA N=40 (%)	p-value[1]
Mean (SD)	4.2 (1.6)	1.7 (0.6)	<0.001	3.5 (1.8)	1.5 (0.4)	<0.001
Median	4.3	1.5		2.8	1.5	
Range	1.5-6.0	1.0-3.5		1.5-6.0	1.0-3.0	

[1]Wilson Rank-Sum test
SD = standard deviation

Table 1

[0053] Gastroduodenal Grade 3 or 4 Lanza scores and incidence of GU/DU for EC-ASA were dose-related. The fixed dose combination of DR ASA and IR omeprazole was associated with a significant reduction in gastroduodenal Grade 3 or 4 Lanza scores and GU/DU that were dose-related to the proton pump inhibitor. PA32540 demonstrated the least gastroduodenal damage and may provide an important option for at-risk patients who require long-term ASA therapy.

Example 2

Two Phase I, 4-Week Endoscopic Studies on PA32520 (Single-Tablet of EC-ASA 325 mg + IR Omeprazole 20 mg) Shows Greater Thromboxane Suppression and Lower Upper Gastrointestinal Damage

[0054] In a randomized, single-blinded controlled Phase I study, gastroduodenal mucosal changes using an established methodology (Lanza score) and urinary 11-dehydrothromboxane ("11-dh-TXB_2") were determined in 80 healthy volunteers (mean ages 57–58 yrs) with no endoscopic evidence of gastroduodenal mucosal damage (Lanza score 0) who were treated with a daily dose of PA32520 or 81 mg EC-ASA. In a separate Phase I study (n=80), the effect of PA32520 vs. 325 mg EC-ASA alone on gastroduodenal mucosal changes was studied in 80 healthy volunteers. The primary endpoint was Lanza Grade 3 or 4 (>20 erosions/hemorrhages or ulcers) at Day 28; secondary endpoints

included Grade 3 or 4 at Day 14, gastric or duodenal ulcers by Day 28, and the change from baseline in urinary 11-dh-TXB_2 after 4 weeks. Study assessments were conducted at baseline, Day 14, and Day 28.

[0055] As shown in Table 2, PA32520 was associated with 50%–84% less gastroduodenal mucosal damage than EC-ASA alone. As shown in Figure 2, PA32520 was associated with a greater reduction in 11-dh-TXB_2 compared to EC-ASA 81 mg (-75% vs -68% mean percentage change from baseline, respectively; p=0.008). Over three times as many subjects in the PA32520 treatment group had reductions in urinary 11-dh-TXB_2 excretion rates from baseline to Day 27 in excess of 80% compared to the EC-ASA 81 mg treatment group.

Endpoint	Study 1			Study 2		
	PA32520 N=41	EC-ASA 81mg N=39	p-Value	PA32520 N=40	EC-ASA 325mg N=40	p-Value
Gastric and duodenal Lanza 3 or 4 Scores **Day 14**	4 (9.8%)	8 (20.5%)	0.22	1 (2.5%)	17 (42.5%)	<0.001
Gastric and duodenal Lanza 3 or 4 Scores **Day 28**	4 (9.8%)	8 (20.5%)	0.22	3 (7.5%)	19 (47.5%)	<0.001

*primary analysis

Table 2

[0056] Treatment with EC-ASA alone is associated with a high prevalence of UGI damage that is ameliorated by PA32520 therapy. Compared to EC-ASA 81 mg, PA32520 produces superior inhibition of *in vivo* thromboxane generation. PA32520 may provide an important option for at patients treated with ASA, as well as the great patient population that takes ASA intermittently, for short-term therapy, or chronically. High-dose ASA in combination with proton pump inhibitors may provide a reduction in UGI damage and greater thromboxane suppression.

Example 3

Four Phase 1, 4-Week Endoscopic Studies on PA32520 (Single-Tablet of EC-ASA 325 mg + IR Omeprazole 20 mg) and PA32540 (Single-Tablet of EC-ASA 325 mg + IR Omeprazole 40 mg) Show Bioequivalence to EC-ASA, Greater Thromboxane Suppression and Lower Upper Gastrointestinal Damage

[0057] Four Phase I studies with PA32520 and PA32540 evaluated bioequivalence to EC-ASA, UGI safety, and inhibition of thromboxane. The bioequivalence of aspirin from

PA32540 vs. EC-ASA 325 mg/day was determined in a single-dose, open-label, crossover study in 36 healthy volunteers (mean age 32 yrs). In three single-blind, multiple-dose, randomized studies, healthy adults >50 yrs with normal baseline endoscopy (Lanza score 0) were treated with either PA32520, PA32540, EC-ASA 81 mg/day or EC-ASA 325 mg/day. For PA32520 vs. EC-ASA 81 mg/day, 11-dh-TXB_2 was also measured. The endpoints were the proportion of subjects with Grade 3 or 4 Lanza scores at Day 14, the proportion of subjects with Grade 3 or 4 Lanza scores at Day 28, and the concentration of urinary 11-d-TXB_2 after 4 weeks of therapy.

[0058] PA32540 was found to be bioequivalent to EC-ASA 325 mg/day; the geometric LSM ratio (90% CI) for $AUC_{0\text{-infinity}}$ was 1.095 (0.967, 1.239) and for C_{max} was 1.077 (0.959, 1.209). Figure 3 shows the release profile of PA32540 at Day 13; IR omeprazole in PA32540 has no effect on the pharmacokinetic profile of salicylic acid. Omeprazole was rapidly absorbed from PA32540 and eliminated from the systematic circulation with a mean elimination half life of approximately 1 hour. Plasma exposure of salicylic acid from PA32540 was similar to marketed EC-ASA 325 mg following both single-dose and repeat-dose administration of PA32540. This observation rules out lower dosage aspirin systematic exposure as the explanation for the reduction in damage associated with PA32540. Additionally, it shows that immediate release omeprazole in PA32540 has no effect on salicylic acid pharmacokinetics. Chronic administration of PA32540 was well tolerated. After 4 weeks of therapy, PA was associated with an 84%-90% reduction in UGI injury (Lanza score 3 or 4, >20 erosions, hemorrhages, or ulcers) compared with EC-ASA 325 mg/day ($p < 0.003$). Lanza score 3 or 4 level injury at Day 28 occurred in 9.8% of PA32520 patients and in 20.5% of EC-ASA 81 mg/day patients ($p=0.22$). Urinary 11-dh-TXB_2 at baseline was 853.2 pg/mg creatinine ("Cr") for PA32520 and 884.6 pg/mg Cr for EC-ASA 81 mg/day ($p=0.97$). As shown in Table 3, after 4 weeks of treatment, 11-dh-TXB_2 was significantly lower for PA32520 (175.5 pg/mg Cr) than for EC-ASA 81 mg/day (245.2 pg/mg Cr); $p=0.005$.

URINARY 11-D-TXB2 AFTER 4 WEEKS OF TREATMENT

Urinary 11-d-TXB2 (pg/mg Cr)	PA 32520 (n=41)	EC-ASA 81 mg (n=39)
Minimum	48.7	48.2
First Quartile	132.6	181.4
Median	188.1	258.4
Third Quartile	233.6	327.8
Maximum	852.2	679.5
Geometric Mean	175.5*	245.2

*P=0.005

Table 3

[0059] PA32540 is bioequivalent to EC-ASA 325 mg/day, but with a significant improvement in UGI safety. Also, PA32520 inhibits urinary 11-dh-TXB_2 significantly more than EC-ASA 81 mg/day. PA was associated with a significant reduction in gastroduodenal injury, and PA32540 demonstrated the least gastroduodenal damage and fewest overall GI adverse events. Thus, while secondary prevention of strokes and transient ischemic attacks with ASA alone is associated with UGI damage and as such may require lower doses of ASA or alternative anti-thrombotic agents, PA may allow for higher doses of ASA, for example for secondary prevention of cardiovascular disease, strokes and transient ischemic attacks.

Example 4

Phase 1, 4-Week Endoscopic Study on PA65020 (Two Tablets of EC-ASA 325 mg + IR Omeprazole 20 mg) at Analgesic Doses that Shows Significant Reduction of Incidence of Gastroduodenal Ulcers

[0060] In a single-center, Phase 1, randomized, double-blind study, PA65020 (n=20) or EC-ASA 650 mg (n=20) was administered in the clinic twice daily for 28 days to healthy volunteers (≥50 yrs) with normal baseline endoscopy (Lanza score 0). Each dose of PA65020 was administered as one tablet of PA32520 and one tablet of EC-ASA 325 mg. EC-ASA 650 mg was administered as two EC-ASA 325 mg tablets. The total daily ASA dose was 1300 mg. Outcome evaluations included the occurrence of endoscopically proven gastric and/or duodenal lesions meeting Grade 3 or Grade 4 Lanza scores on Day 28 (primary endpoint), incidence of gastroduodenal ulcers, as well as assessments of dyspepsia-associated abdominal pain by mSODA (modified severity of dyspepsia assessment score, range 2-47), heartburn, and adverse events.

[0061] A total of 40 subjects (mean age 59.7 years) were treated. As shown in Table 4, at Day 28, the incidence of Grade 3 or 4 Lanza scores was significantly less for the PA65020 group (3, or 15%) than for the EC-ASA 650 mg group (17, or 85%), P<0.001. The incidence of GU/DU on Day 28 was also significantly lower with PA65020 vs. EC-ASA 650 mg (0% vs. 40%, P=0.003). At Day 28, the mean change from baseline in mSODA was 0 for PA65020 and 0.7 for EC-ASA 650 mg. More PA65020 subjects were heartburn-free (90%) throughout the study compared with subjects in the EC-ASA 650 mg group (75%). Mean salicylic acid trough levels were similar between PA65020 and EC-ASA 650 treatment groups on both Day 14 (17.8 mcg/mL vs. 19.0 mc/mL) and Day 28 (13.5 mcg/mL v. 13.3 mcg/mL), so the differences in salicylic acid levels cannot explain the reduction in Lanza scores of the absence of ulcers in the PA65020 treatment as compared to the EC-ASA 650 mg treatment. The most commonly reported adverse events were GI-related, primarily dyspepsia (2 subjects in each treatment group) and stomach discomfort (3 subjects in the EC-ASA 650 mg group vs. 0 subjects in the PA65020 group).

Endpoint	**PA65020 N=20 n (%)**	**EC-ASA 650 mg N=20 n (%)**	**P-value**
Gastric and duodenal Lanza 3 or 4 scores			
Day 14	1 (5%)	18 (90%)	<0.001
Day 28	3 (15%)	17 (85%)	<0.001
GU/DU			
Day 14	0	4 (20%)	0.106
Day 28	0	8 (40%)	0.003

Table 4

[0062] Analgesic doses of over-the-counter ASA produced significant mucosal damage in most subjects following 1 month of treatment. PA65020 is associated with a significantly decreased risk of GU/DU, and may provide an important option for at-risk patients who require analgesic doses of ASA.

[0063] All of the compositions and methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and/or methods and in the steps or in the sequence of steps of the methods described herein without departing from the concept, spirit and scope of the

invention. More specifically, it will be apparent that certain agents that are chemically or physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

What is Claimed is:

1. A method of treating a patient at risk of developing an NSAID-associated ulcer for a disease or disorder that responds to aspirin, comprising administering to said patient a pharmaceutical composition in unit dosage form comprising:
   a) omeprazole or pharmaceutically acceptable salt thereof, that is immediately soluble when the dosage form is placed in an aqueous medium, independent of pH, in an amount effective to raise the gastric pH of the patient to at least 3.5 upon administration of one or more of the unit dosage forms, and
   b) aspirin or a pharmaceutically acceptable salt thereof, wherein the aspirin or a pharmaceutically acceptable salt thereof is surrounded by a coating that is substantially insoluble in an aqueous medium at a pH below 3.5 and at a temperature of 37°C;

   wherein said administration is continued for a period of at least 14 days.

2. The method of claim 1, wherein said patient is administered one or more of said unit dosage forms daily for a period of at least 28 days.

3. The method of either claim 1 or claim 2, wherein said patient is at increased risk of ulcer formation due to said patient's age.

4. The method of any one of claims 1-3, wherein the omeprazole or a pharmaceutically acceptable salt thereof is present in an amount effective to raise the pH of the gastric fluid of the patient to at least 4.5 when the dosage form is administered orally.

5. The method of any one of claims 1-4, wherein the amount of aspirin, or a pharmaceutically acceptable salt thereof, is present in said unit dosage form at 81 – 650 mg.

6. The method of any one of claims 1-4, wherein the amount of aspirin, or a pharmaceutically acceptable salt thereof, is present in said unit dosage form at 325–650 mg.

7. The method of any one of claims 1-4, wherein the amount of omeprazole, or a pharmaceutically acceptable salt thereof, is present in said unit dosage form at 15-40 mg.

8. The method of claim 7, wherein the amount of aspirin, or a pharmaceutically acceptable salt thereof, is present in said unit dosage form at 81– 650 mg.

9. The method of any one of claims 1-4 or 8, wherein said patient is treated for pain, or inflammation.

10. The method of claim 9, wherein said pain or inflammation is associated with osteoarthritis; rheumatoid arthritis; ankylosing spondylitis; headache; toothache; common cold; muscle ache; cardiovascular disease; cancer; cerebrovascular disease; or a combination thereof.

11. The method of claim 1, wherein the pharmaceutical composition in unit dosage form reduces heartburn or dyspepsia associated symptoms in said patient.

12. The method of claim 1 or 2, wherein the unit dosage form is a tablet comprising a core and two or more layers, in which:

a) the core comprises aspirin or a pharmaceutically acceptable salt thereof;

b) a first layer surrounds the core and has a coating substantially insoluble in aqueous medium at a pH below 3.5; and

c) at least one second layer comprising the omeprazole or pharmaceutically acceptable salt thereof said second layer surrounding the coating of said first layer.

13. The method of claim 12, wherein the amount of omeprazole, or a pharmaceutically acceptable salt thereof, is present in said unit dosage form at 15-40 mg and the amount of aspirin, or a pharmaceutically acceptable salt thereof, is present in said unit dosage form at 81 – 650 mg.

14. The method of either claim 12 or 13, wherein said patient is treated for pain or inflammation.

15. The method of any one of claims 12- 14, wherein said unit dosage form provides for the coordinated release of the omeprazole or a pharmaceutically acceptable salt thereof and the aspirin or a pharmaceutically acceptable salt thereof.

16. The method of claim 1, wherein:
    a) said administration continues for a period of at least 28 days;
    b) the amount of omeprazole, or a pharmaceutically acceptable salt thereof, is 15-40 mg; and
    c) the amount of aspirin, or a pharmaceutically acceptable salt thereof, is 81 – 650 mg.

17. The method of claim 16, wherein said patient is treated for pain or inflammation.

18. The method of claim 17, wherein said pain or inflammation is associated with osteoarthritis; rheumatoid arthritis; ankylosing spondylitis; headache; toothache; common cold; muscle ache; cardiovascular disease; cancer; cerebrovascular disease; or a combination thereof.

19. The method of any one of claims 16-18, wherein the unit dosage form is a tablet comprising a core and two or more layers, in which:
    a) the core comprises aspirin or a pharmaceutically acceptable salt thereof;
    b) a first layer surrounds the core and has a coating substantially insoluble in aqueous medium at a pH below 3.5; and
    c) at least one second layer comprising the omeprazole or pharmaceutically acceptable salt thereof said second layer surrounding the coating of said first layer.

20. The method of any one of claims 16-19, wherein the pharmaceutical composition in unit dosage form reduces heartburn or dyspepsia associated symptoms in said patient.

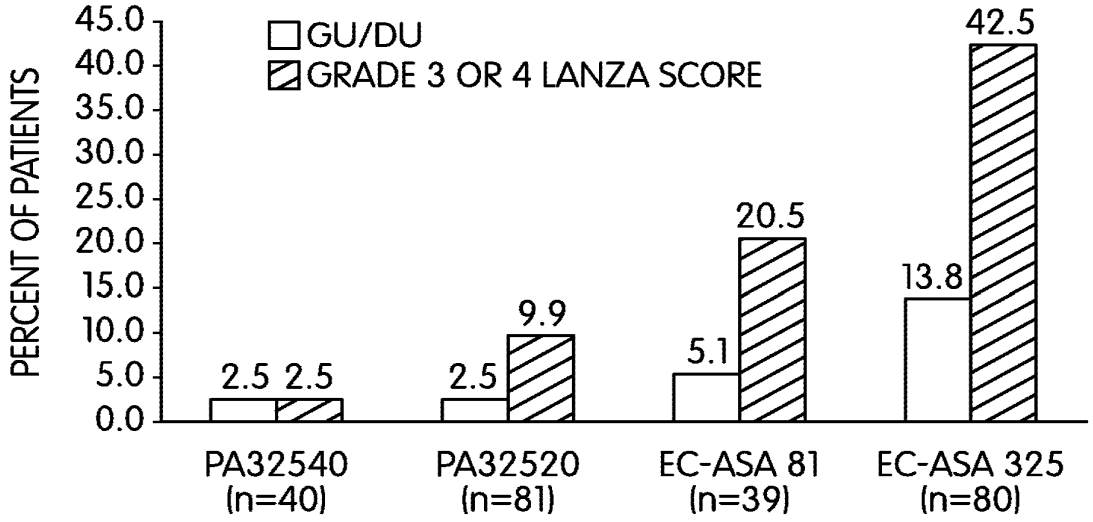

45.0
40.0
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
PERCENT OF PATIENTS
GU/DU
GRADE 3 OR 4 LANZA SCORE
2.5
2.5
2.5
9.9
5.1
20.5
13.8
42.5
PA32540 (n=40)
PA32520 (n=81)
EC-ASA 81 (n=39)
EC-ASA 325 (n=80)

FIG. 1

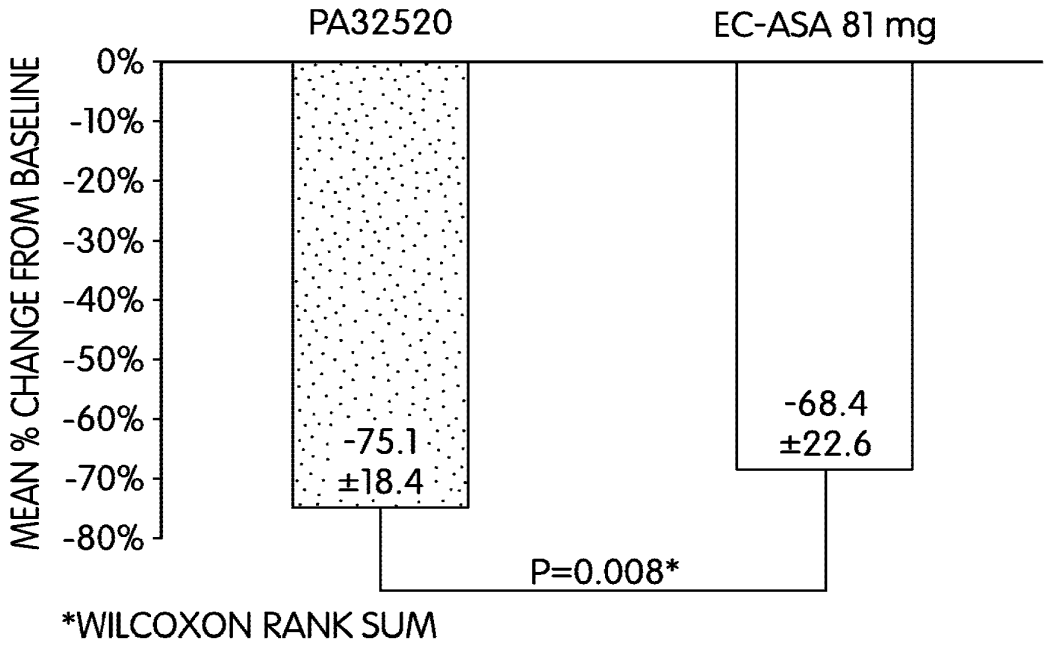

PA32520
EC-ASA 81 mg
0%
-10%
-20%
-30%
-40%
-50%
-60%
-70%
-80%
MEAN % CHANGE FROM BASELINE
-75.1
±18.4
-68.4
±22.6
P=0.008*
*WILCOXON RANK SUM

FIG. 2

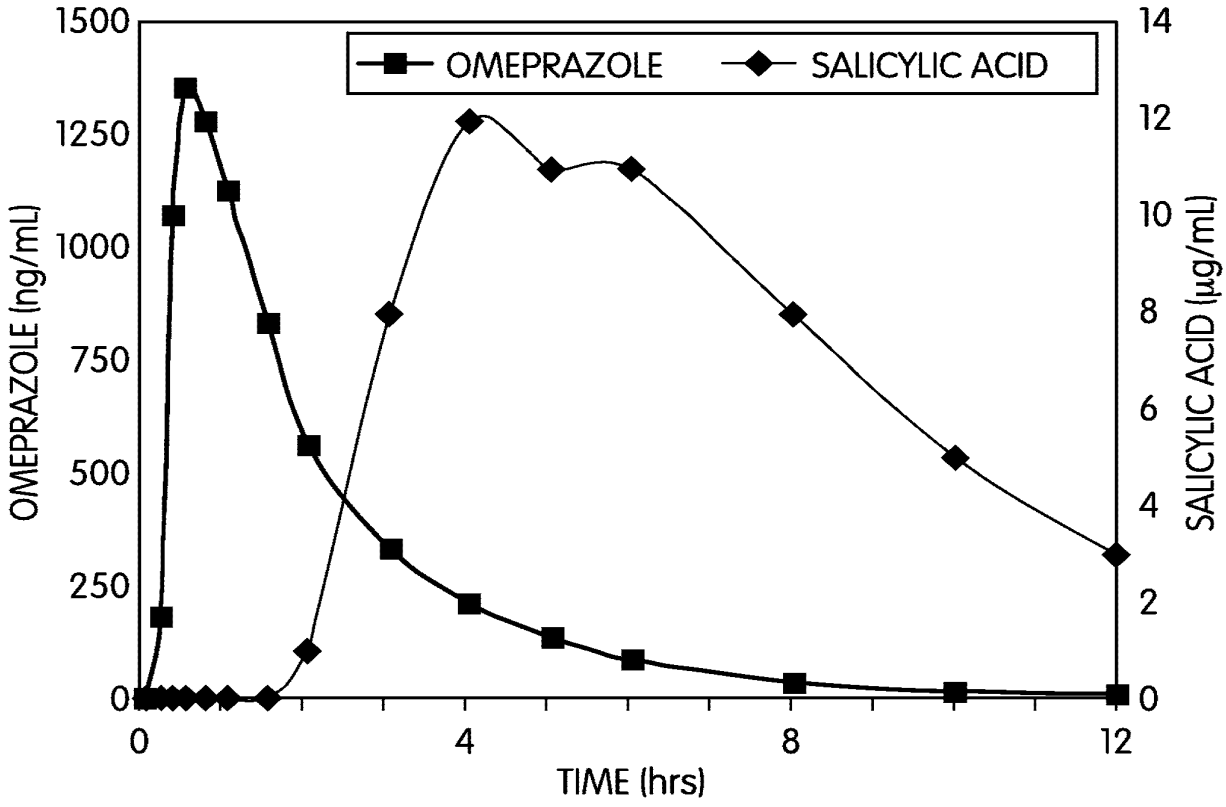

OMEPRAZOLE
SALICYLIC ACID
OMEPRAZOLE (ng/mL)
SALICYLIC ACID (µg/mL)
TIME (hrs)
1500
1250
1000
750
500
250
0
14
12
10
8
6
4
2
0
0
4
8
12

FIG. 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/39864

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/40; A61K 31/44 (2010.01)
USPC - 514/338
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC - 514/338

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 546/272.7, 273.7, 274.4 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB,USPT,USOC,EPAB,JPAB); Google
Search Terms Used: omeprazole, aspirin, ulcer, unit dosage, gastric, pH, independent, risk, age

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2005/0249811 A1 (Plachetka) 10 November 2005 (10.11.2005) para [0011]-[0019], [0046], [0080]-[0100]	1-3, 11-13, 16-19
Y	US 2002/0160046 A1 (Robinson et al.) 31 October 2002 (31.10.2002) para [0003]-[0011], [0032]	1-3, 11-13, 16-19
Y	US 2004/0022846 A1 (Depui et al.) 05 February 2004 (05.02.2004) para [0007]-[0014]	3, 11
A	US 2007/0237820 A1 (Cheng et al.) 11 October 2007 (11.10.2007) entire disclosure	1
A	US 6,869,615 B2 (Chen et al.) 22 March 2005 (22.03.2005) entire disclosure	1

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 August 2010 (15.08.2010)	30 AUG 2010
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/39864

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-10, 14-15 and 20
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Electronic Acknowledgement Receipt

EFS ID:	13604009
Application Number:	12822612
International Application Number:	
Confirmation Number:	6136
Title of Invention:	Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer
First Named Inventor/Applicant Name:	Brian Ault
Customer Number:	22466
Filer:	David Michael Gryte/Elizabeth Ashton
Filer Authorized By:	David Michael Gryte
Attorney Docket Number:	103786-1 US/NS
Receipt Date:	28-AUG-2012
Filing Date:	24-JUN-2010
Time Stamp:	13:03:13
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Foreign Reference	WO2001024777.pdf	1181395 3427b2b68ba05da3f412377bbafd14fad9ad998f	no	30

Warnings:	
Information:	

2	Foreign Reference	WO2001066088.pdf	1510532 35c272ca5523caade7e8d79a1bc1098fd20c3877	no	56
Warnings:					
Information:					
3	Foreign Reference	WO2002066002.pdf	1052334 def5465d68e7e302af56da06376fbd27891c4a12	no	25
Warnings:					
Information:					
4	Foreign Reference	WO2002022108.pdf	2108275 33af321b49a9d751a609e64fcd1a5d001f7c488e	no	47
Warnings:					
Information:					
5	Foreign Reference	WO2003017980.pdf	1825779 018907311005ac75ba987cb8e4d3083edab77207	no	58
Warnings:					
Information:					
6	Foreign Reference	WO2004062552.pdf	1211581 0e0ee1c45c0701ab3f23addc9e5fe614cfba3f5f	no	36
Warnings:					
Information:					
7	Foreign Reference	WO2004064815.pdf	2423490 c8ac07092fb04eaa2fd6cba63db5dca7baedcb26	no	56
Warnings:					
Information:					
8	Foreign Reference	WO2005074536.pdf	1603077 021b6f831feb0dd04b81acfb04c69e4bfc7b0976	no	28
Warnings:					
Information:					
9	Foreign Reference	WO2005074930.pdf	2797963 578c19b13d93d3c226baa3e17c1d753c643a1fea	no	44
Warnings:					
Information:					
10	Foreign Reference	WO2006044202.pdf	8239782 c4eced36c940d665f13d94d4fdac9ec26ae5f141	no	188
Warnings:					
Information:					

11	Foreign Reference	WO2007064274.pdf	2256861 0a5b0eddc3cbc5d3f88d1400eaa0783a80a2c523	no	52
Warnings:					
Information:					
12	Foreign Reference	WO2007078874.pdf	1656400 15b0bcd59c0e2e78f6f56c83099c0a21d9a19b1d	no	36
Warnings:					
Information:					
13	Foreign Reference	WO2008101060.pdf	1631602 134f6e5ecaca79498f53dee93c86380af36b8617	no	18
Warnings:					
Information:					
14	Foreign Reference	WO2009012393.pdf	2524318 61430373f373357dab42269ad72c27d11f743931	no	52
Warnings:					
Information:					
15	Foreign Reference	WO2009145905.pdf	639413 da165c6705dab772f27ba89c33f886837ebc239c	no	14
Warnings:					
Information:					
16	Foreign Reference	WO2010151697.pdf	1687667 a9afc4886e0eb6adb29dcf7619290228d6c205bf	no	33
Warnings:					
Information:					
17	Non Patent Literature	Abelo_etal.pdf	441356 abbd26d97ddcdc0082a3ccb4114c52aa1df92a69	no	8
Warnings:					
Information:					
18	Non Patent Literature	Alexander_etal.pdf	42329 f5bc344cc3de3512c0567472bee03c8864d511e4	no	1
Warnings:					
Information:					
19	Non Patent Literature	Andersson.pdf	1518204 a99e1c436ea497fb500a4dce8fda926dd3e10dd6	no	20
Warnings:					
Information:					

20	Non Patent Literature	Anonymous_1.pdf	127757 b3c4c177a9c880ed658e672fb4b0eacbac595e2e	no	3
Warnings:					
Information:					
21	Non Patent Literature	Anonymous_2.pdf	106437 4326bc5a5dbdceb26242193966b3584dab9da4a9	no	3
Warnings:					
Information:					
22	Non Patent Literature	Anonymous_3.pdf	123565 decb7924b6c0e3a9b7de6f8b1ba3199c379db5a0	no	3
Warnings:					
Information:					
23	Non Patent Literature	Arthrotec_Data_Sheet.pdf	1528114 e773793338643833a30b17c4167999aa9d684cce7	no	24
Warnings:					
Information:					
24	Non Patent Literature	Awtry_etal.pdf	177998 2dad94cc12481af226ed565d7d02715ff5437e2c	no	14
Warnings:					
Information:					
25	Non Patent Literature	Barnett_etal.pdf	1851853 94d34260f77564fa748f8b7d2ef6713894267221	no	9
Warnings:					
Information:					
26	Non Patent Literature	Berardi_etal.pdf	1552338 b0b800487d35bbbcb85e51fae56da834d0991c06	no	11
Warnings:					
Information:					
27	Non Patent Literature	Bergmann_etal.pdf	1039221 7f6e68544f108e03c1e098c5b6487f70a17bd80c	no	4
Warnings:					
Information:					
28	Non Patent Literature	Bianchi_1.pdf	168280 14ad1a563c726b83ea30854b70774d88f4485474	no	1
Warnings:					
Information:					

29	Non Patent Literature	Bianchi_2.pdf	1416136 917bcafc5dcce69c38a6a57f981022602419a69a	no	5
Warnings:					
Information:					
30	Non Patent Literature	Ballinger_etal.pdf	6974099 bba1340da0dccc04b36bcf8c5cd3183768c43b04	no	10
Warnings:					
Information:					
31	Non Patent Literature	Bianchi_3.pdf	1489456 82f9eb472ef73d674aa8494a426ec17d226fc305	no	8
Warnings:					
Information:					
32	Non Patent Literature	Bigard_1.pdf	587692 1d6c48b9e974e705c46f95ce4c8768dab6927e62	no	2
Warnings:					
Information:					
33	Non Patent Literature	Bigard_1_Eng_Trans.pdf	209030 feb54cf04cefae2a81fae80aa14fd349a0633ab0	no	2
Warnings:					
Information:					
34	Non Patent Literature	Bigard_2.pdf	13226188 66088d3320cbe129d0b7ef09a3f8ba376355b276	no	40
Warnings:					
Information:					
35	Non Patent Literature	Bombardier_etal.pdf	125442 dfe9efa8da339c80bf41a15793ea5ea8c4f02670	no	9
Warnings:					
Information:					
36	Non Patent Literature	Brown_etal_2.pdf	679203 cee87cef3d21e1b3bd6f1c98533c8f4c6eefd8ca	no	9
Warnings:					
Information:					
37	Non Patent Literature	Byrn_etal.pdf	2937703 e7d80fb2d93ef7ef365661ea776d3be67b796dab	no	10
Warnings:					
Information:					

38	Non Patent Literature	Carrasco_etal.pdf	987318 58d8d9d075c35c45fc419ca7bb266c9449688736	no	3
Warnings:					
Information:					
39	Non Patent Literature	Chan_etal_1.pdf	158017 f3915726b8542a047a8a2dfa2d519025f8c8baa6	no	1
Warnings:					
Information:					
40	Non Patent Literature	Brown_etal_1.pdf	6266217 09207d0673cf907f2cb5742a80a6b31b8c1e700b	no	10
Warnings:					
Information:					
41	Non Patent Literature	Chan_etal_2.pdf	100550 0855672c9115158c29f928fae8d9586cf308b016	no	7
Warnings:					
Information:					
42	Non Patent Literature	Chandramouli.pdf	404775 a5484923c08bfa21fb15913bcb2b11c8eeddd457	no	14
Warnings:					
Information:					
43	Non Patent Literature	Chang_etal.pdf	480227 9a2a85d1df5b308cac365b2ca33f7ac5f4efec3d	no	10
Warnings:					
Information:					
44	Non Patent Literature	Cullen.pdf	501427 4de53ed0214752e06a17cac62439ff3f81d38391	no	6
Warnings:					
Information:					
45	Non Patent Literature	Dajani.pdf	339914 1ff12830c528abf5182a20efbdcef7664979950a	no	10
Warnings:					
Information:					
46	Non Patent Literature	Daneshmend_1.pdf	187847 38dd3ce771b8be59ce87d2a5ca1a13012dd09d8b	no	4
Warnings:					
Information:					

47	Non Patent Literature	Daneshmend_2.pdf	1536523 0ad79ee8e45a55643085691e8a799903060f812d	no	6
Warnings:					
Information:					
48	Non Patent Literature	Dent.pdf	318302 7435052892b5c4bcaf598ea23c98d636e2bb6b62	no	4
Warnings:					
Information:					
49	Non Patent Literature	Ehsanullah.pdf	1724445 cf630970760bede57f6ad5260ed5f8e89a7b8d57	no	5
Warnings:					
Information:					
50	Non Patent Literature	Ekstrom.pdf	456760 02e6454bc06eeb4901488ddd1720a26bbd8f341a	no	6
Warnings:					
Information:					
51	Non Patent Literature	Ene.pdf	643046 cc38ff350063c6f7caec5863fd84aad439344ef8	no	3
Warnings:					
Information:					
52	Non Patent Literature	Feldman.pdf	448803 b2c65266b0a63563d8f91e9ce74c16d9be8a544d	no	1
Warnings:					
Information:					
53	Non Patent Literature	Florence.pdf	10573410 40f80ed176fbfc4feea771f89b0e9081b2277984	no	44
Warnings:					
Information:					
54	Non Patent Literature	Frank.pdf	290102 de445216e11582cfedfa96428d91f875e9b99e40	no	4
Warnings:					
Information:					
55	Non Patent Literature	Erlandsson.pdf	2900721 28fa98264fbfc909dd1de58500dc37a70dcd1235	no	15
Warnings:					
Information:					

56	Non Patent Literature	Gengo.pdf	115598 14652b7aa2ad2f88fbe1c66ff401de2af30a0572	no	10
Warnings:					
Information:					
57	Non Patent Literature	Goldstein_1.pdf	193642 ba4f1b03d9ef3720f45a0c594690bc49b082ff05	no	1
Warnings:					
Information:					
58	Non Patent Literature	Goldstein_2.pdf	93768 1e2b11e9525119b710de6042e953641bc37390b0	no	3
Warnings:					
Information:					
59	Non Patent Literature	Goldstein_3.pdf	88780 52bb55c4e92610edab151eda5f204fe2cbadf4be	no	3
Warnings:					
Information:					
60	Non Patent Literature	Graham.pdf	1258423 c3dd2ba614dfdf8407b131fdefb16499842efc7d	no	6
Warnings:					
Information:					
		Total Files Size (in bytes):	100741485		

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

New Applications Under 35 U.S.C. 111

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

National Stage of an International Application under 35 U.S.C. 371

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

New International Application Filed with the USPTO as a Receiving Office

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

Electronic Acknowledgement Receipt

EFS ID:	13604587
Application Number:	12822612
International Application Number:	
Confirmation Number:	6136
Title of Invention:	Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer
First Named Inventor/Applicant Name:	Brian Ault
Customer Number:	22466
Filer:	David Michael Gryte/Elizabeth Ashton
Filer Authorized By:	David Michael Gryte
Attorney Docket Number:	103786-1 US/NS
Receipt Date:	28-AUG-2012
Filing Date:	24-JUN-2010
Time Stamp:	13:43:03
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	Grosser.pdf	1054528 70aaf9fccd1e02a435a4f7a1f641e152fac5041f	no	10

Warnings:	
Information:	

2	Non Patent Literature	Gurbel.pdf	582291 0381b4fbdc930a7a9237b28f9c66e7c5a3536b31	no	1
Warnings:					
Information:					
3	Non Patent Literature	Hassan_Alin.pdf	243436 31b97c4650c5dc77a9191f767b2f4e15d06e3dee	no	1
Warnings:					
Information:					
4	Non Patent Literature	Hawkey_1.pdf	426617 7aaad4c7f2700ca5ab9a2225c335d17858881961	no	8
Warnings:					
Information:					
5	Non Patent Literature	Hawkey_2.pdf	197000 54d60b801507bfb2076756d5cc1162af47668235	no	8
Warnings:					
Information:					
6	Non Patent Literature	Hawkey_3.pdf	1590776 b32f27bcc8cb9f7fc6388aeadadb6e56b7d4d30a	no	8
Warnings:					
Information:					
7	Non Patent Literature	Hawkey_4.pdf	294345 449052af99665de0ba2fbc13f47982938c56f39f	no	4
Warnings:					
Information:					
8	Non Patent Literature	Hawkey_5.pdf	132468 edf3a30a0c15a3eb3710c9a9d9b65e86f20c6aae	no	4
Warnings:					
Information:					
9	Non Patent Literature	Hawkins.pdf	881919 443ee461a3fedaf830653273146aa0895bf532dc	no	12
Warnings:					
Information:					
10	Non Patent Literature	Hart.pdf	3510175 9188d4fffb5a2c5330d054c6d6ae839f31af75e9	no	6
Warnings:					
Information:					

11	Non Patent Literature	Helander.pdf	2229319 682001414b182b8fd9f76ba558b125e5098b190e	no	11
Warnings:					
Information:					
12	Non Patent Literature	Histamine_H2.pdf	67713 e926ceef45e2eab3a2989da79aa3bf509b206200	no	2
Warnings:					
Information:					
13	Non Patent Literature	Hogan.pdf	597768 63add2b57d61ea627046d376ab3247db237506cf	no	8
Warnings:					
Information:					
14	Non Patent Literature	Howden.pdf	2842576 f7e7537ce6c5e879a14296f7f69a7e53abfce3c0	no	12
Warnings:					
Information:					
15	Non Patent Literature	Ife.pdf	4384413 5afbb850aae303e79dfe35dfaf83e5d2172655a0	no	10
Warnings:					
Information:					
16	Non Patent Literature	Jiranek.pdf	1899208 df2df46bc32fe59acafb8697ed4dc9f4f9b53d71	no	6
Warnings:					
Information:					
17	Non Patent Literature	Katz.pdf	104813 a73de3c63d071ac177779d0892ea416fefe0596f	no	6
Warnings:					
Information:					
18	Non Patent Literature	Kephart.pdf	682107 789a0bfd096cb7ec74635913bdf86df7d10658b6	no	15
Warnings:					
Information:					
19	Non Patent Literature	Keeling.pdf	3041811 51df5cf2d4ec7c3920607b4e7714f243ae135bf2	no	8
Warnings:					
Information:					

20	Non Patent Literature	Kimmey.pdf	1441010 4bfe8808cfdfecba66e6d2886988b512c56a676e	no	4
Warnings:					
Information:					
21	Non Patent Literature	Kitchingman.pdf	1237322 926507cc970f22a75ecd2e9ccd9cbddebc78a83a	no	5
Warnings:					
Information:					
22	Non Patent Literature	Konturek.pdf	555553 d59a07897bbb6192697627f2f9e064ee8f996588	no	7
Warnings:					
Information:					
23	Non Patent Literature	Lad.pdf	2872057 dace093b5377efa23607c85f00f75c504ca04627	no	8
Warnings:					
Information:					
24	Non Patent Literature	Lanza.pdf	364282 c77688479f3f23993ad0084da9926c834643d691	no	4
Warnings:					
Information:					
25	Non Patent Literature	Lanas.pdf	2538514 1e890ef5638e66b3a63fda98adce7603359607ae	no	3
Warnings:					
Information:					
26	Non Patent Literature	Lanza_2.pdf	1639668 97a583a7d321b51c10912adddbbc8acef25a0d50	no	6
Warnings:					
Information:					
27	Non Patent Literature	Larsson.pdf	1079103 f3500c805e2ec2834d590905428a4cc3177e3353	no	13
Warnings:					
Information:					
28	Non Patent Literature	Lee.pdf	87251 bd17b1a04437c446e0de95128655d493577b6992	no	6
Warnings:					
Information:					

29	Non Patent Literature	Leese.pdf	684027 7a37f47f90e099151f189e0a11af62d11c92983d	no	9
Warnings:					
Information:					
30	Non Patent Literature	Leonards.pdf	1045620 b48aca530512978435e7b0e9c02e87f3d7f1a447	no	5
Warnings:					
Information:					
31	Non Patent Literature	Lichtenbergetr.pdf	327044 1f3f999058f258565558372e2f77f03a6cf530a9	no	6
Warnings:					
Information:					
32	Non Patent Literature	Lin.pdf	482585 785de5402dcf01f5042575da989e0ba1da0ee8ed	no	47
Warnings:					
Information:					
33	Non Patent Literature	Maggi.pdf	346419 29034e5b1f0acf1b9e70379bc9ff5e4f263af0d2	no	7
Warnings:					
Information:					
34	Non Patent Literature	Mason.pdf	1532148 5b06d89f29144142c956b4eb8183b7f2570d81ce	no	4
Warnings:					
Information:					
35	Non Patent Literature	Mattson.pdf	248823 8a754baa5204e35d62eca26c6c19ceb0220e6fe1	no	4
Warnings:					
Information:					
36	Non Patent Literature	Miner_1.pdf	274758 f68e42c454e1ddd4141ce4ce45cea011d7d5dbd3	no	11
Warnings:					
Information:					
37	Non Patent Literature	Miner_2.pdf	86777 05783dccae12902f146661afcb24c2d9fdd468c5	no	1
Warnings:					
Information:					

38	Non Patent Literature	Miner_3.pdf	171338 230a3dbea9a98878e1aecf83b395ef286c2a b25a	no	1
Warnings:					
Information:					
39	Non Patent Literature	Morgner.pdf	378090 e871cb24bfe48513b57e11844e0a9026838 6ed7f	no	14
Warnings:					
Information:					
40	Non Patent Literature	McKeage.pdf	25747047 e7bd434010e5754912e2b8289a97da47af2 b3d5a	no	37
Warnings:					
Information:					
41	Non Patent Literature	Morris.pdf	964003 6160029c0300b72baddf82d470649e9d773 1edf7	no	11
Warnings:					
Information:					
42	Non Patent Literature	Morrison.pdf	3289877 409f99b72ce738c1b2bddb1ca3067279780 8a70f	no	9
Warnings:					
Information:					
43	Non Patent Literature	Muller_1.pdf	861758 e3be7b2bfa4777f67f117caecd555dc8665c 6254	no	3
Warnings:					
Information:					
44	Non Patent Literature	Muller_1_EngTrans.pdf	603072 d3ab6e1cc2a6b5a5d9d511686c11553ed5a 4d5be	no	7
Warnings:					
Information:					
45	Non Patent Literature	Muller_2.pdf	717677 e7e0a12c2c4def5174d5edf59c83d9460f96 b16c	no	2
Warnings:					
Information:					
46	Non Patent Literature	Muller_2_EngTrans.pdf	406366 6f54cdc7cc7bfd16f129650d8c94daeaa2ed 2bd4	no	4
Warnings:					
Information:					

47	Non Patent Literature	Naesdal.pdf	87724 66e804e162a61fc9115d763d8bfea3ccefd3e531	no	6
Warnings:					
Information:					
48	Non Patent Literature	Naprosyn.pdf	1042029 9928d404bf0f80349ae66a63253afebfd95a04ab	no	31
Warnings:					
Information:					
49	Non Patent Literature	Nefesoglu.pdf	1518906 f7877d2061024e809135be5c06ad33dfb07e6517	no	5
Warnings:					
Information:					
50	Non Patent Literature	Neuvonen.pdf	1926146 24eeaad013f58b3ca99224acf501361a55bded65	no	9
Warnings:					
Information:					
51	Non Patent Literature	Oddsson_1.pdf	210847 7fb2e6018970f37d70ca1dbc8e3f05fee8af7fde	no	4
Warnings:					
Information:					
52	Non Patent Literature	Oddsson_2.pdf	1138247 88ce29ab59c68f5c6ad6c471cb234c9042106ffb	no	4
Warnings:					
Information:					
53	Non Patent Literature	Okabe_1.pdf	2153070 aad4da349e88c667761d92b8a10a807871017cb7	no	10
Warnings:					
Information:					
54	Non Patent Literature	Okabe_2.pdf	386357 1e0c142b8a010be24db9ffdce68c1df4ae3a0e02	no	18
Warnings:					
Information:					
55	Non Patent Literature	Panara.pdf	2836254 fb896dbc791524f56c348e1596f0ad0060a7f769	no	9
Warnings:					
Information:					

56	Non Patent Literature	Pang.pdf	394834 51bf1d2a6cdf3d949446026fbdac0b546e39835f	no	13
Warnings:					
Information:					
57	Non Patent Literature	Patrono.pdf	459807 e299e5a808bef09c36704e815e34e9b2883f01be	no	11
Warnings:					
Information:					
58	Non Patent Literature	Peterson.pdf	404688 f0ab6cc2aa1bca86314864d2b58bce3a0200b056	no	3
Warnings:					
Information:					
59	Non Patent Literature	Pilbrant.pdf	1370258 94e1b369a4b0677be8e922a6aca4e2f4b1811e6e	no	8
Warnings:					
Information:					
60	Non Patent Literature	Pirmohamed.pdf	106459 00b1cb80c2dae9c4c806a42b6063560c7ee0e3d5	no	5
Warnings:					
Information:					
		Total Files Size (in bytes):	88781098		

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

New Applications Under 35 U.S.C. 111

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

National Stage of an International Application under 35 U.S.C. 371

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

New International Application Filed with the USPTO as a Receiving Office

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

Electronic Acknowledgement Receipt

EFS ID:	13604932
Application Number:	12822612
International Application Number:	
Confirmation Number:	6136
Title of Invention:	Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer
First Named Inventor/Applicant Name:	Brian Ault
Customer Number:	22466
Filer:	David Michael Gryte/Elizabeth Ashton
Filer Authorized By:	David Michael Gryte
Attorney Docket Number:	103786-1 US/NS
Receipt Date:	28-AUG-2012
Filing Date:	24-JUN-2010
Time Stamp:	14:03:24
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	Porter.pdf	1666028 bcca72b9382ebac333a4e15d1316dbd5e4c493bc	no	12

Warnings:	
Information:	

2	Non Patent Literature	Qureshi.pdf	1118199 67f808744a7890415707d7094034bfcf2a8f8568	no	4
Warnings:					
Information:					
3	Non Patent Literature	Raskin.pdf	1426607 69d6ef6b4f95a9f4b452535a2d6d2c63b0593552	no	7
Warnings:					
Information:					
4	Non Patent Literature	Robinson.pdf	1457818 0728139e92218b4c560c0080a4e6e221048b8487	no	5
Warnings:					
Information:					
5	Non Patent Literature	Richardson.pdf	21317318 e5f3bae431048edbe3d43f6f38f0659f98bcdd6c	no	29
Warnings:					
Information:					
6	Non Patent Literature	Roth.pdf	1448782 65d77139d2a6bc1dbc6d1adee64cab9a6eeabff4	no	5
Warnings:					
Information:					
7	Non Patent Literature	Rubinstein.pdf	2253536 18d1b5cf0abefa03b09e3eacfc5f87e7d8d0d3ea	no	33
Warnings:					
Information:					
8	Non Patent Literature	Sangiah.pdf	1542530 fd749d4df82d315642554df6a305cd802ec0c004	no	5
Warnings:					
Information:					
9	Non Patent Literature	Savarino.pdf	110548 913a0a9903710cfadf76e7ce3d7124f2ac18ba24	no	5
Warnings:					
Information:					
10	Non Patent Literature	Scarpignato.pdf	2603791 0a97ad006ba278e604f41c9555373be4cea3cc28	no	30
Warnings:					
Information:					

11	Non Patent Literature	Scheiman_1.pdf	434728 763e6b99dfcdaad162add44520c515225949a939	no	13
Warnings:					
Information:					
12	Non Patent Literature	Scheiman_2.pdf	772331 dae02c496ff0caf28ac7ce1577a72000f21727ad	no	10
Warnings:					
Information:					
13	Non Patent Literature	Scheiman_3.pdf	2228685 c478e162dc57972431ef1586de391458297a6b57	no	7
Warnings:					
Information:					
14	Non Patent Literature	Scott.pdf	175169 bb675c40fe2d4a5cbd8aa8cf8fae3406feb774fe	no	3
Warnings:					
Information:					
15	Non Patent Literature	Seitz.pdf	2971413 6d00240255cb037626980cf181917a45e562addb	no	30
Warnings:					
Information:					
16	Non Patent Literature	Selway.pdf	519693 cd33918f3657d94e6c95a05013ea65ebea14976b	no	8
Warnings:					
Information:					
17	Non Patent Literature	Sharma.pdf	515981 1d0f303d15c2633e152107d59e4ff3147fc2855c	no	4
Warnings:					
Information:					
18	Non Patent Literature	Silverman_1.pdf	68748 6e205e9f0afc48040c4a680f6d2c197f236321b5	no	2
Warnings:					
Information:					
19	Non Patent Literature	Silverstein_2.pdf	971046 35d37fb89867e413354b82904176ba5f796589fa	no	9
Warnings:					
Information:					

20	Non Patent Literature	Silverstein_1.pdf	8421457 c8c3ebe4960fe93091ea09ebd2b8fbb5a55ed9f1	no	9
Warnings:					
Information:					
21	Non Patent Literature	Simon.pdf	1087365 09312321686c9c6c0b475ee3897bf2bb25de1f0d	no	3
Warnings:					
Information:					
22	Non Patent Literature	Simon_EngTrans.pdf	923711 656796680cc85c41b0280d6f0f995127091807a3	no	8
Warnings:					
Information:					
23	Non Patent Literature	Sung.pdf	259361 04bebfed54b894f1c0f3d58cdea611161596 9021	no	4
Warnings:					
Information:					
24	Non Patent Literature	Tronstad.pdf	686657 cd26abaf477bd216a44ccbbe4abbc432d70add93	no	4
Warnings:					
Information:					
25	Non Patent Literature	Vane.pdf	274936 45ee609aea7e611cfcee73f79c5d53eb2f227f88	no	3
Warnings:					
Information:					
26	Non Patent Literature	VIMOVO_press_release.pdf	128864 1491e4a8f3698762c418e8fde15d3c38fe8b8fa3	no	3
Warnings:					
Information:					
27	Non Patent Literature	vonUnge.pdf	216616 bb567aa34cfa24048819ee1cf1a55152f1bb8431	no	4
Warnings:					
Information:					
28	Non Patent Literature	Wagner.pdf	1696266 cc8e1fe0a4aef7c2f2d5d94269afbbf5c1434409	no	7
Warnings:					
Information:					

29	Non Patent Literature	Wallmark.pdf	1392626 88d17acf044ffbb19aa752a5fbe7e6898e423524	no	4
Warnings:					
Information:					
30	Non Patent Literature	Wakitani.pdf	2502099 e94b4da8e9c5581433d8c2d4436503bfb68ca616	no	7
Warnings:					
Information:					
31	Non Patent Literature	Warner.pdf	567566 bcb89bb481f2dfc6e4136f204ade565d0c1b2da4	no	6
Warnings:					
Information:					
32	Non Patent Literature	Weil.pdf	431128 e3606386ca484bfe9bd4cba8a0c921988f535078	no	4
Warnings:					
Information:					
33	Non Patent Literature	Wolfe_1.pdf	188459 6ed5979fce7dddf182140665ba892fec5d2837c0	no	12
Warnings:					
Information:					
34	Non Patent Literature	Wolfe_2.pdf	2093683 bc52a92f49bb9c33c06659aa99e8d91a902a4cde	no	23
Warnings:					
Information:					
35	Non Patent Literature	Yeomans_1.pdf	578929 0327ca0f51d0018c5891af836e5fcb506ba38cc4	no	8
Warnings:					
Information:					
36	Non Patent Literature	Yeomans_2.pdf	920578 42f1bfd67dee886bf33166d79bfceae9de5bc1ff	no	6
Warnings:					
Information:					
			Total Files Size (in bytes):	65973252	

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

New Applications Under 35 U.S.C. 111

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

National Stage of an International Application under 35 U.S.C. 371

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

New International Application Filed with the USPTO as a Receiving Office

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

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 103786-1P WO	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/SE2010/050712	International filing date *(day/month/year)* 23 June 2010 (23.06.2010)	Priority date *(day/month/year)* 25 June 2009 (25.06.2009)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant ASTRAZENECA AB		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 13 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☒	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 04 January 2012 (04.01.2012)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Nora Lindner e-mail: pt03.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
ASTRAZENECA INTELLECTUAL PROPERTY
AstraZeneca AB
SE-151 85 Södertälje

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* 20-09-2010

Applicant's or agent's file reference
103786-1P WO

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE2010/050712	23-06-2010	25-06-2009

International Patent Classification (IPC) or both national classification and IPC
See Supplemental Box

Applicant
ASTRAZENECA AB et al

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will no be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/SE	Date of completion of this opinion	Authorized officer
Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM	17-09-2010	Ingrid Eklund
Facsimile No. + 46 8 666 02 86		Telephone No. + 46 8 782 25 00

International application No.
PCT/SE2010/050712

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of: cover sheet

International Patent Classification (IPC)

A61K 31/4439 (2006.01)
A61K 9/24 (2006.01)
A61P 19/02 (2006.01)
A61P 29/00 (2006.01)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/SE2010/050712

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

   ☐ on paper

   ☐ in electronic form

   b. (time)

   ☐ in the international application as filed

   ☐ together with the international application in electronic form

   ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/SE2010/050712

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant data (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/SE2010/050712

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 1-63

because:

☒ the said international application, or the said claims Nos. 1-63 relate to the following subject matter which does not require an international search *(specify)*:

Claims 1-63 relate to a method for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods, see PCT rule 67.1.(iv). Nevertheless, an examination has been conducted for these claims. The examination has been made in respect of the technical content of the claims.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for said claims Nos. _____

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/SE2010/050712

Box No. V **Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	see extra sheet	YES
	Claims	see extra sheet	NO
Inventive step (IS)	Claims		YES
	Claims	1-63	NO
Industrial applicability (IA)	Claims	1-63	YES
	Claims		NO

2. Citations and explanations

Claims 1-63 relate to a method for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods, see PCT rule 67.1.(iv). Nevertheless, an examination has been conducted for these claims. The examination has been made in respect of the technical content of the claims.

Documents found during the search

D1: Anonymous: "PK study to evaluate esomeprazole plasma levels following administration of PN 400" INTERNET ARTICLE, 11 Feb 2008, URL:http://clinicaltrials.gov/show/NCT00599404> XP002553435
D2: Anonymous: "Study evaluating the bioavailability of naproxen 500 mg in three formulations" INTERNET ARTICLE, 11 May 2008, URL:http://clinicaltrials.gov/show/NCT00665743> XP002553436
D3: Anonymous: "A 12-month, phase 3, open-label, multi-center stucy to evaluate the long-term safety of PN 400" INTERNET ARTICLE, 11 Sept 2007, URL:http://clinicaltrials.gov/show/NCT00527904> XP002553437
D4: Miner P.B. et al., T1969 Gastric acid suppression with PN400, a single-tablet, multilayer, fixed-dose formulation combining an immediate-release esomeprazole layer and an enteric-coated (EC) naproxen core. Gastroenterology, 2009, 136, 5, A-611
D5: Miner P.B. et al., T1972 Pharmacokinetics of naproxen and esomeprazole in PN400, a single-tablet, multilayer formulation of enteric-coated naproxen coupled with immediate-release esomeprazole. Gastroenterololy 2009, 136, 5, A-612
D6: US20050249811 A1
D7: US2003069255 A1
D8: WO2008101060 A1
D9: US2005249806 A1
D10: Goldstein J.L. et al., 116 A single tablet multilayer formulation of enteric coated naproxen coupled with non-enteric coated omeprazole is associated with a significantly reduced incidence of gastric ulcer vs. Enteric-coated naproxen: A prospective, randomized, double-blind study. Gastroenterology, 2008, 134, 4, A-19
D11: Hassan-Alin M. et al., T1651 Lack of drug-drug interaction between esomeprazole and naproxen in healthy subjects. Digestive disease 2003, Orlando, Florida, USA May 17-22, 2003

.../...

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of: Box No. V

1. Statement

Novelty (N)	Claims	5, 9, 20-21, 26-28, 34, 38-41, 43, 46-50, 52-55, 57-63	YES
	Claims	1-4, 6-8, 10-19, 22-25, 29-33, 35-37, 42, 44-45, 51, 56	NO

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of: Box No. V

D12: McKeage K. et al., Esomeprazole A review of its use in the management of gastric acid-related diseases in adults. Drugs 2008, 68, 11, 1571-1607
D13: US2008031950 A1
D14: Morgner A. et al., Esomeprazole: prevention and treatment of NSAID-induced symptoms and ulcers. Expert opinion on pharmacotherapeutics 2007, 8, 7, 975-988.

Naproxen in combination with esomprazole in a unit dose; documents relevant to novelty of the application.

D1-D3 disclose the use of PN-400 in open-label studies. In D1-D3 it is stated that PN-400 contains 500 mg delayed release naproxen/20 mg immediate release esomeprazole. The subjects are instructed to take 2 tablets a day. PN400 is proposed for the treatment of signs and symptoms of osteoarthritis, rheumoatoid arthritis and ankylosing spondylitis or other medical conditions expected to require daily nonsteroidal anti-inflammatory drug (NSAID) therapy for at least 12 months in patients at risk for developing NSAID-associated gastric ulcers.

D4 and D5 also refers to, and defines, the composition of PN400.

D6 shows a drug dosage form that first releases an agent that raises the pH of a patient's gastrointestinal tract, followed by a NSAID. The agent that raises pH is e.g. a proton pump inhibitor (PPI). In example 6, omeprazole (which is a racemate and thus contains both the S- and the R-form of omeprazole) is combined with naproxen. The dosage form is gastro-protective, antiarthritic/analgesic and is intended to achieve pain and symptom relief with a reduced risk of developing gastrointestinal damage such as ulcers, erosions and hemorrhages. See the abstract, examples 5-6, sections [0012]-[0014] and claim 1.

D7 corresponds to D6. See the abstract, examples 5-6 and claims 1, 5, 10 and 37.

The following documents disclose combined dosage forms containing a NSAID and a PPI, where the PPI is released prior to the NSAID and are relevant for a discussion of inventive step.

D8 discloses a method of treating arthritis, pain or inflammation with a naproxen ester and a PPI. In one embodiment, the naproxen ester is surrounded by a polymeric coating which does not dissolve at a pH of less than 4. See section [0033].

D9 relates to pharmaceutical compositions comprising a PPI, one or more buffering agents, and a NSAID. The design of the composition aims to give a fast rise in serum concentration of the PPI whereas at least some of the NSAID is coated. The compositions are intended for treating gastric acid related disorders and inflammatory disorders. See the abstract and claims 1,4,12 and 27.

D10 discusses a single tablet formulation of enteric coated naproxen coupled with non-enteric coated omeprazole. Omeprazole contains esomeprazole, see D6. Therefore, a

.../...

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of: Box No. V

discussion of novelty could depart also from D10.

Documents that discuss the combination of PPI's and NSAID's and represent the state of the art.

D11 states that there is no drug-drug interaction when esomeprazole and naproxen is co-administered.

D12 concludes that there is data that supports the use of esomeprazole for fist-line treatment of NSAID-associated gastric ulcer disease. See p. 1062 column 1 line 26-column 2 line 3.

D13, section [0006] states that naproxen in combination with a PPI is the safest NSAID combination.

D14 also suggests that a combination drug of PPI, such as esomeprazole, plus an NSAID, would be worthwhile in order to increase compliance in cases where both medications are prescribed.

Novelty

Independent claims

Independent claims 1 and 25 of the present application define a composition comprising esomeprazole and naproxen, where naproxen is released when pH is at least 3.5 whereas esomeprazole is immediately soluble independent of pH. The compositions are intended for use in patients at risk for developing NSAID-associated gastric ulcers. Such compositions are known from D1-D7 and consequently, the application according to claims 1 and 25 lacks the requirement of novelty.

Independent claims 51 and 56 refer to further objectives of administration of the composition, namely reduction of dyspepsia- or heartburn associated symptoms. The skilled person is aware that esomeprazole is prescribed in order to reduce such symptoms (see e.g. D14). Therefore, the application according to claims 51 and 56 also lacks the requirement of novelty.

Dependent claims

From D6-D7 a composition where naproxen is released when pH has been elevated to a safe level by the release of a PPI, e.g. omeprazole (i.e. inherently esomeprazole), is known. The present application as defined in claims 2-4, 6-8, 13-19, 22-24, 29-33, 35-37, 42 and 44-45 is not novel when compared to the composition presented in D6-D7.

.../...

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of: Box No. V

The construction of PN400 is not explicitly shown in D1-D5. However, the effect obtained corresponds to that of the composition of the present application. It is therefore concluded that the dosage form of PN400 implicitly contains features corresponding to that of the present application. Further, the patients receiving PN400 are instructed to take two tablets a day and they are on at least 12 month treatment with NSAID. Therefore, claims 10-12 also lack the requirement of novelty over D1-D5.

Inventive step

The remaining claims (5, 9, 20-21, 26-28, 34, 38-41, 43, 46-50, 52-55 and 57-63) are considered to involve measures or minor details obvious to a person skilled in the art. Therefore, the invention according to these claims is not considered to involve an inventive step.

A discussion of inventive step for all claims (1-63) could also depart from any of D8-D10.

Conclusion

The subject matter of claims 1-4, 6-8, 10-19, 22-25, 29-33, 35-37, 42, 44-45, 51 and 56 lacks novelty and an inventive step. The subject matter of claims 5, 9, 20-21, 26-28, 34, 38-41, 43, 46-50, 52-55, 57-63 is novel, but is not considered to involve an inventive step. The subject matter of all the claims is industrially applicable.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/SE2010/050712

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

	Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
E	US2010/0172983 A1	08.07.2010	03.09.2009	
P,X	US2010/0062064 A1	11.03.2010	03.09.2009	

P,X Miner P. et al., Clinical trial: evaluation of gastric acid suppression with three doses of immediate-release esomeprazole in the fixed-dose combination of PN 400 (naproxen/esomeprazole magnesium) compared with naproxen 500 mg and enteric-coated esomeprazole 20 mg: a randomized, open-label, phase 1 study in healthy volunteers. Aliment pharmacology and therapeutics 2010, 32: 414-424

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 1, 25, 51 and 56 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject matter in terms of the result to be achieved which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result should be added.

The relative term “treated longer” used in claim 9 has no well-recognized meaning and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject matter of said claim unclear (Article 6 PCT).

The relative term “results in a relative risk reduction” used in claims 61-63 has no well-recognized meaning and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject matter of said claims unclear (Article 6 PCT).

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
103786-1P WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/SE2010/050712	23-06-2010	25-06-2009
Applicant		
ASTRAZENECA AB et al		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 7 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of:
      ☒ the international application in the language in which it was filed.
      ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (See Box No. II).

3. ☐ **Unity of invention is lacking** (See Box No. III).

4. With regard to the **title**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   ☐ the text is approved as submitted by the applicant.
   ☒ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,
   a. the figure of the **drawings** to be published with the abstract is Figure No. --
      ☒ as suggested by the applicant.
      ☐ as selected by this Authority, because the applicant failed to suggest a figure.
      ☐ as selected by this Authority, because this figure better characterizes the invention.
   b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2010/050712

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-63
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 1-63 relate to a method for treatment of the human or animal body by surgery or by therapy, as well as diagnostic methods, see PCT rule 39.1(iv). Nevertheless, a search has been made for these claims. The search has been directed to the technical content of the claims.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

The present disclosure is directed to a method for treating a disease or disorder in a patient at risk of developing an NSAID-associated ulcer by administering a pharmaceutical composition in unit dose form comprising naproxen, or pharmaceutically acceptable salt thereof, and esomeprazole, or pharmaceutically acceptable salt thereof. The unit dose is designed to release at least a part of the esomeprazole independent of pH (e.g. at a pH of 0 or more) whereas the naproxen is not released until the pH or the surrounding medium is 3.5 or higher.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2010/050712

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC:A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE, DK, FI, NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, PAJ, WPI data, BIOSIS, CHEM ABS Data, COMPENDEX, EMBASE, INSPEC, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	Miner P. et al., Clinical trial: evaluation of gastric acid suppression with three doses of immediate-release esomeprazole in the fixed-dose combination of PN 400 (naproxen/esomeprazole magnesium) compared with naproxen 500 mg and enteric-coated esomeprazole 20 mg: a randomized, open-label, phase 1 study in healthy volunteers, Alimentary pharmacology and therapeutics 2010, 32, 414-424; Table 1	1-63
	--	
X	Miner P.B. et al., T1969 Gastric acid suppression with PN400, a single-tablet, multilayer, fixed-dose formulation combining an immediate-release esomeprazole layer and an enteric-coated (EC) naproxen core. Gastroenterology, 2009, 136, 5, A-611; whole document; abstract	1-63
	--	
X	Miner P.B. et al., T1972 Pharmacokinetics of naproxen and esomeprazole in PN400, a single-tablet, multilayer formulation of enteric-coated naproxen coupled with immediate-release esomeprazole. Gastroenterololy 2009, 136, 5, A-612; whole document; abstract	1-63
	--	

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17-09-2010	20-09-2010
Name and mailing address of the ISA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. + 46 8 666 02 86	Authorized officer Ingrid Eklund Telephone No. + 46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2010/050712

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Goldstein J.L. et al., 116 A single tablet multilayer formulation of enteric coated naproxen coupled with non-enteric coated omeprazole is associated with a significantly reduced incidence of gastric ulcer vs. Enteric-coated naproxen: A prospective, randomized, double-blind study. Gastroenterology, 2008, 134, 4, A-19; whole document; abstract	1-63
	--	
A	Hassan-Alin M. et al., T1651 Lack of drug-drug interaction between esomeprazole and naproxen in healthy subjects. Digestive disease 2003, Orlando, Florida, USA May 17-22, 2003; whole document; abstract	1-63
	--	
A	McKeage K. et al., Esomeprazole A review of its use in the management of gastric acid-related diseases in adults. Drugs 2008, 68, 11, 1571-1607; whole document; abstract; page 1062, column 1, line 26 - page 1062, column 2, line 3	1-63
	--	
A	Morgner A. et al., Esomeprazole: prevention and treatment of NSAID-induced symptoms and ulcers. Expert opinion on pharmacotherapeutics 2007, 8, 7, 975-988; whole document; abstract; 7. Conclusion	1-63
	--	
X	Anonymous: "PK study to evaluate esomeprazole plasma levels following administration of PN 400" INTERNET ARTICLE, 11 Feb 2008, URL:http://clinicaltrials.gov/show/NCT00599404>; whole document	1-63
	--	
X	US 20050249811 A1 (PLACHETKA JOHN R), 10 November 2005 (2005-11-10); abstract; claim 1; Examples 5-6, sections [0012]-[0014]	1-63
	--	
X	Anonymous: "Study evaluating the bioavailability of naproxen 500 mg in three formulations" INTERNET ARTICLE, 11 May 2008, URL:http://clinicaltrials.gov/show/NCT00665743>; whole document	1-63
	--	
X	US 20030069255 A1 (PLACHETKA JOHN R), 10 April 2003 (2003-04-10); abstract; claims 1, 5, 10, 37; Examples 5-6	1-63
	--	
X	WO 2008101060 A1 (LOGICAL THERAPEUTICS INC ET AL), 21 August 2008 (2008-08-21); Section [0033]	1-63
	--	
X	Anonymous: "A 12-month, phase 3, open-label, multi-center stucy to evaluate the long-term safety of PN 400" INTERNET ARTICLE, 11 Sept 2007, URL:http://clinicaltrials.gov/show/NCT00527904>; whole document	1-63
	--	
X	US 20050249806 A1 (PROEHL GERALD T ET AL), 10 November 2005 (2005-11-10); abstract; claims 1, 4, 12, 27	1-63
	--	
A	US 20080031950 A1 (SESHA RAMESH), 7 February 2008 (2008-02-07); Section [0006]	1-63
	--	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2010/050712

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	US 20100062064 A1 (AULT BRIAN ET AL), 11 March 2010 (2010-03-11); abstract; claims 19, 40-45 ---	1-63
E	US 20100172983 A1 (PLACHETKA JOHN R), 8 July 2010 (2010-07-08); abstract; claims 57-76 --- ----------	1-63

Continuation of: second sheet

International Patent Classification (IPC)

A61K 31/4439 (2006.01)
A61K 9/24 (2006.01)
A61P 19/02 (2006.01)
A61P 29/00 (2006.01)

Download your patent documents at www.prv.se

The cited patent documents can be downloaded:

- From "Cited documents" found under our online services at www.prv.se (English version)
- From "Anförda dokument" found under "e-tjänster" at www.prv.se (Swedish version)

Use the application number as username. The password is **DGAPDUJIQN**.

Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.

US	20050249811	A1	10/11/2005	NONE			
US	20030069255	A1	10/04/2003	AU	2006235929	B2	11/12/2008
				AU	2002305758	C1	16/12/2002
				AU	2009200966	B2	10/06/2010
				CA	2449098	C	05/01/2010
				DE	60237087	D1	02/09/2010
				EA	006398	B1	29/12/2005
				EP	1411900	B1	21/07/2010
				EP	2163241	A1	17/03/2010
				JP	2004536809	T	09/12/2004
				MX	PA03011017	A	29/04/2005
				US	6926907	B2	09/08/2005
				WO	02098352	A3	26/06/2003
WO	2008101060	A1	21/08/2008	US	20100221337	A1	02/09/2010
				US	20100221336	A1	02/09/2010
				WO	2008101064	A1	21/08/2008
US	20050249806	A1	10/11/2005	AU	2005213472	A1	25/08/2005
				CA	2554271	A1	25/08/2005
				EP	1718303	A4	01/09/2010
				JP	2007522217	T	09/08/2007
				WO	2005076987	A3	08/06/2006
US	20080031950	A1	07/02/2008	NONE			
US	20100062064	A1	11/03/2010	NONE			
US	20100172983	A1	08/07/2010	NONE			

PATENT COOPERATION TREATY

PCT

SUPPLEMENTARY INTERNATIONAL SEARCH REPORT

(PCT Rule 45*bis*)

Applicant's or agent's file reference	International application No.
103786-1 WO	PCT/SE 2010/050712
International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)
23 June 2010 (23.06.2010)	25 June 2009 (25.06.2009)
Applicant	
ASTRAZENECA AB	

This supplementary international search report has been prepared by this Authority specified for supplementary search and it is transmitted to the applicant in accordance with Rule 45*bis*.8(a). A copy is being transmitted to the International Bureau.

☐ This report is a corrected version of a previously issued supplementary international search report

This supplementary international search report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the supplementary international search was carried out on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of:

- ☐ the international search (Rules 12.3(a) and 23.1(b)).
- ☐ the international publication (Rule 12.4)
- ☐ the supplementary international search (Rule 45*bis*.1(c)(i))

b. ☐ This supplementary international search report has been established taking into account the **rectification of an obvious mistake** notified to this Authority under Rule 91 (Rules 43.6*bis*(a) and 45*bis*.7(c)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No.I.

d. ☐ This supplementary international search report has been established taking due account of the international search report, or the declaration under Article 17(2)(a) that no international search report will be established, and the written opinion established under Rule 43*bis*.1.

2. ☐ **Certain claims were found unsearchable** (see Box No. II)

3. ☐ **Unity of invention is lacking** (see Box No. III)

SUPPLEMENTARY INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2010/050712

A. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K , 9/24, 31/4439, A61P 19/02, 29/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the supplementary international search (name of database and, where practicable, search terms used) DWPI, NCBI (PubMed), SpringerLink

B. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EA 006398 B1 (POUZEN INC.) 29.12.2005, abstract, p.2,5, claims 1, 5, 9-16, 22-24	1-63
A	RU 2158138 C2 (ASTRA AKTIEBOLAG) 27.10.2000	1-63

☐ Further documents are listed in the continuation of second sheet B ☐ See Patent Family Annex.

☐ See Scope Annex for details of the scope of the supplementary international search.

* Special categories of cited documents:
"A" document defining the general state of the art which is nit considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the supplementary international search	Date of mailing of the supplementary international search report
28 September 2011 (28.09.2011)	20 October 2011 (20.10.2011)
Name and mailing address of the Authority/ Russia, 123995, Moscow, G-59, GSP-5, Berezhkovskaya nab., 30-1 Facsimile No. 243-3337	Authorized officer M. Pustovalova Telephone No. (499) 240-2591

Form PCT/SISA/501 (second sheet) (July 2010)

SUPPLEMENTARY INTERNATIONAL SEARCH REPORT
Explanations with regard to the citations and/or the scope of the search
(Rule 45*bis*.7(e))

International application No.
PCT/SE 2010/050712

D1 : EA 006398 B1 (POZEN INC.), 29.12.2005

From D1(abstract, claims 1,5,9–16, 22–24, pages 2,5 of the description) there is known a method for treating diseases or disorders of patients with the risk of development of the NSAID-associated ulcers by means of introduction of pharmaceutical composition, including the composition in the form of multi–layer tablets, in a single dosed form, including: a) esomeprazole in the amount, which is sufficient one in order to increase pH of stomach of the mentioned patient up to no less than 3.5 upon the introduction one or more the mentioned single dosed form, and b) therapeutically effective amount of naproxen, therewith, the mentioned single form envisages a coordinated releasing of the esomeprazole and naproxen, providing an indication, consisting in that the naproxen is not released from the mentioned single form until pH of environment will be equal to 3.5 or more, and wherein the mentioned pharmaceutical composition in the single dosed form decreases a risk of the mentioned patient ulcer development.

From D1 there is also known, that the naproxen, included in the pharmaceutical composition, may be surrounded by means of barrier covering, which is practically is not solvable upon pH, which is less than 3.5.

Therewith, from D1 it is known, that preferable doses of naproxen content in a composition make up from 200 to 600 mg, but for the esomeprazole these doses ranges from 5 to 100 mg. The compositions are destined for a long-term treatment.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
ASTRAZENECA INTELLECTUAL PROPERTY
AstraZeneca AB
SE-151 85 Södertälje

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* 20-09-2010

Applicant's or agent's file reference
103786-1P WO

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE2010/050712	23-06-2010	25-06-2009

International Patent Classification (IPC) or both national classification and IPC
See Supplemental Box

Applicant
ASTRAZENECA AB et al

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will no be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/SE	Date of completion of this opinion	Authorized officer
Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM	17-09-2010	Ingrid Eklund
Facsimile No. + 46 8 666 02 86		Telephone No. + 46 8 782 25 00

International application No.
PCT/SE2010/050712

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of: cover sheet

International Patent Classification (IPC)

A61K 31/4439 (2006.01)
A61K 9/24 (2006.01)
A61P 19/02 (2006.01)
A61P 29/00 (2006.01)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/SE2010/050712

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

   ☐ on paper

   ☐ in electronic form

   b. (time)

   ☐ in the international application as filed

   ☐ together with the international application in electronic form

   ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/SE2010/050712

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant data (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/SE2010/050712

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 1-63

because:

☒ the said international application, or the said claims Nos. 1-63 relate to the following subject matter which does not require an international search *(specify)*:

Claims 1-63 relate to a method for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods, see PCT rule 67.1.(iv). Nevertheless, an examination has been conducted for these claims. The examination has been made in respect of the technical content of the claims.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for said claims Nos. _____

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/SE2010/050712

Box No. V **Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	see extra sheet	YES
	Claims	see extra sheet	NO
Inventive step (IS)	Claims		YES
	Claims	1-63	NO
Industrial applicability (IA)	Claims	1-63	YES
	Claims		NO

2. Citations and explanations

Claims 1-63 relate to a method for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods, see PCT rule 67.1.(iv). Nevertheless, an examination has been conducted for these claims. The examination has been made in respect of the technical content of the claims.

Documents found during the search

D1: Anonymous: "PK study to evaluate esomeprazole plasma levels following administration of PN 400" INTERNET ARTICLE, 11 Feb 2008, URL:http://clinicaltrials.gov/show/NCT00599404> XP002553435
D2: Anonymous: "Study evaluating the bioavailability of naproxen 500 mg in three formulations" INTERNET ARTICLE, 11 May 2008, URL:http://clinicaltrials.gov/show/NCT00665743> XP002553436
D3: Anonymous: "A 12-month, phase 3, open-label, multi-center stucy to evaluate the long-term safety of PN 400" INTERNET ARTICLE, 11 Sept 2007, URL:http://clinicaltrials.gov/show/NCT00527904> XP002553437
D4: Miner P.B. et al., T1969 Gastric acid suppression with PN400, a single-tablet, multilayer, fixed-dose formulation combining an immediate-release esomeprazole layer and an enteric-coated (EC) naproxen core. Gastroenterology, 2009, 136, 5, A-611
D5: Miner P.B. et al., T1972 Pharmacokinetics of naproxen and esomeprazole in PN400, a single-tablet, multilayer formulation of enteric-coated naproxen coupled with immediate-release esomeprazole. Gastroenterololy 2009, 136, 5, A-612
D6: US20050249811 A1
D7: US2003069255 A1
D8: WO2008101060 A1
D9: US2005249806 A1
D10: Goldstein J.L. et al., 116 A single tablet multilayer formulation of enteric coated naproxen coupled with non-enteric coated omeprazole is associated with a significantly reduced incidence of gastric ulcer vs. Enteric-coated naproxen: A prospective, randomized, double-blind study. Gastroenterology, 2008, 134, 4, A-19
D11: Hassan-Alin M. et al., T1651 Lack of drug-drug interaction between esomeprazole and naproxen in healthy subjects. Digestive disease 2003, Orlando, Florida, USA May 17-22, 2003

.../...

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of: Box No. V

1. Statement

Novelty (N)	Claims	5, 9, 20-21, 26-28, 34, 38-41, 43, 46-50, 52-55, 57-63	YES
	Claims	1-4, 6-8, 10-19, 22-25, 29-33, 35-37, 42, 44-45, 51, 56	NO

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of: Box No. V

D12: McKeage K. et al., Esomeprazole A review of its use in the management of gastric acid-related diseases in adults. Drugs 2008, 68, 11, 1571-1607
D13: US2008031950 A1
D14: Morgner A. et al., Esomeprazole: prevention and treatment of NSAID-induced symptoms and ulcers. Expert opinion on pharmacotherapeutics 2007, 8, 7, 975-988.

Naproxen in combination with esomprazole in a unit dose; documents relevant to novelty of the application.

D1-D3 disclose the use of PN-400 in open-label studies. In D1-D3 it is stated that PN-400 contains 500 mg delayed release naproxen/20 mg immediate release esomeprazole. The subjects are instructed to take 2 tablets a day. PN400 is proposed for the treatment of signs and symptoms of osteoarthritis, rheumoatoid arthritis and ankylosing spondylitis or other medical conditions expected to require daily nonsteroidal anti-inflammatory drug (NSAID) therapy for at least 12 months in patients at risk for developing NSAID-associated gastric ulcers.

D4 and D5 also refers to, and defines, the composition of PN400.

D6 shows a drug dosage form that first releases an agent that raises the pH of a patient's gastrointestinal tract, followed by a NSAID. The agent that raises pH is e.g. a proton pump inhibitor (PPI). In example 6, omeprazole (which is a racemate and thus contains both the S- and the R-form of omeprazole) is combined with naproxen. The dosage form is gastro-protective, antiarthritic/analgesic and is intended to achieve pain and symptom relief with a reduced risk of developing gastrointestinal damage such as ulcers, erosions and hemorrhages. See the abstract, examples 5-6, sections [0012]-[0014] and claim 1.

D7 corresponds to D6. See the abstract, examples 5-6 and claims 1, 5, 10 and 37.

The following documents disclose combined dosage forms containing a NSAID and a PPI, where the PPI is released prior to the NSAID and are relevant for a discussion of inventive step.

D8 discloses a method of treating arthritis, pain or inflammation with a naproxen ester and a PPI. In one embodiment, the naproxen ester is surrounded by a polymeric coating which does not dissolve at a pH of less than 4. See section [0033].

D9 relates to pharmaceutical compositions comprising a PPI, one or more buffering agents, and a NSAID. The design of the composition aims to give a fast rise in serum concentration of the PPI whereas at least some of the NSAID is coated. The compositions are intended for treating gastric acid related disorders and inflammatory disorders. See the abstract and claims 1,4,12 and 27.

D10 discusses a single tablet formulation of enteric coated naproxen coupled with non-enteric coated omeprazole. Omeprazole contains esomeprazole, see D6. Therefore, a

.../...

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of: Box No. V

discussion of novelty could depart also from D10.

Documents that discuss the combination of PPI's and NSAID's and represent the state of the art.

D11 states that there is no drug-drug interaction when esomeprazole and naproxen is co-administered.

D12 concludes that there is data that supports the use of esomeprazole for fist-line treatment of NSAID-associated gastric ulcer disease. See p. 1062 column 1 line 26-column 2 line 3.

D13, section [0006] states that naproxen in combination with a PPI is the safest NSAID combination.

D14 also suggests that a combination drug of PPI, such as esomeprazole, plus an NSAID, would be worthwhile in order to increase compliance in cases where both medications are prescribed.

Novelty

Independent claims

Independent claims 1 and 25 of the present application define a composition comprising esomeprazole and naproxen, where naproxen is released when pH is at least 3.5 whereas esomeprazole is immediately soluble independent of pH. The compositions are intended for use in patients at risk for developing NSAID-associated gastric ulcers. Such compositions are known from D1-D7 and consequently, the application according to claims 1 and 25 lacks the requirement of novelty.

Independent claims 51 and 56 refer to further objectives of administration of the composition, namely reduction of dyspepsia- or heartburn associated symptoms. The skilled person is aware that esomeprazole is prescribed in order to reduce such symptoms (see e.g. D14). Therefore, the application according to claims 51 and 56 also lacks the requirement of novelty.

Dependent claims

From D6-D7 a composition where naproxen is released when pH has been elevated to a safe level by the release of a PPI, e.g. omeprazole (i.e. inherently esomeprazole), is known. The present application as defined in claims 2-4, 6-8, 13-19, 22-24, 29-33, 35-37, 42 and 44-45 is not novel when compared to the composition presented in D6-D7.

.../...

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of: Box No. V

The construction of PN400 is not explicitly shown in D1-D5. However, the effect obtained corresponds to that of the composition of the present application. It is therefore concluded that the dosage form of PN400 implicitly contains features corresponding to that of the present application. Further, the patients receiving PN400 are instructed to take two tablets a day and they are on at least 12 month treatment with NSAID. Therefore, claims 10-12 also lack the requirement of novelty over D1-D5.

Inventive step

The remaining claims (5, 9, 20-21, 26-28, 34, 38-41, 43, 46-50, 52-55 and 57-63) are considered to involve measures or minor details obvious to a person skilled in the art. Therefore, the invention according to these claims is not considered to involve an inventive step.

A discussion of inventive step for all claims (1-63) could also depart from any of D8-D10.

Conclusion

The subject matter of claims 1-4, 6-8, 10-19, 22-25, 29-33, 35-37, 42, 44-45, 51 and 56 lacks novelty and an inventive step. The subject matter of claims 5, 9, 20-21, 26-28, 34, 38-41, 43, 46-50, 52-55, 57-63 is novel, but is not considered to involve an inventive step. The subject matter of all the claims is industrially applicable.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/SE2010/050712

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

	Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
E	US2010/0172983 A1	08.07.2010	03.09.2009	
P,X	US2010/0062064 A1	11.03.2010	03.09.2009	

P,X Miner P. et al., Clinical trial: evaluation of gastric acid suppression with three doses of immediate-release esomeprazole in the fixed-dose combination of PN 400 (naproxen/esomeprazole magnesium) compared with naproxen 500 mg and enteric-coated esomeprazole 20 mg: a randomized, open-label, phase 1 study in healthy volunteers. Aliment pharmacology and therapeutics 2010, 32: 414-424

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 1, 25, 51 and 56 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject matter in terms of the result to be achieved which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result should be added.

The relative term “treated longer” used in claim 9 has no well-recognized meaning and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject matter of said claim unclear (Article 6 PCT).

The relative term “results in a relative risk reduction” used in claims 61-63 has no well-recognized meaning and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject matter of said claims unclear (Article 6 PCT).

Electronic Acknowledgement Receipt

EFS ID:	13605186
Application Number:	12822612
International Application Number:	
Confirmation Number:	6136
Title of Invention:	Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer
First Named Inventor/Applicant Name:	Brian Ault
Customer Number:	22466
Filer:	David Michael Gryte/Elizabeth Ashton
Filer Authorized By:	David Michael Gryte
Attorney Docket Number:	103786-1 US/NS
Receipt Date:	28-AUG-2012
Filing Date:	24-JUN-2010
Time Stamp:	14:16:51
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	US20100062064_OA_05Jan2012.pdf	322250 c5b3db91929d707f6790e69582d4e1b3ebde1485	no	9

Warnings:	
Information:	

2	Non Patent Literature	US20100062064_OfficeAction_30July12.pdf	552014 6bae6cdc012b5f8017b3563c6f1ff841ba20185c	no	11
Warnings:					
Information:					
3	Non Patent Literature	US6926907_OA_22April2004.pdf	231419 1fc2bfd5e533315ddb3ccfd9137ef60f2d317cdf	no	6
Warnings:					
Information:					
4	Non Patent Literature	US6926907_OA_20Oct2004.pdf	218341 48d113e3587c07a4d103377180c60ffcd5c4952d	no	6
Warnings:					
Information:					
5	Non Patent Literature	US6926907_NOA_29Mar2005.pdf	326860 d9e6ee8df589c7c1587507167389b88937c3bba3	no	7
Warnings:					
Information:					
6	Non Patent Literature	US8206741_OA_30Mar2009.pdf	656929 99d55e243472b7bf65cf03e2dda4791de20ed5d3	no	20
Warnings:					
Information:					
7	Non Patent Literature	US8206741_OA_19Nov2009.pdf	447228 8fdb296a0a02c9bf3787d43172c034f663fc01dd	no	13
Warnings:					
Information:					
8	Non Patent Literature	US8206741_OA_25Oct2010.pdf	644221 5d7557f1def0c0a4922757fd62f8e80e868136ad	no	17
Warnings:					
Information:					
9	Non Patent Literature	US8206741_OA_16June2011.pdf	300791 db308d126e8ba4dc21e0e61d2050e8c90a048295	no	9
Warnings:					
Information:					
10	Non Patent Literature	US8206741_Interview_15Nov2011.pdf	162211 9e98532b634359f62187e73ba503d47a005c2111	no	3
Warnings:					
Information:					

11	Non Patent Literature	US8206741_Interview_07Mar2012.pdf	163192 fce45658a04849b74dedf92788e4205002921058	no	3
Warnings:					
Information:					
12	Non Patent Literature	US8206741_Interview_19April2012.pdf	161887 0d8962fdcd0e073d86be02c7dc8e12ef6daa6ae4	no	3
Warnings:					
Information:					
13	Non Patent Literature	US8206741_NOA_11May2012.pdf	392892 e7fa0ed44daa49a0aaca10b05b3b0b25cdce152c	no	8
Warnings:					
Information:					
14	Non Patent Literature	WO2010151216_IPER.pdf	449874 8f5e85f223fd971bcde76d305698e0e24e84d916	no	13
Warnings:					
Information:					
15	Non Patent Literature	WO2010151216_ISR.pdf	292389 b28a67e9d935156d37759df9017660f6bafef325	no	8
Warnings:					
Information:					
16	Non Patent Literature	WO2010151216_Supp_ISR.pdf	130168 286f39c2141025748e6e5120914b2308a03bffae	no	3
Warnings:					
Information:					
17	Non Patent Literature	WO2010151216_Written_Opinion.pdf	412863 f3cf7b9f73403d0d5c3faf9c505c98137c3eedc9	no	12
Warnings:					
Information:					
18	Non Patent Literature	USSN_13475446_Spec.pdf	1912235 147f0d81638e86e53ff81def77a0a8c10c5670ab	no	45
Warnings:					
Information:					
19	Non Patent Literature	USSN_13475446_PrelimAmend_18May12.pdf	55338 cca6487df70a206bc70bc60484d5fe3f43fdb33c	no	3
Warnings:					
Information:					

Total Files Size (in bytes):	7833102

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

New Applications Under 35 U.S.C. 111

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

National Stage of an International Application under 35 U.S.C. 371

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

New International Application Filed with the USPTO as a Receiving Office

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/822,612	06/24/2010	Brian Ault	103786-1 US/NS

CONFIRMATION NO. 6136

22466
ASTRA ZENECA PHARMACEUTICALS LP
GLOBAL INTELLECTUAL PROPERTY
1800 CONCORD PIKE
WILMINGTON, DE 19850-5437

PUBLICATION NOTICE

OC00000045211115

Title: Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer

Publication No.US-2010-0330179-A1
Publication Date:12/30/2010

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
12/822,612	06/24/2010	1614	4326	103786-1 US/NS	62	4

CONFIRMATION NO. 6136

UPDATED FILING RECEIPT

22466
ASTRA ZENECA PHARMACEUTICALS LP
GLOBAL INTELLECTUAL PROPERTY
1800 CONCORD PIKE
WILMINGTON, DE 19850-5437

Date Mailed: 09/08/2010

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

Brian Ault, Wilmington, DE;
Clara Hwang, Wilmington, DE;
Everardus Orlemans, Chapel Hill, NC;
John R. Plachetka, Chapel Hill, NC;
Mark Sostek, Wilmington, DE;

Assignment For Published Patent Application

ASTRAZENECA AB, Sodertalje, SWEDEN
POZEN INC., Chapel Hill, NC

Power of Attorney: The patent practitioners associated with Customer Number 22466

Domestic Priority data as claimed by applicant

This appln claims benefit of 61/220,420 06/25/2009
and claims benefit of 61/225,970 07/16/2009
and claims benefit of 61/310,525 03/04/2010

Foreign Applications

If Required, Foreign Filing License Granted: 07/01/2010

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/822,612**

Projected Publication Date: 12/30/2010

Non-Publication Request: No

Early Publication Request: No

Title

Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as

set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

AstraZeneca

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.: 12/822,612	Applicant: Ault *et al.*
Filing Date: June 24, 2010	Attorney Docket No.: 103786-1 US/NS
Examiner: Unknown	Group Art Unit : 1614
Customer No.: 22466	Confirmation No.: 6136
Title: Method for treating a patient at risk for developing an NSAID-associated ulcer	

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO NOTICE TO FILE MISSING PARTS

Sir:

Responsive to the Notice to File Missing Parts, dated July 6, 2010, applicant hereby encloses the executed Declaration. Applicant authorizes payment of the $130.00 fee to be charged to deposit account number 26-0166.

Respectfully submitted,

/Jacqueline Cohen/

Name: Jacqueline Cohen
Dated: September 1, 2010
Reg. No.: 51,574
Phone No.: 302-885-4269
Intellectual Property, Patents,
AstraZeneca
1800 Concord Pike
Wilmington, DE-19850-5437

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter that is claimed and for which a patent is sought on the invention entitled:

METHOD FOR TREATING A PATIENT AT RISK FOR DEVELOPING AN NSAID-ASSOCIATED ULCER

the specification of which:

☐ is attached hereto.

OR

☐ was filed on _____ with Express Mail No. (Application Number not yet known).

OR

☒ was filed on 24 June 2010 as United States Application Number 12/822612 or PCT International Application Number _____ and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the office all information known to me to be material to patentability as defined in 37 CFR §1.56.

I hereby claim the benefit under Title 35, United States Code, §119(e)(1) of any United States provisional application(s) listed below:

U.S. Serial No.	Filing Date	Status
61/220420	25 June 2009	
61/225970	16 July 2009	
61/310525	04 March 2010	

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s), or §365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose all information known to be material to patentability as defined in 37 CFR §1.56 of which I became aware between the filing date of the prior application and the national or PCT international filing date of this application:

U.S. Serial No.	Filing Date	Status

I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT International application designating at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

Country	Application No.	Filing Date	Priority Claimed
			☐Yes ☐No
			☐Yes ☐No

I hereby appoint all registered practitioners associated with **Customer Number 22466** to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith, and direct that all correspondence be addressed to:

Customer Number 22466

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full Name of Inventor: AULT Brian

Inventor's Signature: R Ault Date: 7/26/10

Residence Address: Wilmington, Delaware, USA

Citizenship: US

Post Office Address: AstraZeneca R&D Wilmington, 1800 Concord Pike, P.O. Box 15437, Wilmington, DE 19850-5437, USA

Full Name of Inventor: HWANG Clara

Inventor's Signature: Clara Hwang Date: 7/26/2010

Residence Address: Wilmington, Delaware, USA

Citizenship: US

Post Office Address: AstraZeneca R&D Wilmington, 1800 Concord Pike, P.O. Box 15437, Wilmington, DE 19850-5437, USA

Full Name of Inventor: ORLEMANS Everardus

Inventor's Signature: _____ Date: _____

Residence Address: Chapel Hill, North Carolina, USA

Citizenship: NL

Post Office Address: POZEN Inc. 1414 Raleigh Road, Chapel Hill, NC 27517, USA

Full Name of Inventor: PLACHETKA John R

Inventor's Signature: _____ Date: _____

Residence Address: Chapel Hill, North Carolina, USA

Citizenship: US

Post Office Address: POZEN Inc. 1414 Raleigh Road, Chapel Hill, NC 27517, USA

Full Name of Inventor: SOSTEK Mark

Inventor's Signature: Mark B. Sostek Date: July 26, 2010

Residence Address: Wilmington, Delaware, USA

Citizenship: US

Post Office Address: AstraZeneca R&D Wilmington, 1800 Concord Pike, P.O. Box 15437, Wilmington, DE 19850-5437, USA

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter that is claimed and for which a patent is sought on the invention entitled:

METHOD FOR TREATING A PATIENT AT RISK FOR DEVELOPING AN NSAID-ASSOCIATED ULCER

the specification of which:

☐ is attached hereto.

OR

☐ was filed on _____ with Express Mail No. (Application Number not yet known).

OR

☒ was filed on 24 June 2010 as United States Application Number 12/822612 or PCT International Application Number _____ and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the office all information known to me to be material to patentability as defined in 37 CFR §1.56.

I hereby claim the benefit under Title 35, United States Code, §119(e)(1) of any United States provisional application(s) listed below:

U.S. Serial No.	Filing Date	Status
61/220420	25 June 2009	
61/225970	16 July 2009	
61/310525	04 March 2010	

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s), or §365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose all information known to be material to patentability as defined in 37 CFR §1.56 of which I became aware between the filing date of the prior application and the national or PCT international filing date of this application:

U.S. Serial No.	Filing Date	Status

I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT International application designating at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

Country	Application No.	Filing Date	Priority Claimed
			☐Yes ☐No
			☐Yes ☐No

I hereby appoint all registered practitioners associated with **Customer Number 22466** to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith, and direct that all correspondence be addressed to:

Customer Number 22466

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full Name of Inventor: AULT Brian

Inventor's Signature: _____ Date: _____

Residence Address: Wilmington, Delaware, USA

Citizenship: US

Post Office Address: AstraZeneca R&D Wilmington, 1800 Concord Pike, P.O. Box 15437, Wilmington, DE 19850-5437, USA

Full Name of Inventor: HWANG Clara

Inventor's Signature: _____ Date: _____

Residence Address: Wilmington, Delaware, USA

Citizenship: US

Post Office Address: AstraZeneca R&D Wilmington, 1800 Concord Pike, P.O. Box 15437, Wilmington, DE 19850-5437, USA

Full Name of Inventor: ORLEMANS Everardus

Inventor's Signature: _____ Date: Aug 13, 2010

Residence Address: Chapel Hill, North Carolina, USA

Citizenship: NL

Post Office Address: POZEN Inc. 1414 Raleigh Road, Chapel Hill, NC 27517, USA

Full Name of Inventor: PLACHETKA John R

Inventor's Signature: _____ Date: Aug 20, 2010

Residence Address: Chapel Hill, North Carolina, USA

Citizenship: US

Post Office Address: POZEN Inc. 1414 Raleigh Road, Chapel Hill, NC 27517, USA

Full Name of Inventor: SOSTEK Mark

Inventor's Signature: _____ Date: _____

Residence Address: Wilmington, Delaware, USA

Citizenship: US

Post Office Address: AstraZeneca R&D Wilmington, 1800 Concord Pike, P.O. Box 15437, Wilmington, DE 19850-5437, USA

Electronic Patent Application Fee Transmittal

Application Number:	12822612
Filing Date:	24-Jun-2010
Title of Invention:	Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer
First Named Inventor/Applicant Name:	Brian Ault
Filer:	Jacqueline Marie Cohen/Elizabeth Ashton
Attorney Docket Number:	103786-1 US/NS

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Late filing fee for oath or declaration	1051	1	130	130
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**130**

Electronic Acknowledgement Receipt

EFS ID:	8332981
Application Number:	12822612
International Application Number:	
Confirmation Number:	6136
Title of Invention:	Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer
First Named Inventor/Applicant Name:	Brian Ault
Customer Number:	22466
Filer:	Jacqueline Marie Cohen/Elizabeth Ashton
Filer Authorized By:	Jacqueline Marie Cohen
Attorney Docket Number:	103786-1 US/NS
Receipt Date:	01-SEP-2010
Filing Date:	24-JUN-2010
Time Stamp:	08:46:31
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$130
RAM confirmation Number	7900
Deposit Account	260166
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Applicant Response to Pre-Exam Formalities Notice	103786US_RespMissingParts.pdf	80506 e82a3702004585fae49c638fb9787c6352081eaf	no	1
Warnings:					
Information:					
2	Oath or Declaration filed	103786US_Dec.pdf	266505 ce3505977d7b45891ca810acd36090d79308e6c0	no	6
Warnings:					
Information:					
3	Fee Worksheet (PTO-875)	fee-info.pdf	30222 d5ef3a8e8136c6129d6b5404274669317c140dba	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	377233		

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

New Applications Under 35 U.S.C. 111

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

National Stage of an International Application under 35 U.S.C. 371

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

New International Application Filed with the USPTO as a Receiving Office

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
12/822,612	06/24/2010	1614	4196	103786-1 US/NS	62	4

CONFIRMATION NO. 6136

22466
ASTRA ZENECA PHARMACEUTICALS LP
GLOBAL INTELLECTUAL PROPERTY
1800 CONCORD PIKE
WILMINGTON, DE 19850-5437

FILING RECEIPT

OC000000042417945

Date Mailed: 07/06/2010

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

Brian Ault, Wilmington, DE;
Clara Hwang, Wilmington, DE;
Everardus Orlemans, Chapel Hill, NC;
John R. Plachetka, Chapel Hill, NC;
Mark Sostek, Wilmington, DE;

Assignment For Published Patent Application

ASTRAZENECA AB, Sodertalje, SWEDEN
POZEN INC., Chapel Hill, NC

Power of Attorney: None

Domestic Priority data as claimed by applicant

This appln claims benefit of 61/220,420 06/25/2009
and claims benefit of 61/225,970 07/16/2009
and claims benefit of 61/310,525 03/04/2010

Foreign Applications

If Required, Foreign Filing License Granted: 07/01/2010

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/822,612**

Projected Publication Date: To Be Determined - pending completion of Missing Parts

Non-Publication Request: No

Early Publication Request: No

Title

Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as

set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/822,612	06/24/2010	Brian Ault	103786-1 US/NS

CONFIRMATION NO. 6136

22466
ASTRA ZENECA PHARMACEUTICALS LP
GLOBAL INTELLECTUAL PROPERTY
1800 CONCORD PIKE
WILMINGTON, DE 19850-5437

FORMALITIES LETTER

Date Mailed: 07/06/2010

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The oath or declaration is missing.
  A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.
  Note: If a petition under 37 CFR 1.47 is being filed, an oath or declaration in compliance with 37 CFR 1.63 signed by all available joint inventors, or if no inventor is available by a party with sufficient proprietary interest, is required.

The applicant needs to satisfy supplemental fees problems indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- To avoid abandonment, a surcharge (for late submission of filing fee, search fee, examination fee or oath or declaration) as set forth in 37 CFR 1.16(f) of $**130** for a non-small entity, must be submitted with the missing items identified in this notice.

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is $**130** for a non-small entity
- $**130** Surcharge.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web.
https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

/hteffera/

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

PTO/SB/05 (08-08)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office. U.S. DEPARTMENT OF COMMERCE

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	103786-1 US/NS
First Inventor	Ault
Title	Method for treating a patient at
Express Mail Label No.	

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. ☐ **Fee Transmittal Form** (e.g., PTO/SB/17)
2. ☐ **Applicant claims small entity status.** See 37 CFR 1.27.
3. ☑ **Specification** [*Total Pages* 44]
   Both the claims and abstract must start on a new page
   (For information on the preferred arrangement, see MPEP 608.01(a))
4. ☐ **Drawing(s)** (*35 U.S.C. 113*) [*Total Sheets* _____]
5. **Oath or Declaration** [*Total Sheets* _____]
   a. ☐ Newly executed (original or copy)
   b. ☐ A copy from a prior application (37 CFR 1.63(d))
   (for continuation/divisional with Box 18 completed)
   i. ☐ DELETION OF INVENTOR(S)
   Signed statement attached deleting inventor(s) name in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).
6. ☑ **Application Data Sheet.** See 37 CFR 1.76
7. ☐ **CD-ROM or CD-R** in duplicate, large table or Computer Program *(Appendix)*
   ☐ Landscape Table on CD
8. **Nucleotide and/or Amino Acid Sequence Submission**
   (if applicable, items a. – c. are required)
   a. ☐ Computer Readable Form (CRF)
   b. Specification Sequence Listing on:
      i. ☐ CD-ROM or CD-R (2 copies); or
      ii. ☐ Paper
   c. ☐ Statements verifying identity of above copies

ADDRESS TO:

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

ACCOMPANYING APPLICATION PARTS

9. ☐ **Assignment Papers** (cover sheet & document(s))
   Name of Assignee_____
10. ☐ **37 CFR 3.73(b) Statement** *(when there is an assignee)* ☐ **Power of Attorney**
11. ☐ **English Translation Document** *(if applicable)*
12. ☐ **Information Disclosure Statement** (PTO/SB/08 or PTO-1449)
    ☐ Copies of citations attached
13. ☑ **Preliminary Amendment**
14. ☐ **Return Receipt Postcard** (MPEP 503)
    (*Should be specifically itemized)*
15. ☐ **Certified Copy of Priority Document(s)**
    (if foreign priority is claimed)
16. ☐ **Nonpublication Request** under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.
17. ☐ Other:_____

18. If a CONTINUING APPLICATION, *check appropriate box, and supply the requisite information below and in the first sentence of the specification following the title, or in an Application Data Sheet under 37 CFR 1.76:*

☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No.: .....

Prior application information: *Examiner* _____ *Art Unit:* _____

19. CORRESPONDENCE ADDRESS

☑ The address associated with Customer Number: 22466 ***OR*** ☐ Correspondence address below

Name					
Address					
City		State		Zip Code	
Country		Telephone		Email	

Signature	/Jacqueline Cohen/	Date	June 24, 2010
Name (Print/Type)	Jacqueline M. Cohen	Registration No. (Attorney/Agent)	51574

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/SB/14 (07-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	103786-1 US/NS
	Application Number	
Title of Invention	Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Applicant Information:

Applicant 1 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Brian		Ault	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Wilmington	State/Province	DE	Country of Residence[i]	US

Citizenship under 37 CFR 1.41(b)[i] US

Mailing Address of Applicant:

Address 1	AstraZeneca R&D Wilmington		
Address 2	1800 Concord Pike, P.O. Box 15437		
City	Wilmington	State/Province	DE
Postal Code	19850	Country[i]	US

Applicant 2 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Clara		Hwang	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Wilmington	State/Province	DE	Country of Residence[i]	US

Citizenship under 37 CFR 1.41(b)[i] US

Mailing Address of Applicant:

Address 1	AstraZeneca R&D Wilmington		
Address 2	1800 Concord Pike, P.O. Box 15437		
City	Wilmington	State/Province	DE
Postal Code	19850	Country[i]	US

Applicant 3 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Everardus		Orlemans	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Chapel Hill	State/Province	NC	Country of Residence[i]	US

PTO/SB/14 (07-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	103786-1 US/NS
	Application Number	
Title of Invention	Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer	

Citizenship under 37 CFR 1.41(b) i	NL				
Mailing Address of Applicant:					
Address 1	Pozen Inc.				
Address 2	1414 Raleigh Road				
City	Chapel Hill	**State/Province**	NC		
Postal Code	27517	**Country**i	US		

Applicant 4 Remove

Applicant Authority (•) Inventor ( ) Legal Representative under 35 U.S.C. 117 ( ) Party of Interest under 35 U.S.C. 118

Prefix	**Given Name**	**Middle Name**	**Family Name**	**Suffix**
	John	R.	Plachetka	

Residence Information (Select One) (•) US Residency ( ) Non US Residency ( ) Active US Military Service

City	Chapel Hill	**State/Province**	NC	**Country of Residence** i	US
Citizenship under 37 CFR 1.41(b) i	US				
Mailing Address of Applicant:					
Address 1	Pozen Inc.				
Address 2	1414 Raleigh Road				
City	Chapel Hill	**State/Province**	NC		
Postal Code	27517	**Country**i	US		

Applicant 5 Remove

Applicant Authority (•) Inventor ( ) Legal Representative under 35 U.S.C. 117 ( ) Party of Interest under 35 U.S.C. 118

Prefix	**Given Name**	**Middle Name**	**Family Name**	**Suffix**
	Mark		Sostek	

Residence Information (Select One) (•) US Residency ( ) Non US Residency ( ) Active US Military Service

City	Wilmington	**State/Province**	DE	**Country of Residence** i	US
Citizenship under 37 CFR 1.41(b) i	US				
Mailing Address of Applicant:					
Address 1	AstraZeneca R&D Wilmington				
Address 2	1800 Concord Pike, P.O. Box 15437				
City	Wilmington	**State/Province**	DE		
Postal Code	19850	**Country**i	US		

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	22466

PTO/SB/14 (07-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	103786-1 US/NS
	Application Number	
Title of Invention	Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer	

Email Address		Add Email	Remove Email

Application Information:

Title of the Invention	Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer		
Attorney Docket Number	103786-1 US/NS	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Suggested Class (if any)		**Sub Class (if any)**	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)		**Suggested Figure for Publication (if any)**	

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S. C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Enter either Customer Number or complete the Representative Name section below. If both sections are completed the Customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	22466		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78(a)(2) or CFR 1.78(a)(4), and need not otherwise be made part of the specification.

Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61/220420	2009-06-25
Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61/225970	2009-07-16
Prior Application Status			Remove

PTO/SB/14 (07-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	103786-1 US/NS
	Application Number	
Title of Invention	Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer	

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61/310525	2010-03-04

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(a).

Remove

Application Number	Country [i]	Parent Filing Date (YYYY-MM-DD)	Priority Claimed
			(•) Yes ( ) No

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Assignee Information:

Providing this information in the application data sheet does not substitute for compliance with any requirement of part 3 of Title 37 of the CFR to have an assignment recorded in the Office.

Assignee 1 Remove

If the Assignee is an Organization check here. ☒			
Organization Name	AstraZeneca AB		
Mailing Address Information:			
Address 1	SE-151 85		
Address 2			
City	Sodertalje	**State/Province**	
Country [i] SE		Postal Code	
Phone Number		Fax Number	
Email Address			

Assignee 2 Remove

If the Assignee is an Organization check here. ☒			
Organization Name	Pozen Inc.		
Mailing Address Information:			
Address 1	1414 Raleigh Road		
Address 2			
City	Chapel Hill	**State/Province**	NC
Country [i] US		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee Data may be generated within this form by selecting the **Add** button. Add

PTO/SB/14 (07-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	103786-1 US/NS
	Application Number	
Title of Invention	Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer	

Signature:

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18. Please see 37 CFR 1.4(d) for the form of the signature.					
Signature	/Jacqueline Cohen/			Date (YYYY-MM-DD)	2010-06-24
First Name	Jacqueline	Last Name	Cohen	Registration Number	51574

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Ault *et al*.	Filed: Herewith
Application No.: Not yet assigned	Attorney Docket No.: 103786-1 US/NS
Examiner: Not yet assigned	
Title: Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer	

Mail Stop Amendment
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

PRELIMINARY AMENDMENT

This preliminary amendment is being filed simultaneously with the filing of the above-identified U.S. Utility application. Prior to calculation of the claim fees and examination of the application on its merits, please amend it as follows:

Amendments to the specification begin on page 2 of this paper.

Amendments to the claims begin on page 3 of this paper.

Remarks/Arguments begin on page 11 of this paper.

In the Specification

On page 1, after the title please insert the following paragraph:

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit under 35 U.S.C. § 119(e) to U.S. Application Nos. 61/220420 filed 25 June 2009, 61/225970 filed 16 July 2009, and 61/310525 filed 04 March 2010, each of which is incorporated herein by reference.

In the Claims

This listing of claims shall replace all prior versions and listings of claims in the application.

1. (original) A method comprising: treating a disease or disorder in a patient at risk of developing an NSAID-associated ulcer by administering to said patient in need thereof a pharmaceutical composition in unit dose form comprising a) esomeprazole, or pharmaceutically acceptable salt thereof, in an amount sufficient to raise the gastric pH of said patient to at least 3.5 upon administration of one or more of said unit dose forms, and b) a therapeutically effective amount of naproxen, or pharmaceutically acceptable salt thereof; wherein said unit dose form provides for coordinated release of the esomeprazole and the naproxen such that: (i) at least a portion of said esomeprazole, or pharmaceutically acceptable salt thereof, is released independent of the pH of the surrounding medium; and (ii) the naproxen, or pharmaceutically acceptable salt thereof, is not released from said unit dose form until the pH of the surrounding medium is 3.5 or higher; and wherein said pharmaceutical composition in unit dose form decreases the risk of said patient developing an ulcer.

2. (original) The method according to claim 1, wherein said patient is in need of chronic NSAID treatment.

3. (currently amended) The method according to claim 1~~claims 1 or 2~~, wherein said disease or disorder is selected from pain and inflammation.

4. (currently amended) The method according to claim 1~~claims 1 or 2~~, wherein said disease or disorder is selected from osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and a combination thereof.

5. (currently amended) The method according to claim 1~~any one of claims 1-4~~, wherein said patient is taking low dose aspirin.

6. (currently amended) The method according to claim 1~~any one of claims 1-5~~, wherein said pharmaceutical composition decreases the risk of said patient developing a gastroduodenal ulcer.

7. (currently amended) The method according to claim 1~~any one of claims 1-5~~, wherein said pharmaceutical composition decreases the risk of said patient developing a duodenal ulcer.

8. (currently amended) The method according to claim 1~~any of claims one of claims 1-5~~, wherein said pharmaceutical composition decreases the risk of said patient developing a gastric ulcer.

9. (currently amended) The method according to claim 1~~any one of claims 1-8~~, wherein said patient is treated longer with said pharmaceutical composition in unit dose form than with EC-naproxen, or pharmaceutically acceptable salt thereof.

10. (currently amended) The method according to claim 1~~any one of claims 1-8~~, wherein said pharmaceutical composition in unit dose form is administered to said patient twice a day for at least about 1 month.

11. (currently amended) The method according to claim 1~~any one of claims 1-8~~, wherein said pharmaceutical composition in unit dose form is administered to said patient twice a day for at least about 3 months.

12. (currently amended) The method according to claim 1~~any one of claims 1-8~~, wherein said pharmaceutical composition in unit dose form is administered to said patient twice a day for at least about 6 months.

13. (currently amended) The method according to claim 1~~any one of claim 1-12~~, wherein said pharmaceutical composition in unit dose form is a multilayer tablet comprising at least one core and at least a first layer and a second layer, wherein:

(a) said core comprises naproxen, or a pharmaceutically acceptable salt thereof;

(b) said first layer is a coating that at least begins to release the naproxen, or a pharmaceutically acceptable salt thereof, when the pH of the surrounding medium is about 3.5 or greater; and

(c) said second layer is esomeprazole, or a pharmaceutically acceptable salt thereof, wherein said esomeprazole, or a pharmaceutically acceptable salt thereof, is released at a pH of from about 0 or greater.

14. (original) The method according to claim 13, wherein said esomeprazole, or a pharmaceutically acceptable salt thereof, is released at a pH of from about 1 or greater.

15. (original) The method according to claim 13, wherein said esomeprazole, or a pharmaceutically acceptable salt thereof, is released at a pH of from about 0 to about 2.

16. (original) The method according to any one of claims 13-15, wherein at least a portion of said esomeprazole, or a pharmaceutically acceptable salt thereof, is not coated with an enteric coating.

17. (currently amended) The method according to claim 13~~any one of claims 13-16~~, wherein said first layer is an enteric coating.

18. (currently amended) The method according to claim 13~~any one of claims 13-17~~, wherein said multi-layer tablet is substantially free of sodium bicarbonate.

19. (currently amended) The method according to claim 13~~any one of claims 13-18~~, wherein said first layer begins to release the naproxen, or a pharmaceutically acceptable salt thereof, when the pH of the surrounding medium is at about 4.0 or greater.

20. (currently amended) The method according to claim 13~~any one of claims 13-18~~, wherein said first layer begins to release the naproxen, or a pharmaceutically acceptable salt thereof, when the pH of the surrounding medium is at about 4.5 or greater.

21. (currently amended) The method according to claim 13~~any one of claims 1-20~~, wherein the amount of esomeprazole, or a pharmaceutically acceptable salt thereof, sufficient to raise the gastric pH is 20 mg.

22. (currently amended) The method according to claim 1 or claim 13 ~~any one of claims 1-20~~, wherein the therapeutically effective amount of naproxen, or a pharmaceutically acceptable salt thereof, is selected from 375 mg and 500 mg.

23. (original) The method according to claim 22, wherein the therapeutically effective amount of naproxen, or a pharmaceutically acceptable salt thereof, is 375 mg.

24. (original) The method according to claim 22, wherein the therapeutically effective amount of naproxen, or a pharmaceutically acceptable salt thereof, is 500 mg.

25. (original) A method comprising: treating a disease or disorder in a patient at risk of developing an NSAID-associated ulcer by administering to the patient a pharmaceutical composition in unit dosage form suitable for oral administration comprising:

(a) esomeprazole or a pharmaceutically acceptable salt thereof, that is immediately soluble when the dosage form is placed in an aqueous medium, independent of pH, in an amount effective to raise the gastric pH of the patient to at least 3.5 upon administration of one or more of the unit dosage forms, and

(b) naproxen or pharmaceutically acceptable salt thereof, wherein the naproxen or a pharmaceutically acceptable salt thereof is surrounded by a coating that is substantially insoluble in an aqueous medium at a pH below 3.5 and at a temperature of about 37°C; and

wherein said pharmaceutical composition in unit dose form decreases the risk of said patient developing an ulcer.

26. (original) The method of claim 25, wherein the risk is associated with chronic NSAID treatment.

27. (original) The method of claim 25, wherein the risk is associated with age of the patient.

28. (original) The method of claim 25, wherein the risk is associated with chronic NSAID treatment and administration of low dose aspirin prior to or during NSAID treatment.

29. (currently amended) The method of claim 25~~any one of claims 25-28~~, wherein the method decreases the risk of the occurrence of a gastroduodenal ulcer.

30. (currently amended) The method of claim 25~~any one of claims 25-28~~, wherein the method decreases the risk of the occurrence of a duodenal ulcer.

31. (currently amended) The method of claim 25~~any one of claims 25-30~~, wherein the patient is treated for a disease or disorder selected from pain, inflammation, osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and combinations thereof.

32. (cancel)

33. (currently amended) The method of claim 25~~any one of claims 25-32~~, wherein the esomeprazole or a pharmaceutically acceptable salt thereof is present in an amount of from 10 mg to 50 mg.

34. (currently amended) The method of claim 25~~any one of claims 25-32~~, wherein the esomeprazole or a pharmaceutically acceptable salt thereof is present in an amount of 20 mg.

35. (currently amended) The method of claim 25~~any one of claims 25-34~~, wherein the amount of naproxen, or a pharmaceutically acceptable salt thereof, is from 200 mg to 600 mg.

36. (currently amended) The method of claim 25~~any one of claims 25-34~~, wherein the amount of naproxen, or a pharmaceutically acceptable salt thereof, is 375 mg.

37. (currently amended) The method of claim 25~~any one of claims 25-34~~, wherein the amount of naproxen, or a pharmaceutically acceptable salt thereof, is 500 mg.

38. (currently amended) The method of claim 25~~any one of claims 25-37~~, wherein the pharmaceutical composition is formulated to be administered to a patient twice daily.

39. (currently amended) The method according to claim 25~~any one of claims 25-38~~, wherein said pharmaceutical composition in unit dose form is administered to said patient twice a day for at least about 1 month.

40. (currently amended) The method according to claim 25~~any one of claims 25-38~~, wherein said pharmaceutical composition in unit dose form is administered to said patient twice a day for at least about 3 months.

41. (currently amended) The method according to claim 25~~any one of claims 25-38~~, wherein said pharmaceutical composition in unit dose form is administered to said patient twice a day for at least about 6 months.

42. (currently amended) The method according to claim 25~~of any one of claims 25-41~~, wherein the unit dosage form is a tablet.

43. (currently amended) The method according to claim 25~~of any one of claims 25-41~~, wherein the unit dosage form is a capsule containing beads or minitablets.

44. (currently amended) The method according to claim 25~~of claim 25-42~~, wherein the unit dosage form is a tablet comprising a core and two or more layers, in which

(a) the naproxen, or a pharmaceutically acceptable salt thereof, is in the core;

(b) a first layer surrounds the core and is a coating substantially insoluble in aqueous medium at a pH below 3.5 and at a temperature of about 37°C; and

(c) at least one second layer comprising the esomeprazole, or a pharmaceutically acceptable salt thereof, surrounds the coating of the first layer.

45. (currently amended) The method according to claim 25~~of any one of claims 25-42~~, wherein the unit dosage form is a multilayer tablet comprising a core and at least a first layer enclosing the core, and a second layer enclosing the first layer, wherein:

(a) the core comprises naproxen, or a pharmaceutically acceptable salt thereof;

(b) the first layer is a coating that releases less than 10% of the naproxen or a pharmaceutically acceptable salt thereof after 2 hours when tested using the USP Paddle Method in 1000 ml of 0.1N HCl at 75 rpm at 37°C. + - 0.5°C; and

(c) the second layer comprises esomeprazole, or a pharmaceutically acceptable salt thereof and at least one excipient, wherein the second layer is at least 95% soluble after 30 minutes when tested using the USP

Paddle Method in 1000 ml of 0.1N HCl for two hours at 75 rpm at 37°C. + - 0.5°C.

46. (currently amended) The method according to claim 44 ~~of any one of claims 25-44~~, wherein the unit dosage form further comprises a pharmacologically inert, water soluble coating or film surrounding the outermost layer of the unit dosage form.

47. (currently amended) The method of claim 46~~claim 47~~, wherein the inert coating or film comprises a water soluble sugar.

48. (currently amended) The method of claim 25~~any one of claims 25-47~~, wherein administration of the unit dosage form is more effective at reducing the risk of ulcer than treatment with enteric coated naproxen or a pharmaceutically acceptable salt thereof.

49. (original) A method comprising improving compliance in a patient who requires frequent daily dosages of naproxen or a pharmaceutically acceptable salt thereof by administering the unit dosage form of claim 1.

50. (original) A method comprising improving compliance in a patient who requires long-term daily dosages of naproxen or a pharmaceutically acceptable salt thereof by administering the unit dosage form of claim 1.

51. (original) A method comprising: treating a disease or disorder in a patient at risk of developing an NSAID-associated ulcer by administering to the patient a pharmaceutical composition in unit dosage form suitable for oral administration comprising:

(a) esomeprazole, or a pharmaceutically acceptable salt thereof, that is immediately soluble when the dosage form is placed in an aqueous medium, independent of pH, in an amount effective to raise the gastric pH of the patient to at least 3.5 upon administration of one or more of the unit dosage forms, and

(b) naproxen, or a pharmaceutically acceptable salt thereof, wherein the naproxen, or a pharmaceutically acceptable salt thereof, is surrounded by a coating substantially insoluble in an aqueous medium at a pH below 3.5 and at a temperature of about 37°C; and

wherein said pharmaceutical composition in unit dose form reduces said patient's heartburn associated symptoms.

52. (original) The method of claim 51, wherein administration of the unit dosage form reduces said patient's heartburn associated symptoms more than treating said patient with enteric coated naproxen, or a pharmaceutically acceptable salt thereof.

53. (currently amended) The method of claim 51~~claims 51 or 52~~, wherein said pharmaceutical composition in unit dose form is administered to said patient twice a day for at least about 1 month.

54. (currently amended) The method of claim 51~~claims 51 or 52~~, wherein said pharmaceutical composition in unit dose form is administered to said patient twice a day for at least about 3 months.

55. (currently amended) The method of claim 51~~claims 51 or 52~~, wherein said pharmaceutical composition in unit dose form is administered to said patient twice a day for at least about 6 months.

56. (original) A method comprising: treating a disease or disorder in a patient at risk of developing an NSAID-associated ulcer by administering to the patient a pharmaceutical composition in unit dosage form suitable for oral administration comprising:

(a) esomeprazole, or a pharmaceutically acceptable salt thereof, that is immediately soluble when the dosage form is placed in an aqueous medium, independent of pH, in an amount effective to raise the gastric pH of the patient to at least 3.5 upon administration of one or more of the unit dosage forms, and

(b) naproxen, or a pharmaceutically acceptable salt thereof, wherein the naproxen or a pharmaceutically acceptable salt thereof is surrounded by a coating substantially insoluble in an aqueous medium at a pH below 3.5 and at a temperature of about 37°C; and

wherein the pharmaceutical composition reduces said patient's dyspepsia associated symptoms.

57. (original) The method of claim 56, wherein administration of the unit dosage form to the patient reduces the patient's dyspepsia associated symptoms more than treating said patient with enteric coated naproxen, or a pharmaceutically acceptable salt thereof.

58. (currently amended) The method of claim~~s 55 or~~ 56, wherein said pharmaceutical composition in unit dose form is administered to said patient twice a day for at least about 1 month.

59. (currently amended) The method of claims ~~55 or~~ 56, wherein said pharmaceutical composition in unit dose form is administered to said patient twice a day for at least about 3 months.

60. (currently amended) The method of claims ~~55 or~~ 56, wherein said pharmaceutical composition in unit dose form is administered to said patient twice a day for at least about 6 months.

61. (original) The method according to claim 1, wherein said ulcer is a gastric ulcer, said patient is ≥ 60 years of age, and administration of said unit dose form to said patient results in an 70 to 100% relative risk reduction of said patient developing a gastric ulcer than a patient ≥ 60 years of age who is treated with enteric coated naproxen, or a pharmaceutically acceptable salt thereof.

62. (original) The method according to claim 25, wherein said ulcer is a gastric ulcer, said patient is ≥ 60 years of age, and administration of said unit dosage form to said patient results in an 70 to 100% relative risk reduction of said patient developing a gastric ulcer than a patient ≥ 60 years of age who is treated with enteric coated naproxen, or a pharmaceutically acceptable salt thereof.

63. (original) The method according to claims 61 or 62, wherein the administration of said unit dose form to said patient results in an 89.2% relative risk reduction of said patient developing a gastric ulcer than a patient ≥ 60 years of age who is treated with enteric coated naproxen, or a pharmaceutically acceptable salt thereof.

Remarks/Arguments

Applicants have amended the specification to provide the priority claim. The claims have been amended to remove multiple dependencies and to otherwise place the claims in an appropriate U.S. format. No new matter has been added by these amendments.

The above amendments have been made without prejudice to Applicants right to prosecute any cancelled subject matter in a timely filed continuation application.

Applicants believe the application is in condition for allowance, which action is respectfully requested.

Although Applicants believe no fees are due, the Commissioner is hereby authorized to charge any deficiency in the fees or credit any overpayment to deposit account No. 26-0166, referencing Attorney Docket No. 103786-1 US/NS.

Respectfully submitted,

/Jacqueline M. Cohen/

Name: Jacqueline M. Cohen
Dated: June 24, 2010
Reg. No.: 51,574
Phone No.: 302-885-4269
Intellectual Property, Patents,
AstraZeneca
1800 Concord Pike
Wilmington, DE 19850-5437

Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer

The present disclosure is directed to a method for treating a disease or disorder in a patient at risk of developing an NSAID-associated ulcer by administering to said patient in need thereof a pharmaceutical composition in unit dose form comprising naproxen, or pharmaceutically acceptable salt thereof, and esomeprazole, or pharmaceutically acceptable salt thereof to said at risk patient and thereby decreasing the patient's risk of developing an ulcer.

Over 15 million Americans take NSAIDs each day to treat pain and/or inflammation. While NSAIDs remain a key therapy for pain and inflammation, there is a substantial risk of upper gastrointestinal (UGI) ulcerations and ulcer complications, such as, for example, bleedings and perforations, with chronic NSAID therapy. The cumulative incidence of gastroduodenal ulcers (GDUs) with conventional NSAID use has been reported to be as high as 25-30% at 3 months and 45% at 6 months versus 3-7% for placebo. At any given time, the incidence of UGI ulcers in NSAID users has been estimated to be as high as 30%. The risk factors associated with an NSAID user developing UGI ulcers include: age $\geq$ 50 years, history of UGI ulcer or bleeding, or concomitant aspirin use. The mechanism associated with the increased incidence of ulcers in chronic NSAID users may be complex but it is thought that gastric acid, combined with a reduction in protective mechanisms of the UGI mucosa, contribute to this pathology. UGI mucosal injury includes petechia, erosions and ulcers. In addition, once mucosal injury occurs, acid has the ability to impair normal hemostasis and healing. These factors, coupled with the known anti-platelet effect of some NSAIDs, may increase the risk for gastrointestinal (GI) injury and bleeding. UGI effects of NSAIDs also include: dyspepsia (experienced by up to 40% of patients on NSAID therapy), erosive esophagitis (EE) (experienced by 21% of regular NSAID users), and an increase in gastroesophageal reflux disease symptoms. Additionally, the concurrent use of aspirin and an NSAID increases the risk of serious GI events.

A pharmaceutical formulation comprising immediate release (IR) esomeprazole magnesium and enteric-coated (EC) naproxen has been found to reduce the incidence of ulcers in patients at risk for developing NSAID-associated ulcers when compared to EC-naproxen. Such a formulation has also been found to reduce the incidence of ulcers in patients taking low dose aspirin (LDA) who are at risk for developing NSAID-associated ulcers when compared to EC-naproxen. Furthermore, patients taking this new formulation of IR esomeprazole and EC-naproxen were able to continue treatment longer than patients taking EC-naproxen.

In one aspect, the disclosure is directed to a method comprising: treating a disease or disorder in a patient at risk of developing an NSAID-associated ulcer by administering to said patient in need thereof a pharmaceutical composition in unit dose form comprising (a) esomeprazole, or pharmaceutically acceptable salt thereof, in an amount sufficient to raise the gastric pH of said patient to at least 3.5 upon administration of one or more of said unit dose forms, and (b) a therapeutically effective amount of naproxen, or pharmaceutically acceptable salt thereof; wherein said unit dose form provides for coordinated release of the esomeprazole and the naproxen such that: (i) at least a portion of said esomeprazole, or pharmaceutically acceptable salt thereof, is released independent of the pH of the surrounding medium; and (ii) the naproxen, or pharmaceutically acceptable salt thereof, is not released from said unit dose form until the pH of the surrounding medium is 3.5 or higher; and wherein said pharmaceutical composition in unit dose form decreases the risk of said patient developing an ulcer.

In another aspect, the disclosure is directed to a method of treating a disease or disorder in a patient at risk of developing an NSAID-associated ulcer by administering to the patient a pharmaceutical composition in unit dosage form suitable for oral administration comprising: (a) esomeprazole or pharmaceutically acceptable salt thereof, that is immediately soluble when the dosage form is placed in an aqueous medium, independent of pH, in an amount effective to raise the gastric pH of the patient to at least 3.5 upon administration of one or more of the unit dosage forms, and (b) naproxen or pharmaceutically acceptable salt thereof, wherein the naproxen or pharmaceutically acceptable salt thereof is surrounded by a coating that is substantially insoluble in an aqueous medium at a pH below 3.5 and at a temperature of about 37°C; and wherein said pharmaceutical composition in unit dose form decreases the risk of said patient developing an ulcer.

In yet another aspect, the risk of NSAID-associated gastrointestinal ulcer in a patient may be associated with chronic NSAID treatment, age of the patient (for example if the patient is 50 years of age or older), the administration of aspirin prior to or during NSAID treatment (short-term or chronic treatment), or any combination thereof.

In still another aspect, the pharmaceutical composition in unit dose form disclosed herein decreases the risk of said patient developing a gastric ulcer, duodenal ulcer (DU), gastroduodenal ulcer, or combinations thereof.

In yet another aspect, the disease or disorder may be, for example, pain, inflammation, osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, or any combination thereof.

In another aspect, the pharmaceutical composition in unit dose form disclosed herein is administered to said patient every day, for example twice a day. In further aspects, the pharmaceutical composition in unit dose form disclosed herein is administered to said patient for at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about 18 months, or at least about 24 months, for example twice a day.

In a further aspect, the pharmaceutical compositions in unit dosage form disclosed herein may comprise esomeprazole or pharmaceutically acceptable salt thereof in an amount effective to raise the pH of the gastric fluid of a patient to at least 3.5, at least 4.0, at least 4.5, at least 5.0, or at least 5.5 when the dosage form is administered orally to said patient. The esomeprazole or pharmaceutically acceptable salt thereof may be present in the unit dosage form in an amount of from about 10 mg to about 50 mg, or in an amount of about 20 mg. In other embodiments, the pharmaceutical compositions in unit dosage form disclosed herein may comprise naproxen, or pharmaceutically acceptable salt thereof, in an amount of, for example, from about 200 mg to about 600 mg, about 375 mg, or about 500 mg.

In a still further aspect, the pharmaceutical composition is formulated for administration to a patient once daily or twice daily. In certain embodiments, the unit dosage form may be a tablet, a sequential-delivery tablet formulation, a capsule, a capsule containing beads, or minitablets. In one aspect, the unit dosage form is a tablet comprising a core and two or more layers, in which (i) the naproxen or pharmaceutically acceptable salt thereof is in the core; (ii) a first layer surrounds the core and said layer is a coating that is substantially insoluble in aqueous medium at a pH below 3.5 and/or at a temperature of about 37°C; and (iii) at least one second layer that surround the first layer and comprises esomeprazole or pharmaceutically acceptable salt thereof. In some embodiments, the first layer may be, for example, an enteric coating or a time-release coating. In other embodiments, the unit dosage form may be surrounded by a pharmacologically inert, water soluble coating or film.

In yet still a further aspect, administering a unit dosage form disclosed herein to a patient in need thereof reduces the risk said patient will develop an ulcer more than if said patient were

administered an enteric coated naproxen, or pharmaceutically acceptable salt thereof. In another embodiment, the administration of the unit dosage form disclosed herein improves compliance in a patient who requires short-term or chronic daily dosages of an NSAID, such as, for example, naproxen or pharmaceutically acceptable salt thereof.

In another aspect, the unit dosage form is a multilayer tablet comprising a core and at least a first layer enclosing the core, and a second layer enclosing the first layer, wherein: (i) the core comprises naproxen, or pharmaceutically acceptable salt thereof; (ii) the first layer is a coating that releases less than 10% of the naproxen after 2 hours when tested using the USP Paddle Method in 1000 ml of 0.1N HCl at 75 rpm at 37°C. + -0.5°C; and (iii) the second layer comprises esomeprazole, or pharmaceutically acceptable salt thereof and at least one excipient, wherein the second layer is at least 95% soluble after 30 minutes when tested using the USP Paddle Method in 1000 ml of 0.1N HCl for two hours at 75 rpm at 37°C. + -0.5°C. The unit dosage form may further have a pharmacologically inert, water soluble coating or film surrounding the outermost layer of the unit dosage form, for example wherein the inert coating or film comprises a water soluble sugar.

In a further aspect, administering a unit dosage form disclosed herein to a patient in need thereof reduces said patient's heartburn associated symptoms more than treating said patient in need thereof with enteric coated naproxen, or pharmaceutically acceptable salt thereof.

Yet a further aspect is directed to a method of treating a disease or disorder in a patient at risk of developing an NSAID-associated ulcer by administering to the patient a pharmaceutical composition in unit dosage form suitable for oral administration comprising: (a) esomeprazole or pharmaceutically acceptable salt thereof, that is immediately soluble when the dosage form is placed in an aqueous medium, independent of pH, in an amount effective to raise the gastric pH of the patient to at least 3.5, at least 4.0, at least 4.5, at least 5.0, or at least 5.5 upon administration of one or more of the unit dosage forms, and (b) naproxen or pharmaceutically acceptable salt thereof, wherein the naproxen or pharmaceutically acceptable salt thereof is surrounded by a coating that is substantially insoluble in an aqueous medium at a pH below 3.5 and at a temperature of about 37°C; wherein the pharmaceutical composition reduces said patient's dyspepsia associated symptoms. In certain embodiments, administering a unit dosage form disclosed herein to a patient in need thereof reduces said patient's dyspepsia associated

symptoms more than treating said patient with enteric coated naproxen, or pharmaceutically acceptable salt thereof.

Abbreviations and/or special terms that may be used herein are set forth in Table 1 and the text that follows.

The definitions set forth herein take precedence over definitions set forth in any patent, patent application, and/or patent application publication incorporated herein by reference.

Table 1: Abbreviations and Special Terms

Abbreviation	**Explanation**
AE	*adverse event*
ALT	*alanine aminotransferase*
ANCOVA	*analysis of covariance*
AST	*aspartate aminotransferase*
bid	*twice daily*
BUN	*Blood urea nitrogen*
CI	*confidence interval*
CMH	*Cochran-Mantel-Haenszel*
COX-2	*cyclo-oxygenase-2*
ECG	*electrocardiogram*
eCRF	*electronic case report form*
GCP	*Good Clinical Practice*
GERD	*Gastroesophageal reflux disease*
GI	*gastrointestinal*
IRB	*institutional review board*
ITT	*intent-to-treat*
LSM	*least squares mean*
MedDRA	*Medical Dictionary for Regulatory Activities*
OTE-DP	*Overall Treatment Evaluation – Dyspepsia*
PDS	*Phoenix Data Systems*
PP	*per-protocol*
PRO	*patient reported outcomes*
AE	*adverse event*
ALT	*alanine aminotransferase*
SAE	*serious adverse event*
SD	*standard deviation*
SOC	*system organ class*
SODA	*Severity of Dyspepsia Assessment*
UGI	*upper gastrointestinal*

The term "at risk patient" refers to patient(s) at risk for NSAID associated ulcer due to age ≥ 50 years, history of UGI ulcer or bleeding, and/or concomitant aspirin use. In one

embodiment, the at risk patient is a patient at risk for NSAID associated ulcer due to age greater than or equal to 50 years. In another embodiment, the at risk patient is a patient at risk for NSAID associated ulcer due to concomitant aspirin use. In yet another embodiment, the at risk patient is a patient at risk for NSAID associated ulcer due to history of UGI ulcer or bleeding.

The term "enantiomerically pure" refers to a compound containing at least about 75% of the named enantiomer out of the total amount of the two possible enantiomers contained therein. In a particular embodiment, "enantiomerically pure" refers to a compound containing at least about 90% of the named enantiomer out of the total amount of the two possible enantiomers contained therein. In a more particular embodiment, "enantiomerically pure" refers to a compound containing at least about 95% of the named enantiomer out the total amount of the two possible enantiomers contained therein. In still a more particular embodiment, "enantiomerically pure" refers to a compound containing at least about 96% of the named enantiomer out the total amount of the two possible enantiomers contained therein. In still a further embodiment, "enantiomerically pure" refers to a compound containing at least about 97% of the named enantiomer out the total amount of the two possible enantiomers contained therein. In yet still a further embodiment, "enantiomerically pure" refers to a compound containing at least about 98% of the named enantiomer out the total amount of the two possible enantiomers contained therein. In yet a still even further embodiment, "enantiomerically pure" refers to a compound containing at least about 99% of the named enantiomer out the total amount of the two possible enantiomers contained therein. In another embodiment, "enantiomerically pure" refers to a compound containing at least about 99.9% of the named enantiomer out the total amount of the two possible enantiomers contained therein.

The term "low dose aspirin" refers to dosages of aspirin that are $\leq$ 325 mg.

The term "pharmaceutically acceptable", as employed herein, indicates the subject matter being identified as "pharmaceutically acceptable" is suitable and physiologically acceptable for administration to a patient/subject. For example, the term "pharmaceutically acceptable salt(s)" denotes suitable and physiologically acceptable salt(s).

The phrase "naproxen, or pharmaceutically acceptable salt thereof refers to the free base of naproxen, pharmaceutically acceptable salt(s) of naproxen, and/or mixtures of the free base of naproxen and at least one pharmaceutically acceptable salt of naproxen.

The phrase "esomeprazole, or pharmaceutically acceptable salt thereof refers to the free base of esomeprazole, pharmaceutically acceptable salt(s) of esomeprazole, and/or mixtures of the free base of esomeprazole and at least one pharmaceutically acceptable salt of esomeprazole.

The term "unit dosage form" (or "unit dose form") as used herein refers to a single entity for drug administration. For example, a single tablet or capsule containing both esomeprazole and naproxen is a unit dosage form. Unit dosage forms of the present disclosure provide for sequential drug release in a way that elevates gastric pH and reduces the deleterious effects of naproxen on the gastroduodenal mucosa, *e.g.*, the esomeprazole is released first and the release of naproxen is delayed until after the pH in the GI tract has risen to 3.5 or greater. A "unit dosage form" (or "unit dose form") may also be referred to as a "fixed dosage form" (or "fixed dose form") or fixed dosage combination (or "fixed dose combination") and are otherwise interchangeable.

With regard to the dosages of each of naproxen, or pharmaceutically acceptable salt thereof and/or esomeprazole, or pharmaceutically acceptable salt thereof the term "about" is intended to reflect variations from the specifically identified dosages that are acceptable within the art.

With regard to the pH values and/or ranges recited herein, the term "about" is intended to capture variations above and below the stated number that may achieve substantially the same results as the stated number.

With regard to the term numerical values used in conjunction with the phrase "substantially free", the term is intended to capture variations above and below the stated number that may achieve substantially the same results as the stated number.

The phrase "substantially free" means from about 95% to about 99.99% free. In one embodiment, substantially free means about 95% free. In another embodiment, the term substantially free means about 96% free. In still another embodiment, the term substantially free means about 97% free. In yet another embodiment, the term substantially free means about 98% free. In a further embodiment, the term substantially free means about 99% free. In still a further embodiment, the term substantially free means about 99.99% free.

In the present disclosure, each of the variously stated ranges is intended to be continuous so as to include each numerical parameter between the stated minimum and maximum value of

each range. For Example, a range of about 1 to about 4 includes about 1, 1, about 2, 2, about 3, 3, about 4, and 4.

One embodiment is directed to a method comprising: treating a disease or disorder in a patient at risk of developing an NSAID-associated ulcer by administering to said patient in need thereof a pharmaceutical composition in unit dose form comprising (a) esomeprazole, or pharmaceutically acceptable salt thereof, in an amount sufficient to raise the gastric pH of said patient to at least 3.5 upon administration of one or more of said unit dose forms, and (b) a therapeutically effective amount of naproxen, or pharmaceutically acceptable salt thereof; wherein said unit dose form provides for coordinated release of the esomeprazole and the naproxen such that: (i) at least a portion of said esomeprazole, or pharmaceutically acceptable salt thereof, is released independent of the pH of the surrounding medium; and (ii) the naproxen, or pharmaceutically acceptable salt thereof, is not released from said unit dose form until the pH of the surrounding medium is 3.5 or higher; and wherein said pharmaceutical composition in unit dose form decreases the risk of said patient developing an ulcer. Such pharmaceutical compositions have been described in U.S. Patent No. 6,926,907, which is incorporated herein by reference in its entirety.

Another embodiment is directed to a method comprising: treating a disease or disorder in a patient in need of chronic NSAID treatment and at risk of developing an NSAID-associated ulcer by administering to said patient in need thereof a pharmaceutical composition in unit dose form comprising (a) esomeprazole, or pharmaceutically acceptable salt thereof, in an amount sufficient to raise the gastric pH of said patient to at least 3.5 upon administration of one or more of said unit dose forms, and (b) a therapeutically effective amount of naproxen, or pharmaceutically acceptable salt thereof; wherein said unit dose form provides for coordinated release of the esomeprazole and the naproxen such that: (i) at least a portion of said esomeprazole, or pharmaceutically acceptable salt thereof, is released independent of the pH of the surrounding medium; and (ii) the naproxen, or pharmaceutically acceptable salt thereof, is not released from said unit dose form until the pH of the surrounding medium is 3.5 or higher; and wherein said pharmaceutical composition in unit dose form decreases the risk of said patient developing an ulcer.

Still another embodiment, is directed to a method comprising: treating signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis in a patient at risk of

developing an NSAID-associated ulcer by administering to said patient in need thereof a pharmaceutical composition in unit dose form comprising (a) esomeprazole, or pharmaceutically acceptable salt thereof, in an amount sufficient to raise the gastric pH of said patient to at least 3.5 upon administration of one or more of said unit dose forms, and (b) a therapeutically effective amount of naproxen, or pharmaceutically acceptable salt thereof; wherein said unit dose form provides for coordinated release of the esomeprazole and the naproxen such that: (i) at least a portion of said esomeprazole, or pharmaceutically acceptable salt thereof, is released independent of the pH of the surrounding medium; and (ii) the naproxen, or pharmaceutically acceptable salt thereof, is not released from said unit dose form until the pH of the surrounding medium is 3.5 or higher; and wherein said pharmaceutical composition in unit dose form decreases the risk of said patient developing an ulcer.

Still yet another embodiment is directed to a method comprising: treating signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis in a patient in need of chronic NSAID treatment and at risk of developing an NSAID-associated ulcer by administering to said patient in need thereof a pharmaceutical composition in unit dose form comprising (a) esomeprazole, or pharmaceutically acceptable salt thereof, in an amount sufficient to raise the gastric pH of said patient to at least 3.5 upon administration of one or more of said unit dose forms, and (b) a therapeutically effective amount of naproxen, or pharmaceutically acceptable salt thereof; wherein said unit dose form provides for coordinated release of the esomeprazole and the naproxen such that: (i) at least a portion of said esomeprazole, or pharmaceutically acceptable salt thereof, is released independent of the pH of the surrounding medium; and (ii) the naproxen, or pharmaceutically acceptable salt thereof, is not released from said unit dose form until the pH of the surrounding medium is 3.5 or higher; and wherein said pharmaceutical composition in unit dose form decreases the risk of said patient developing an ulcer.

In a further embodiment, said disease or disorder treated by the pharmaceutical compositions disclosed herein is selected from pain and inflammation.

In yet another embodiment, said disease or disorder treated by the pharmaceutical compositions disclosed herein is selected from osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and a combination thereof.

In yet a further embodiment, said patient at risk of developing an NSAID associated ulcer is $\geq$ 50 years old.

In still yet another embodiment, said patient at risk of developing an NSAID associated ulcer has a history of UGI ulcer or bleeding.

In still even yet another embodiment, said patient is taking low dose aspirin.

In a still even further embodiment, said pharmaceutical composition in unit dose form decreases the risk of said patient developing a gastroduodenal ulcer.

In yet a further embodiment, said pharmaceutical composition in unit dose form decreases the risk of said patient developing a duodenal ulcer.

In a further embodiment, said pharmaceutical composition in unit dose form decreases the risk of said patient developing a gastric ulcer.

In yet another embodiment, administering said pharmaceutical composition in unit dose form to patients in need of NSAID treatment resulted in fewer patients developing a gastric ulcer than patients in need of NSAID treatment who were administered EC-naproxen.

In another embodiment, administering said pharmaceutical composition in unit dose form to patients in need of NSAID treatment resulted in from about 1% to about 12% of said patients developing a gastric ulcer.

In still another embodiment, administering EC-naproxen to patients in need of NSAID treatment resulted in from about 17% to about 31% of said patients developing a gastric ulcer.

In yet another embodiment, administering said pharmaceutical composition in unit dose form to patients in need of NSAID treatment resulted in fewer patients developing a duodenal ulcer than patients in need of NSAID treatment who were administered EC-naproxen.

In another embodiment, administering said pharmaceutical composition in unit dose form to patients in need of NSAID treatment resulted in from about 0% to about 2% of said patients developing a duodenal ulcer.

In still another embodiment, administering EC-naproxen to patients in need of NSAID treatment resulted in from about 3.5% to about 8% of said patients developing a duodenal ulcer.

In yet another embodiment, administering said pharmaceutical composition in unit dose form and low dose aspirin to patients in need of NSAID treatment resulted in fewer patients developing a gastric ulcer than patients administered EC-naproxen and low dose aspirin.

In another embodiment, administering said pharmaceutical composition in unit dose form and low dose aspirin to patients in need of NSAID treatment resulted in from about 0% to about 9% of said patients developing a gastric ulcer.

In still another embodiment, administering EC-naproxen and low dose aspirin to patients in need of NSAID treatment resulted in from about 20% to about 38% of said patients developing a gastric ulcer.

In yet another embodiment, administering said pharmaceutical composition in unit dose form and low dose aspirin to patients in need of NSAID treatment resulted in fewer patients developing a gastroduodenal ulcer than patients administered EC-naproxen and low dose aspirin.

In another embodiment, administering said pharmaceutical composition in unit dose form and low dose aspirin to patients in need of NSAID treatment resulted in from about 1.0% to about 10% of said patients developing a gastroduodenal ulcer.

In still another embodiment, administering EC-naproxen and low dose aspirin to patients in need of NSAID treatment resulted in from about 23% to about 42% of said patients developing a gastroduodenal ulcer.

In a yet still further embodiment, said patient was treated longer with said pharmaceutical composition in unit dose form than with EC-naproxen.

In yet another embodiment, patient compliance with long-term treatment is improved with the pharmaceutical compositions disclosed herein as compared to EC-naproxen.

In a yet even further embodiment, said pharmaceutical composition in unit dose form is a multilayer tablet comprising at least one core and at least a first layer and a second layer, wherein:

(i) said core comprises naproxen, or pharmaceutically acceptable salt thereof;

(ii) said first layer is a coating that at least begins to release the naproxen, or pharmaceutically acceptable salt thereof, when the pH of the surrounding medium is about 3.5 or greater; and

(iii) said second layer is esomeprazole, or pharmaceutically acceptable salt thereof, wherein said esomeprazole, or pharmaceutically acceptable salt thereof, is released at a pH of from about 0 or greater.

In a further embodiment, said esomeprazole, or pharmaceutically acceptable salt thereof, is released from said multilayer tablet at a pH of from about 1 or greater.

In a yet further embodiment, said esomeprazole, or pharmaceutically acceptable salt thereof, is released from said multilayer tablet at a pH of from about 0 to about 2.

In yet still a further embodiment, esomeprazole, or pharmaceutically acceptable salt thereof, is released at a pH of from 0 to 2.

In a still further embodiment, at least a portion of said esomeprazole, or pharmaceutically acceptable salt thereof, contained in said multilayer tablet is not coated with an enteric coating.

In a yet still further embodiment, said first layer of said multilayer tablet is an enteric coating.

In a yet even still further embodiment, said multi-layer tablet is substantially free of sodium bicarbonate.

In another embodiment, the first layer is a coating that at least begins to release the naproxen, or pharmaceutically acceptable salt thereof, when the pH of the surrounding medium is about 4.0, 4.5, 5.0 or greater.

In a further embodiment, said first layer of said multi-layer tablet begins to release the naproxen, or pharmaceutically acceptable salt thereof, when the pH of the surrounding medium is at about 4.0 or greater.

In a yet still even further embodiment, said first layer of said multi-layer tablet begins to release the naproxen, or pharmaceutically acceptable salt thereof, when the pH of the surrounding medium is at about 4.5 or greater.

In yet a further embodiment, said first layer of said multi-layer tablet begins to release the naproxen, or pharmaceutically acceptable salt thereof, when the pH of the surrounding medium is at about 5.0 or greater.

In a still even further embodiment, the amount of esomeprazole, or pharmaceutically acceptable salt thereof, sufficient to raise the gastric pH is 20 mg.

In another embodiment, the esomeprazole is enantiomerically pure.

In still yet another embodiment, the therapeutically effective amount of naproxen, or pharmaceutically acceptable salt thereof, is selected from 375 mg and 500 mg.

In a still yet further embodiment, the therapeutically effective amount of naproxen, or pharmaceutically acceptable salt thereof, is 375 mg.

In an even still further embodiment, the therapeutically effective amount of naproxen, or pharmaceutically acceptable salt thereof, is 500 mg.

In another embodiment, naproxen can be present as the free base.

In yet another embodiment, naproxen can be present in equivalent amounts of pharmaceutically acceptable salts of naproxen, *e.g.*, sodium naproxen.

In a further embodiment, esomeprazole can be present as a magnesium salt.

In a further embodiment, esomeprazole, or pharmaceutically acceptable salt thereof, can be present in an amount to provide about 15 mg of esomeprazole.

In still yet another embodiment, esomeprazole, or pharmaceutically acceptable salt thereof, can be present in an amount to provide about 30 mg of esomeprazole.

In one embodiment, the pharmaceutical composition in unit dose form comprises about 500 mg of said naproxen, or pharmaceutically acceptable salt thereof, and about 20mg of said esomeprazole, or pharmaceutically acceptable salt thereof.

In another embodiment, the pharmaceutical composition in unit dose form comprises about 500 mg of said naproxen, or pharmaceutically acceptable salt thereof, and about 30mg of said esomeprazole, or pharmaceutically acceptable salt thereof.

In yet another embodiment, the pharmaceutical composition in unit dose form comprises about 500 mg of said naproxen, or pharmaceutically acceptable salt thereof, and about 15mg of said esomeprazole, or pharmaceutically acceptable salt thereof.

In still another embodiment, the pharmaceutical composition in unit dose form comprises about 375 mg of said naproxen, or pharmaceutically acceptable salt thereof, and about 15mg of said esomeprazole, or pharmaceutically acceptable salt thereof.

In still yet another embodiment, the pharmaceutical composition in unit dose form comprises about 375 mg of said naproxen, or pharmaceutically acceptable salt thereof, and about 20 mg of said esomeprazole, or pharmaceutically acceptable salt thereof.

In a further embodiment, the pharmaceutical composition in unit dose form comprises about 375 mg of said naproxen, or pharmaceutically acceptable salt thereof, and about 30 mg of said esomeprazole, or pharmaceutically acceptable salt thereof.

In certain embodiments, the unit dosage form of the pharmaceutical compositions disclosed herein may comprise esomeprazole, or pharmaceutically acceptable salt thereof, naproxen, or pharmaceutically acceptable salt thereof, carnauba wax, colloidal silicon dioxide, croscarmellose sodium, iron oxide yellow, glyceryl monostearate, hypromellose, iron oxide black, magnesium stearate, methacrylic acid copolymer dispersion, methylparaben, polysorbate

80, polydextrose, polyethylene glycol, povidone, propylene glycol, propylparaben, titanium dioxide, and triethyl citrate.

In an even further embodiment, the pharmaceutical composition in unit dose form is a multilayer tablet comprising a core comprising naproxen, or pharmaceutically acceptable salt thereof, and a first layer comprising a coating that at least begins releasing the naproxen when the pH of the surrounding medium is about 3.5 or greater and a second layer comprising esomeprazole, or pharmaceutically acceptable salt thereof, wherein at least a portion of said esomeprazole, or pharmaceutically acceptable salt thereof, is not surrounded by an enteric coating.

In one embodiment, at least about 95% of the esomeprazole, or pharmaceutically acceptable salt thereof, is not surrounded by an enteric coating.

In another embodiment, at least about 99% of the esomeprazole, or pharmaceutically acceptable salt thereof, is not surrounded by an enteric coating. In yet another embodiment, at least about 99.5% of the esomeprazole, or pharmaceutically acceptable salt thereof, is not surrounded by an enteric coating.

In yet another embodiment, the multilayer tablet is substantially free of sodium bicarbonate.

In still another embodiment, the multilayer tablet is completely (*i.e.*, 100%) free of sodium bicarbonate.

In one embodiment, the dosing regimen of the pharmaceutical compositions disclosed herein is twice a day.

In another embodiment, the doses can be separated by a period of at least about 10 hours.

In another embodiment, the pharmaceutical composition in unit dose form is given before a patient ingests a meal, for example about 30-60 minutes prior to ingesting a meal.

In another embodiment, the pharmaceutical compositions of the present disclosure may be administered therapeutically to patients either short term or over a longer period of time, for example chronically.

In yet another embodiment, fewer patients in need of NSAID treatment discontinued treatment with said pharmaceutical composition in unit dose form than discontinued EC-naproxen.

In still another embodiment, at least one upper gastrointestinal adverse event led from about 1% to about 9% of said patients in need of NSAID treatment to discontinue treatment with said pharmaceutical composition in unit dose form.

In yet still another embodiment, at least one upper gastrointestinal adverse event led from about 8% to about 17% of said patients in need of NSAID treatment to discontinue treatment with EC-naproxen.

In a still further embodiment, at least one upper gastrointestinal adverse event led from about 1% to about 9% of said patients in need of NSAID treatment to discontinue treatment with said pharmaceutical composition in unit dose form versus from about 8% to about 17% of said patients in need of NSAID treatment to discontinue treatment with EC-naproxen.

In yet another embodiment, a patient is ≥ 60 years of age and administration of the unit dose form to the patient results in an 70 to 100% relative risk reduction of the patient developing a gastric ulcer than a patient ≥ 60 years of age who is treated with enteric coated naproxen, or pharmaceutically acceptable salt thereof.

In still yet another embodiment, a patient is ≥ 60 years of age and administration of the unit dose form to the patient results in an 89.2% relative risk reduction of the patient developing a gastric ulcer than a patient ≥ 60 years of age who is treated with enteric coated naproxen, or pharmaceutically acceptable salt thereof.

In a further embodiment, a patient is 60-69 years of age and administration of the unit dose form to the patient results in an 86.4% relative risk reduction of the patient developing a gastric ulcer than a patient 60-69 years of age who is treated with enteric coated naproxen, or pharmaceutically acceptable salt thereof.

In an even further embodiment, a patient is ≥ 70 years of age and administration of the unit dose form to the patient results in a 100% relative risk reduction of the patient developing a gastric ulcer than a patient ≥ 70 years of age who is treated with enteric coated naproxen, or pharmaceutically acceptable salt thereof.

The pharmaceutical compositions disclosed herein include, but are not limited to, for example, tablets and capsules that can be made in accordance with methods that are standard in the art (see, *e.g.*, Remington's Pharmaceutical Sciences, 16th ed., A Oslo editor, Easton, Pa. (1980)).

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; carnauba wax; colloidal silicon dioxide; croscarmellose sodium; glyceryl monostearate; hypromellose; methacrylic acid copolymer dispersion; methylparaben; polysorbate 80; polydextrose; povidone; propylene glycol; propylparaben; titanium dioxide; and triethyl citrate.

The pharmaceutical compositions disclosed herein can be sterilized and, if desired, mixed with, for example, auxiliary agents, such as, for example, preservatives; stabilizers; buffers; coloring agents; and flavoring agents.

In one embodiment, at least one of the layers comprising the pharmaceutical compositions disclosed herein may be applied using standard coating techniques. The layer materials may be dissolved or dispersed in organic or aqueous solvents. The layer materials may include, but are not limited to, for example, one or more of the following materials: methacrylic acid copolymers, shellac, hydroxypropylmethcellulose phthalate, polyvinyl acetate phthalate, hydroxypropylmethyl-cellulose trimellitate, carboxymethylethyl-cellulose, cellulose acetate phthalate, and/or other suitable polymer(s). The pH at which the first layer dissolves can be controlled by the polymer or combination of polymers selected and/or ratio of pendant groups. For example, dissolution characteristics of the polymer film can be altered by the ratio of free carboxyl groups to ester groups. The layers may also contain pharmaceutically acceptable plasticizers, such as, for example, triethyl citrate, dibutyl phthalate, triacetin, polyethylene glycols, polysorbates or other plasticizers. Additives, such as, for example, dispersants, colorants, anti-adhering, and anti-foaming agents may also be used.

In one embodiment, the pharmaceutical compositions disclosed herein can be in the form of a bi- or multi-layer tablet. In a bi-layer tablet, one portion/layer of the tablet contains the esomeprazole, or pharmaceutically acceptable salt thereof, in the required dose along with appropriate excipients, agents to aid dissolution, lubricants, fillers, etc.; and a second portion/layer of the tablet contains the NSAID in the required dose along with other excipients, dissolution agents, lubricants, fillers, etc.

In another embodiment, the naproxen portion/layer is surrounded by a polymeric coating that dissolves at a pH of at least about 3.5 or greater.

In yet another embodiment, the naproxen portion/layer is surrounded by a polymeric coating that dissolves at a pH of at least about 4 or greater.

The naproxen, or pharmaceutically acceptable salt thereof, may be granulated by methods such as slugging, low- or high- shear granulation, wet granulation, or fluidized-bed granulation. Of these processes, slugging generally produces tablets of less hardness and greater friability. Low-shear granulation, high-shear granulation, wet granulation and fluidized-bed granulation generally produce harder, less friable tablets.

Example(s)

The invention is further defined in the following Example(s). It should be understood the Example(s) are given by way of illustration only. From the above discussion and the Example(s), one skilled in the art can ascertain the essential characteristics of the invention, and without departing from the spirit and scope thereof, can make various changes and modifications to adapt the invention to various uses and conditions. As a result, the invention is not limited by the illustrative example(s) set forth hereinbelow, but rather defined by the claims appended hereto.

Example 1

A 6-Month, Phase 3, Randomized, Double-Blind, Parallel-Group, Controlled, Multi-Center Study to Evaluate the Incidence of Gastric Ulcers (GUs) Following Administration of Either PN400, which is a single-tablet formulation designed to provide sequential delivery of immediate-release (IR) esomeprazole (20 mg) and enteric-coated (EC) naproxen (500 mg), or EC- Naproxen (500mg) Alone in Subjects Who are at Risk for Developing NSAID-Associated Ulcers

METHODOLOGY:

Two randomized, 6 month, Phase 3, double-blind, parallel group, controlled, multicenter studies (hereinafter known as Study A and Study B) enrolled *H. pylori*-negative male or non-pregnant, non-breastfeeding female subjects with osteoarthritis (OA), rheumatoid arthritis (RA), ankylosing spondylitis or other medical condition(s) expected to require daily NSAID therapy for at least 6 months, who were either (i) 18-49 years of age and had a history of a documented, uncomplicated gastric or duodenal ulcer (a mucosal break of at least 3 mm in diameter with depth, without any concurrent bleeding, clot or perforation) within the past 5 years, OR (ii) 50 years of age and older (these subjects did not require a history of a documented, uncomplicated gastric or duodenal ulcer within the past 5 years.).

Eligible subjects were randomized 1:1 to receive either PN400 (EC-naproxen 500 mg/immediate-release esomeprazole 20 mg) twice daily (bid) (one dose 30-60 minutes before breakfast or first meal of the day and the other dose 30-60 minutes before dinner) or EC-naproxen 500 mg bid (one dose 30-60 minutes before breakfast or first meal of the day and the other dose 30-60 minutes before dinner), stratified by low-dose aspirin (LDA) use (Yes/No) at randomization for 6 months or until gastroduodenal ulcer (GDU) was confirmed by endoscopy. The Primary endpoint was the incidence of gastric ulcer (GU) ($\geq$ 3 mm diameter with depth) as determined by endoscopy at 1, 3 and 6 mos. A post-hoc pooled analysis of GU incidence in the 20-25% of patients using LDA was conducted. The incidence of endoscopic duodenal ulcer (DU), pre-specified NSAID-associated upper gastro intestinal adverse events (UGI AEs), and safety were secondary endpoints. This study consisted of a Screening Visit, a washout period for disallowed medications of 14 days, a second Screening/Baseline Endoscopy Visit and up to 4 outpatient visits over a 6-month period, or until GUs or DUs were confirmed by endoscopy. If a GU, DU or esophageal ulcer was detected, study drug was discontinued and the subject was discontinued from the study and placed on appropriate medication to treat the ulcer. A subject was considered to have completed the study if all scheduled assessments at the 6 month visit had been performed, or the primary efficacy endpoint (GU confirmed by endoscopy) had been reached prior to 6 months.

Clinical laboratory safety testing, measurement of vital signs, and endoscopy were performed at the Screening Visit and each Follow-up Visit. In addition, subjects had assessments for dyspepsia and related gastrointestinal (GI) symptoms using the Severity of Dyspepsia Assessment (SODA) instrument and heartburn symptoms at baseline (the day of randomization) and each post-baseline visit. Subjects who completed 6 months of therapy, discontinued due to GU, or discontinued prematurely returned for a Final Visit for endoscopy (excluding subjects with GU or DU), SODA and Overall Treatment for Dyspepsia (OTE-DP) questionnaires and heartburn assessments.

NUMBER OF SUBJECTS (planned and analyzed):

Study A: 438 subjects were randomized, 434 subjects were treated, and 333 subjects completed the study. The data from 434 subjects was analyzed for efficacy.

Study B: 423 subjects were randomized, 420 subjects were treated, and 304 subjects completed the study. The data from 420 subjects was analyzed for efficacy.

DEMOGRAPHICS ITT POPULATION:

Study A:

Approximately 69% were female and 84% were white. The mean age was approximately 61 years, with about half of the subjects in both treatment groups being 50-59 years of age and ≥ 60 years of age; a small percentage of the subjects (< 3%) were < 50 years of age. The majority (> 85%) were non-smokers. There were no relevant differences in demographic characteristics between treatments. The 2 treatment groups were also similar with regard to baseline characteristics of ulcer history and NSAID use. Approximately 7% of the PN400 treatment group and 6% of the EC-naproxen group reported an ulcer within the last 5 years. Approximately 24% of PN400 subjects and 24% of EC-naproxen subjects were using LDA at randomization. OA was the most frequently reported reason for NSAID use. There were small differences in distribution of underlying etiologies between the two treatment groups. Most of the "other" indications for NSAID use were back pain, chronic back pain, low back pain (in 49 subjects). Of the LDA users, 89% in PN400 and 78% in EC-Naproxen treatment groups took an 81 mg dosage and 8% in PN400 and 20% in EC-Naproxen treatment groups took a 325 mg dosage.

Study B:

Approximately 2/3 were female and 89% were white. The mean age was approximately 60 years, with about half of the subjects in both treatment groups being 50-59 years of age and half being ≥ 60 years of age; a small percentage of the subjects (approximately 3%) was < 50 years of age. The majority (approximately 82%) were non-smokers. There were no relevant differences in demographic characteristics between treatments. The 2 treatment groups were similar with regard to most baseline characteristics. Approximately 22% of PN400 subjects and 24% of EC-naproxen subjects were using LDA at randomization. Approximately 9% of the PN400 treatment group and 11% of the EC-naproxen group reported an ulcer within the last 5 years. OA was the most frequently reported reason for NSAID use. There were small differences in distribution of underlying etiologies between the two treatment groups. Most of the "other" indications for NSAID use were back pain, chronic back pain, or low back pain (in 42 subjects). Of the LDA users, 80% in PN400 and 77% in EC-Naproxen treatment groups took

an 81 mg dosage and 17% in PN400 and 20% in EC-Naproxen treatment groups took a 325 mg dosage.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Subjects were males or non-pregnant, non-breastfeeding females at least 18 years of age with a medical condition expected to require daily NSAID therapy for at least 6 months, and, if less than 50 years old, with a documented history of GU or DU within the past 5 years. Eligible subjects were *Helicobacter pylori*-negative and did not have a GU or DU at Baseline.

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION:

PN400 tablets were manufactured by Patheon Pharmaceuticals, Inc. (Cincinnati, OH) and contain EC-naproxen 500 mg and IR esomeprazole 20 mg (present as 22.3 mg esomeprazole magnesium trihydrate salt) given orally bid.

REFERENCE THERAPY, DOSE, AND MODE OF ADMINISTRATION:

EC-naproxen 500 mg tablet (manufactured by Patheon Pharmaceuticals, Inc., Cincinnati, OH) given orally bid.

VISIT WINDOWS:

Visit windows used for determining the month of observed gastric or duodenal ulcer for efficacy analysis were as follows: (1) the 1 month visit included a planned visit day at 30 ± 6 days (visit window based on actual study day was 1-36 days); (2) the 3 months visit included a planned visit day at 90 ± 12 days (visit window based on actual study day was 37-108 days); and (3) the 6 months visit included a planned visit day at 180 ± 12 days (visit window based on actual study day was ≥ 109 days). The study windows were used to determine the month of observation throughout the 6-month treatment period.

OBJECTIVES:

Primary:

To demonstrate that PN400 is effective in reducing the risk of GUs in subjects at risk for developing NSAID-associated GUs.

Secondary:

(1) To determine if PN400 is effective in reducing the risk of DUs in subjects at risk for developing NSAID-associated ulcers.

(2) To compare UGI symptoms in subjects treated with PN400 versus EC-naproxen as measured by scores on SODA instrument and the OTE-DP.

(3) To compare heartburn symptoms in subjects treated with PN400 versus EC-naproxen.

(4) To evaluate the safety and tolerability of PN400 versus EC-naproxen.

Other:

To assess the effect of concomitant use of LDA (≤ 325 mg) on the incidence of GDUs within each treatment group.

CRITERIA FOR EVALUATION:

Efficacy:

Efficacy was assessed by gastroduodenal endoscopy at Screening and at 1, 3 and 6 months visits and by Patient Reported Outcomes (PRO) questionnaires throughout the study.

Safety:

Safety was assessed by monitoring adverse events (AEs), serious AEs (SAEs), clinical laboratory evaluations, vital signs, and physical examinations.

STATISTICAL METHODS:

All statistical analyses and data listings were completed using the SAS® system, version 9.1 or higher. Unless otherwise specified, all statistical tests were 2-sided, and statistical significance was tested at the 5% level.

Analysis Populations:

The following analysis populations were used:

- Intent-to-treat (ITT) population: All randomized subjects who received at least 1 dose of study drug and had no ulcer detected by endoscopy at the Screening Visit.
- Per-protocol (PP) population: All subjects in the ITT population who did not violate the protocol in any major way that would have impacted the evaluation of efficacy and had at least 70% overall treatment compliance. Subjects excluded from the PP population were identified prior to unblinding of the treatment code, and the reason for exclusion was documented.
- Safety population: All randomized subjects who received at least 1 dose of study drug.

Sample size:

The sample size of 200 subjects per treatment group per Study A and Study B was based on the assumption that 15% of subjects treated with EC-naproxen would have a GU over the 6 months study duration compared to 5% of subjects treated with PN400. The computation used a Fisher's exact test, with a 2-sided significance level of 5% and 90% power to detect the difference between EC-naproxen and PN400.

Efficacy and tolerability:

The primary efficacy endpoint was the proportion of subjects developing GUs throughout 6 months of study treatment. The observed cumulative incidence of GUs at 1, 3 and 6 months was summarized with its associated 95% confidence interval (CI) for each treatment group. Treatment groups were compared using a Cochran-Mantel-Haenszel (CMH) test stratified by use of LDA(Yes/No) at randomization.

In addition, the proportion of subjects developing GUs was estimated using the Kaplan-Meier method. Time to GU was calculated from the first day of study drug dispensed to the date of confirmed GU or was censored at the 6-month endoscopic assessment date or at the last assessment date if no GU developed. The Kaplan-Meier estimate and corresponding 95% CI for regrouped by-month data were calculated by treatment group at 1, 3, and 6 months. Kaplan-Meier time-to-event curves for the cumulative proportion of subjects developing GUs were plotted by treatment group. A log-rank test stratified by use of LDA (Yes/No) at randomization was used to test the difference between treatment groups in the survival curves.

The estimated and observed proportions of subjects developing GDUs throughout 6 months of treatment with LDA use (Yes/No) at randomization were summarized between treatment groups and within each treatment group in a similar fashion to the primary efficacy endpoint. To obtain an adequate power to assess the effect of LDA use between treatment groups, the statistical inference test was performed using the pooled data from Study A and Study B.

Concomitant medications were tabulated by therapeutic drug class and generic drug name using the World Health Organization Drug classification (March, 2007). The percentage of subjects who took acetaminophen and/or liquid antacid was tabulated for each treatment. The treatment difference in liquid antacid and acetaminophen use was analyzed using a Cochran-Mantel-Haenszel (CMH) test adjusting for use of LDA (Yes/No) at randomization. The total

tablets/ounces taken per subject and average tablets/ounces taken per subject were summarized for each medication by treatment group.

The exposure to study drug was evaluated by days on study drug, total number of doses taken per subject and average doses taken per month for each subject and summarized using descriptive statistics. The duration of study drug exposure was also categorized as ≤ 1 month (days ≤ 36), 1-3 months ($36 <$ days ≤ 108), and 3-6 months (days > 108) and tabulated by treatment group.

Treatment compliance for each visit per subject was defined as the percentage of total number of doses taken out of the scheduled number of doses between visits when the subject was in the study. Treatment compliance over the entire duration of study drug per subject was defined as the total number of doses taken out of the scheduled number of doses during the treatment period. Treatment compliance for each visit and overall was categorized as $< 50\%$, 50% to $< 70\%$, and $\geq 70\%$ and summarized by treatment group. The overall treatment compliance was summarized using descriptive statistics.

Key secondary efficacy and tolerability endpoints were:

1. proportion of subjects with pre-specified NSAID-associated UGI AEs or DUs;
2. proportion of subjects discontinuing from the study due to NSAID-associated UGI AEs or DUs; and
3. proportion of subjects developing DUs throughout 6 months of study treatment.

Analyses of these endpoints were in sequential order, and the hierarchical fixed-sequence testing approach was used to adjust for multiple comparisons. These endpoints were tested in the specified sequence with the rule that once a p-value exceeded 0.05, endpoints further down in the sequence were not claimed for statistical significance. Treatment comparisons of the first 2 key secondary (tolerability) endpoints were performed using a CMH test adjusting for low-dose aspirin use (Yes/No) at randomization. Subjects who developed both GUs and DUs were not counted as discontinued due to DUss since subjects developing GUs were considered as completers. The proportion of subjects developing DUs throughout 6 months was analyzed in the same manner as the primary efficacy endpoint.

Non-key secondary efficacy and tolerability endpoints included:

- proportion of subjects with resolution of symptoms on the heartburn questionnaire;
- responses on the OTE-DP questionnaire;

- mean change from Baseline on each of the SODA subscales; and
- proportion of subjects discontinuing from the study due to any AE (including DU).

These were analyzed using a CMH test, modified Wilcoxon rank-sum (Van Elteren) test, ANCOVA, and a CMH test, respectively. In addition, the proportion of subjects developing GUs and/or DUs was analyzed in the same manner as the primary endpoint. All analyses were adjusted for use of LDA at randomization.

Safety:

All AEs were coded into preferred terms according to MedDRA (Medical Dictionary for Regulatory Activities) and classified by system organ class (SOC). Summaries of the incidence of all treatment-emergent AEs, treatment-related AEs, SAEs, and AEs leading to study drug discontinuation were prepared. Treatment-emergent AEs were also summarized by maximum severity and by quartile of number of doses taken.

Vital signs at each visit, ECG at Screening, and physical examination findings at Screening and any unfavorable changes at the Final Visit were summarized by treatment and listed. Clinical laboratory values and change from baseline at each visit were summarized by treatment group using descriptive statistics. Shifts in laboratory values from Baseline to post-baseline (most abnormal value from any post-baseline sample) were tabulated. A separate listing was created of clinically significant laboratory abnormalities.

RESULTS:

Overview:

Baseline demographics were similar between Study A and Study B groups. Approximately 82% of patients had OA and 6% had RA. The cumulative observed incidence of GUs over 6 mos was significantly lower in the PN400 groups versus the EC-naproxen groups ($P<0.001$ for both studies) (See Table 2). Of the 854 subjects in Study A + Study B, 201 were concomitant LDA users; the incidence of GUs in concomitant LDA users was lower in the PN400 group versus the EC-naproxen group [3.0% vs 28.4%, respectively, $P<0.001$] (See Table 3). Of the 201 concomitant LDA users out of the 854 total subjects in Study A + Study B, the incidence of GDUs in concomitant LDA users was lower in the PN400 group versus the EC-naproxen group [4.0% vs 32.4%, respectively, $P<0.001$] (See Table 4). The incidence of GUs in non-LDA users (n=653) across Study A + Study B subjects (n=854) was lower in the PN400

group versus the EC-naproxen group [6.4% vs 22.2%, P<0.001] (See Table 5). A pooled analysis of Study A and Study B demonstrated PN400 was associated with a significantly lower incidence of GU versus EC-naproxen regardless of age. (See Table 6). The relative risk reduction (RRR) for GUs in patients treated with PN400 was 64.9% (95% confidence interval [CI] 39.0, 79.8) in patients aged 50-59 yrs and 89.2% (95% CI 75.6, 95.3) in patients aged ≥ 60 yrs.

While the overall incidence of adverse events (AEs), treatment-related AEs, and SAEs was similar among treatment groups, pre-specified UGI AEs, including dyspepsia (See Table 9 for list of UGI AEs), occurred less frequently in the PN400 group. Indeed, patients treated with PN400 reported significantly improved SODA scores in all 3 patient domains after 6 months of treatment with PN400 versus EC-naproxen (See Table 8). For example, on the pain intensity domain of SODA questionnaire, PN400 patients showed significantly more improvement than EC-naproxen patients as early as the 1-month visit. The difference in LS means increased at each subsequent visit, with LS mean pain scores at 6-month (with last observation carried forward) in Study A of -5.51 in PN400 group and -0.15 points in EC-naproxen group ($p<0.001$) and in Study B of -2.64 in PN400 group and 0.09 points in EC-naproxen group ($p=0.004$). In the case of SODA pain intensity and non-pain intensity, a negative value for LS mean change implies improvement. In the case of SODA satisfaction, a positive value for LS mean change implies improvement.

PN400 was also associated with significantly higher rates of heartburn resolution and greater response in the OTE-DP scale for PN400 versus EC-naproxen (See Table 8). In the OTE-DP questionnaire, subjects in the PN400 group showed significantly more improvement than subjects in the EC-naproxen group, with a higher percentage of "better" response and a lower percentage of "worse" response in the PN400 group. Resolution of heartburn at each post-baseline visit was defined as a severity rating of "None" on the heartburn questionnaire. Only subjects with heartburn severity at baseline and post-baseline were included in the analysis. The comparison between treatment groups at each time point was made using a CMH test taking into account baseline severity stratified by LDA use at baseline. Table 10 presents the heartburn resolution by baseline symptom severity and by visit. From an early time point (month 1), PN400 treatment demonstrated a significantly higher resolution rate than EC-naproxen. The difference in heartburn resolution was consistent throughout the study period.

Based on a preliminary assessment of pooled data correlated between OTE-DP and SODA, the changes from baseline in SODA scores for PN400 were clinically relevant. An analysis of tolerability revealed fewer patients discontinued due to pre-specified UGI AEs/DUs in the PN400 group versus EC-naproxen group (Study A: 3.2% PN400 vs 12% EC-Naproxen, $p<0.001$; Study B: 4.8% PN400 vs 11.0% EC-naproxen, $p=0.009$) (See Table 7). The discontinuation rate due to any AE (including DU) was significantly lower in the PN400 group versus EC-naproxen group (Study A: 7% PN400 vs 16% EC-naproxen, $p=0.004$; Study B: 11% PN400 vs 18% EC-naproxen, $p=0.029$).

PN400 is associated with significantly improved UGI tolerability, as measured by Patient Reported Outcomes (PROs) and discontinuation rates due to NSAID-associated UGI AEs/DUs, compared with EC-naproxen. PN400 may provide a treatment option for at-risk patients to impart longer NSAID utilization patterns when GI intolerability is controlled.

Discussion:

This study demonstrates a clinically meaningful reduction in the occurrence of GUs in subjects taking PN400 versus EC-naproxen throughout 6 months of bid treatment in subjects requiring chronic NSAID treatment and who are at risk for NSAID-associated ulcers. The difference was apparent as early as 1 month into therapy and persisted throughout the study. PN400 treatment also resulted in a significantly lower incidence of DUs than EC-naproxen throughout 6 months of treatment.

Minimization of gastric side effects is of particular importance in chronic NSAID users who also take LDA for cardiovascular prophylaxis. The study results show that the benefit of PN400 over EC-naproxen was maintained in subjects who also took LDA.

PN400 was also better tolerated than EC-naproxen as demonstrated by decreased incidence of pre-specified NSAID associated UGI AEs, increased proportion of heartburn resolution, fewer discontinuations due to UGI AEs or DUs, improvement in patient reported outcomes as measured by SODA and OTE-DP.

PN400 was generally safe and well-tolerated. Overall AE rates were similar between the treatment groups. GI AE rates were lower among PN400 treated subjects compared to EC-naproxen treated subjects. This difference was primarily due to the difference in UGI AEs. While the mean duration of treatment for PN400 was longer than for EC-naproxen, the incidence of AEs did not increase with increased duration of exposure. An improved safety and tolerability

profile of PN400 was also demonstrated by a higher proportion of subjects on PN400 (71%) completing 6 months of treatment without developing: (i) a GU or DU than subjects on EC-naproxen (42%), or (ii) a GU than subjects on EC-naproxen (48%).

Based on the results of this study, PN400 significantly reduced the incidence of both GUs and/or DUs and provided a better UGI safety profile than EC-naproxen. As such, PN400 appears to be a safe and well-tolerated treatment option for subjects at risk for NSAID-associated GUs and/or DUs.

Summary:

The results of these studies demonstrated that bid treatment with PN400 compared to EC-naproxen alone throughout 6 months in subjects at risk for NSAID-associated ulcers resulted in the following:

- The cumulative observed incidence of gastric ulcers throughout 1, 3 and 6 months was lower with PN 400 compared to EC-naproxen alone;
- A significantly lower proportion of subjects with NSAID-associated GU(s) in subjects with and without concomitant LDA;
- A significantly lower proportion of subjects with at least one pre-specified NSAID-associated UGI AE or DU;
- A significantly lower proportion of subjects discontinuing due to any pre-specified NSAID-associated UGI AE or DU;
- A significantly lower proportion of subjects with NSAID-associated DUs;
- A trend of a lower proportion of subjects with GUs regardless of LDA use, ulcer history, age < 60 and ≥ 60 years, gender, race or ethnicity;
- A significantly higher proportion of subjects with heartburn resolution;
- A significantly better overall treatment effect on dyspepsia as measured by OTE-DP;
- Significantly improved dyspepsia symptoms as measured by SODA domains of pain, non-pain symptoms and subject satisfaction; and
- A significantly lower proportion of subjects discontinuing treatment due to an AE or DU.

TABLE 2

Cumulative Observed Data at 1, 3 and 6 Months in ITT Population

		GUs		DUs		UGI AEs and/or DUs	
		No. (%) (*95% CI*)	p-value[1]	No. (%) (*95% CI*)	p-value[1]	No. (%) (*95% CI*)	p-value[1]
Study A 0-1 month	PN400 (n=218)	3 (1.4) (*0.3-4.0*)	<0.001	1 (0.5) (*0.0-2.5*)	0.010		
	EC-naproxen (n=216)	28 (13.0) (*8.8-18.2*)		9 (4.2) (*1.9-7.8*)			
Study A 0-3 months	PN400 (n=218)	4 (1.8) (*0.5-4.6*)	<0.001	1 (0.5) (*0.0-2.5*)	0.003		
	EC-naproxen (n=216)	42 (19.4) (*14.4-25.4*)		11 (5.1) (*2.6-8.9*)			
Study A 0-6 months	PN400 (n=218)	9 (4.1) (*1.9-7.7*)	<0.001	1 (0.5) (*0.0-2.5*)	0.003	114 (52.3) (*45.4-59.1*)	<0.001
	EC-naproxen (n=216)	50 (23.1) (*17.7-29.4*)		11 (5.1) (*2.6-8.9*)		149 (69) (*62.4-75.1*)	
Study B 0-1 months	PN400 (n=210)	4 (1.9) (*0.5-4.8*)	<0.001	2 (1.0) (*0.1-3.4*)	0.168		
	EC-naproxen (n=210)	21 (10.0) (*6.3-14.9*)		6 (2.9) (*1.1-6.1*)			
Study B 0-3 months	PN400 (n=210)	10 (4.8) (*2.3-8.6*)	<0.001	2 (1.0) (*0.1-3.4*)	0.013		
	EC-naproxen (n=210)	37 (17.6) (*12.7-23.5*)		11 (5.2) (*2.6-9.2*)			
Study B 0-6 months	PN400 (n=210)	15 (7.1) (*4.1-11.5*)	<0.001	2 (1.0) (*0.1-3.4*)	0.007	114 (54.3) (*47.3-61.2*)	<0.001
	EC-naproxen (n=210)	51 (24.3) (*18.6-30.7*)		12 (5.7) (*3.0-9.8*)		151 (71.9) (*65.3-77.9*)	
Study A + Study B 0-6 months	PN400 (n=428)	24 (5.6) (*3.6-8.2*)	–	3(0.7) (*0.1-2.0*)	<0.001	228 (53.3) (*48.4-58.1*)	<0.001
	EC-naproxen (n=426)	101 (23.7) (*19.7-28*)		23 (5.4) (*3.5-8.0*)		300 (70.4) (*65.8-74.7*)	

[1] p-Value for ulcer occurrence is from a CMH test stratified by low-dose aspirin use, at randomization.

TABLE 3

Cumulative Observed Incidence of GUs for LDA Users at 1, 3 and 6 Months in ITT Population

		GUs	
		No. (%) (*95% CI*)	p-value
Study A 0-1 month	PN400 (n=53)	0 (*0.0-6.7*)	–
	EC-naproxen (n=51)	6 (11.8) (*4.4-23.9*)	

Study A 0-3 months	PN400 (n=53)	0 (*0.0-6.7*)	–
	EC-naproxen (n=51)	10 (19.6) (*9.8-33.1*)	
Study A 0-6 months	PN400 (n=53)	1 (1.9) (*0.0-10.1*)	–
	EC-naproxen (n=51)	12 (23.5) (*12.8-37.5*)	
Study B 0-1 month	PN400 (n=46)	0 (*0.0-7.7*)	–
	EC-naproxen (n=51)	10 (19.6) (*9.8-33.1*)	
Study B 0-3 months	PN400 (n=46)	0 (*0.0-7.7*)	–
	EC-naproxen (n=51)	14 (27.5) (*15.9-41.7*)	
Study B 0-6 months	PN400 (n=46)	2 (4.3) (*0.5-14.8*)	–
	EC-naproxen (n=51)	17 (33.3) (*20.8-47.9*)	
Study A + Study B 0-6 months	PN400 (n=99)	3 (3.0) (*0.6-8.6*)	P<0.001
	EC-naproxen (n=102)	29 (28.4) (*19.9-38.2*)	

TABLE 4

Cumulative Observed Incidence of GDUs for LDA Users at 6 Months in ITT Population

		GDUs	
		No. (%) (*95% CI*)	p-value
Study A	PN400 (n=53)	1 (1.9) (*0.0-10.1*)	–
	EC-naproxen (n=51)	14 (27.5) (*15.9-41.7*)	
Study B	PN400 (n=46)	3 (6.5) (*1.4-17.9*)	–
	EC-naproxen (n=51)	19 (37.3) (*24.1-51.9*)	

Study A + Study B	PN400 (n=99)	4 (4.0) (*1.1-10.0*)	P<0.001
	EC-naproxen (n=102)	33 (32.4) (*23.4-42.3*)	

TABLE 5

Incidence of GUs for Non-LDA Users at 1, 3 and 6 Months in ITT Population

		GUs	
		No. (%) (*95% CI*)	p-value
Study A 0-1 month	PN400 (n=165)	3 (1.8) (*0.4-5.2*)	–
	EC-naproxen (n=165)	22 (13.3) (*8.5-19.5*)	
Study A 0-3 months	PN400 (n=165)	4 (2.4) (*0.7-6.1*)	–
	EC-naproxen (n=165)	32 (19.4) (*13.7-26.3*)	
Study A 0-6 months	PN400 (n=165)	8 (4.8) (*2.1-9.3*)	–
	EC-naproxen (n=165)	38 (23.0) (*16.8-30.2*)	
Study B 0-1 month	PN400 (n=164)	4 (2.4) (*0.7-6.1*)	–
	EC-naproxen (n=159)	11 (6.9) (*3.5-12.0*)	
Study B 0-3 months	PN400 (n=164)	10 (6.1) (*3.0-10.9*)	–
	EC-naproxen (n=159)	23 (14.5) (*9.4-20.9*)	
Study B 0-6 months	PN400 (n=164)	13 (7.9) (*4.3-13.2*)	–
	EC-naproxen (n=159)	34 (21.4) (*15.3-28.6*)	
Study A + Study B 0-6 months	PN400 (n=329)	21 (6.4) (*4.0-9.6*)	<0.001
	EC-naproxen (n=324)	72 (22.2) (*17.8-27.7*)	

TABLE 6

Pooled Cumulative Incidence of GUs in Patients Aged < 60 or ≥ 60 yrs

	Incidence of GUs, n (%)*			
Age (yrs)	**PN400**	**EC-naproxen**	**RRR** *(95% CI)*	**p**
< 60	**18/216 (8.3)**	**46/217 (21.2)**	**60.7%** *(34.4, 76.4)*	**<0.001**
50-59	15/202 (7.4)	44/208 (21.2)	64.9% *(39.0, 79.8)*	<0.001
≥ 60	**6/212 (2.8)**	**55/209 (26.3)**	**89.2%** *(75.6, 95.3)*	**<0.001**
60-69	6/157 (3.8)	40/142 (28.2)	86.4% *(69.0, 94.1)*	<0.001
≥ 70	0/55 (0.0)	15/67 (22.4)	100%	<0.001

* Cochran-Mantel-Haenszel test comparing GU rate

TABLE 7

Subjects Discontinuing from Study Due to Any Pre-Specified NSAID-Associated UGI AE or DU in ITT Population

		UGI AE and/or DU that led to discontinuation	
		No. (%) *(95% CI)*	p-value
Study A	PN400 (n=218)	7 (3.2) *(1.3-6.5)*	<0.001
	EC-naproxen (n=216)	26 (12) *(8.0-17.1)*	
Study B	PN400 (n=210)	10 (4.8) *(2.3-8.6)*	0.009
	EC-naproxen (n=210)	25 (11.9) *(7.9-17.1)*	
Study A + Study B	PN400 (n=428)	17 (4.0) *(2.3-6.3)*	<0.001
	EC-naproxen (n=426)	51 (12.0) *(9.0-15.4)*	

TABLE 8
SODA, OTE-DP, And Heartburn Data After 6 mo of Treatment With PN400 vs. EC-naproxen

	Study A			Study B		
Secondary end points	**PN400 (n=218)**	**EC-naproxen (n=216)**	**p-value**	**PN400 (n=218)**	**EC-naproxen (n=216)**	**p-value**
SODA pain intensity, change from baseline	-5.51	-0.15	<0.001	-2.64	0.09	0.004
SODA non-pain symptoms, change from baseline	-2.16	-0.47	<0.001	-1.11	0.11	<0.001
SODA satisfaction domain, change from baseline	3.35	0.87	<0.001	1.88	0.47	0.003
OTE-DP, improvement since start of treatment n (%)	93/204 (45.6)	52/187 (27.8)	<0.001	79/184 (42.9)	63/183 (34.4)	0.017
Resolution of heartburn, n (%)	140/177 (79.1)	65/115 (56.5)	<0.001	102/141 (72.3)	62/121 (51.2)	<0.001

Secondary end points	**PN400 (n=428)**	**EC-naproxen (n=426)**	**p-value**
SODA pain intensity, change from baseline	-4.14	-0.06	<0.001
SODA non-pain symptoms, change from baseline	-1.65	-0.19	<0.001
SODA satisfaction domain, change from baseline	2.65	0.69	<0.001
OTE-DP, improvement since start of treatment n (%)	172/388 (44.3)	115/370 (31.1)	<0.001
Resolution of heartburn, n (%)	242/318 (76.1)	127/236 (53.8)	<0.001

TABLE 9

List of Pre-Specified NSAID-Associated UGI AEs

Preferred Term		
Gastritis	Gastrointestinal erosion	Abdominal tenderness
Erosive gastritis	Esophageal hemorrhage	Abdominal discomfort
Esophagitis	Gastric hemorrhage	Abdominal pain
Duodenitis	Duodenal hemorrhage	Esophageal discomfort
Esophageal stenosis	Gastric mucosal lesion	Esophageal disorder
Esophageal ulcer	Duodenal scarring	Gastroesophageal reflux disease
Reflux esophagitis	Gastritis hemorrhagic	Stomach discomfort
Erosive duodenitis	Gastrointestinal mucosal	Vomiting

	disorder	
Erosive esophagitis	Abdominal pain, upper	Gastroesophagitis
Hyperchlorhydria	Dyspepsia	Epigastric discomfort
Gastrointestinal hemorrhage	Nausea	Duodenal ulcer hemorrhage
Varices esophageal	Duodenitis hemorrhagic	–

TABLE 10

Resolution of Heartburn by Baseline Severity and Visit in ITT Population

		Study A			Study B		
Month	**Baseline Severity**	**PN400 N (%)**	**NAP N (%)**	**p-value**	**PN400 N (%)**	**NAP N (%)**	**p-value**
1	None	65/78 (83%)	58/94 (62%)		67/88 (76%)	67/91 (74%)	
	Mild	37/62 (60%)	11/57 (19%)		25/49 (51%)	18/58 (31%)	
	Moderate	16/38 (42%)	7/37 (19%)		17/34 (50%)	3/30 (10%)	
	Severe	9/17 (53%)	1/5 (20%)		3/9 (33%)	1/5 (20%)	
	Total	127/195 (65.1%)	77/193 (39.9%)	<0.001	112/180 (62.2%)	89/184 (48.4%)	0.003
3	None	72/80 (90%)	50/75 (67%)		70/85 (82%)	52/76 (68%)	
	Mild	43/62 (69%)	11/41 (27%)		22/48 (46%)	11/43 (26%)	
	Moderate	16/37 (43%)	7/28 (25%)		18/28 (64%)	6/29 (21%)	
	Severe	13/18 (72%)	1/5 (20%)		5/7 (71%)	1/3 (33%)	
	Total	144/197 (73.1%)	69/149 (46.3%)	<0.001	115/168 (68.5%)	70/151 (46.4%)	<0.001
6	None	66/71 (93%)	44/59 (75%)		60/68 (88%)	43/58 (74%)	
	Mild	43/60 (72%)	14/31 (45%)		19/40 (48%)	13/39 (33%)	
	Moderate	19/31 (61%)	7/21 (33%)		21/28 (75%)	4/21 (19%)	
	Severe	12/15 (80%)	0/4 (0%)		2/5 (40%)	2/3 (67%)	
	Total	140/177 (79.1%)	65/115 (56%)	<0.001	102/141 (72.3%)	62/121 (51.2%)	<0.001

SEVERITY OF DYSPEPSIA ASSESSMENT (SODA) INSTRUMENT:

The SODA instrument was completed at Baseline and at each subsequent study visit. The questionnaire is a self-administered, multi-dimensional measure of dyspepsia-related health. Dyspepsia and related GI symptoms, including burping/belching, heartburn, bloating, passing gas, sour taste, nausea and bad breath, are commonly reported by patients taking NSAIDs and significantly impact treatment effectiveness, cost and quality of life. To capture dyspepsia and related GI symptoms, the SODA instrument was developed and validated for use in NSAID patients. Concepts measured within the 3 scales that comprise the SODA instrument are dyspepsia pain intensity, non-pain symptoms, and satisfaction with dyspepsia-related health.

The SODA contains 17 questions and can be completed in 5 minutes. It uses a 7-day recall period for questions in the pain intensity and non-pain symptoms domains. The questions

are phrased as, "during the past 7 days, on average ..." or, "during the past 7 days, how intense was your worst...". The satisfaction domain questions are phrased to ask respondents about how satisfied or dissatisfied they are about their "present level" of abdominal discomfort.

SODA scores at Baseline and each post-baseline visit and change from Baseline for the 3 subscales (pain intensity, non-pain symptom, and satisfaction) were tabulated by treatment group at 1, 3 and 6 months using descriptive statistics. The mean change from Baseline at each timepoint was compared between treatment groups using an ANCOVA model with treatment and LDA use (Yes/No) at randomization as main effects, and baseline score as a covariate. The least squares mean (LSM) for each treatment group and the difference of LSMs between treatment groups along with the 95% CIs were calculated. Only subjects with both baseline and post-baseline scores were included in the ANCOVA. For the last assessment date for SODA more than 10 days after the last dosing date of study drug, the SODA scores were excluded from the analysis of each subscale. The last-observation-carried-forward imputation approach was used.

HEARTBURN ASSESSMENT:

At Baseline and 1, 3 and 6 months during the treatment period subjects were asked the following question regarding heartburn symptoms within the 7 days prior to the visit:

Over the last 7 days, please rate your heartburn symptoms as

- none: no symptoms
- mild: awareness of symptom, but easily tolerated
- moderate: discomforting symptom sufficient to cause interference with normal activities (including sleep)
- severe: incapacitating symptom, with inability to perform normal activities (including sleep)

Heartburn was defined as a burning feeling rising from the stomach or lower part of the chest towards the neck.

Heartburn resolution at each post-baseline visit was defined as a response of "none" for the heartburn severity question. The proportion of subjects with heartburn resolution was tabulated by baseline severity and treatment group at 1, 3, and 6 months. Treatment groups were compared using a CMH test stratified by baseline heartburn severity and LDA use (Yes/No) at randomization. If the number of subjects in a cell of cross-strata was too small, only the

Baseline heartburn was stratified in the CMH test. Subjects with both Baseline and post-baseline responses were included in this analysis. For the last assessment date of heartburn more than 10 days after the last dosing date of study drug, the heartburn severity was excluded from the analysis of this endpoint.

OVERALL TREATMENT FOR DYSPEPSIA (OTE-DP):

The OTE-DP has been developed based on, and is considered a derivative work of, the Global Ratings of Change Questionnaire, which was originally developed at McMaster University. It consists of the question: "Since treatment started, has there been any change in your upper abdominal pain and/or discomfort?" Responses may be rated as "Better", "the Same", or "Worse". Follow-up questions are asked if the response is anything other than "the Same".

The OTE-DP takes approximately 2 minutes to complete and was administered at the time of the final SODA administration. Any subject who had an ulcer confirmed by endoscopy at Visits 4 or 5 could complete the assessment by phone with study staff within 48 hours following the visit. All subjects completing the 6-month visit were to complete the OTE-DP with all other assessments prior to the final endoscopy.

The percentage of subjects with each of the 3 possible responses ("Better", "Same", "Worse") on the OTE-DP questionnaire, along with the follow-up response on the "Better" and "Worse" rating, was tabulated by treatment group. The difference between treatment groups in the distribution of responses was analyzed using a modified Wilcoxon rank-sum (Van Elteren) test, stratified by LDA use (Yes/No) at randomization.

***What is Claimed is*:**

1. A method comprising: treating a disease or disorder in a patient at risk of developing an NSAID-associated ulcer by administering to said patient in need thereof a pharmaceutical composition in unit dose form comprising a) esomeprazole, or pharmaceutically acceptable salt thereof, in an amount sufficient to raise the gastric pH of said patient to at least 3.5 upon administration of one or more of said unit dose forms, and b) a therapeutically effective amount of naproxen, or pharmaceutically acceptable salt thereof; wherein said unit dose form provides for coordinated release of the esomeprazole and the naproxen such that: (i) at least a portion of said esomeprazole, or pharmaceutically acceptable salt thereof, is released independent of the pH of the surrounding medium; and (ii) the naproxen, or pharmaceutically acceptable salt thereof, is not released from said unit dose form until the pH of the surrounding medium is 3.5 or higher; and wherein said pharmaceutical composition in unit dose form decreases the risk of said patient developing an ulcer.
2. The method according to claim 1, wherein said patient is in need of chronic NSAID treatment.
3. The method according to claims 1 or 2, wherein said disease or disorder is selected from pain and inflammation.
4. The method according to claims 1 or 2, wherein said disease or disorder is selected from osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and a combination thereof.
5. The method according to any one of claims 1-4, wherein said patient is taking low dose aspirin.
6. The method according to any one of claims 1-5, wherein said pharmaceutical composition decreases the risk of said patient developing a gastroduodenal ulcer.
7. The method according to any one of claims 1-5, wherein said pharmaceutical composition decreases the risk of said patient developing a duodenal ulcer.
8. The method according to any of claims one of claims 1-5, wherein said pharmaceutical composition decreases the risk of said patient developing a gastric ulcer.
9. The method according to any one of claims 1-8, wherein said patient is treated longer with said pharmaceutical composition in unit dose form than with EC-naproxen.

10. The method according to any one of claims 1-8, wherein said pharmaceutical composition in unit dose form is administered to said patient twice a day for at least about 1 month.

11. The method according to any one of claims 1-8, wherein said pharmaceutical composition in unit dose form is administered to said patient twice a day for at least about 3 months.

12. The method according to any one of claims 1-8, wherein said pharmaceutical composition in unit dose form is administered to said patient twice a day for at least about 6 months.

13. The method according to any one of claim 1-12, wherein said pharmaceutical composition in unit dose form is a multilayer tablet comprising at least one core and at least a first layer and a second layer, wherein:

    (a) said core comprises naproxen, or a pharmaceutically acceptable salt thereof;

    (b) said first layer is a coating that at least begins to release the naproxen, or a pharmaceutically acceptable salt thereof, when the pH of the surrounding medium is about 3.5 or greater; and

    (c) said second layer is esomeprazole, or a pharmaceutically acceptable salt thereof, wherein said esomeprazole, or a pharmaceutically acceptable salt thereof, is released at a pH of from about 0 or greater.

14. The method according to claim 13, wherein said esomeprazole, or a pharmaceutically acceptable salt thereof, is released at a pH of from about 1 or greater.

15. The method according to claim 13, wherein said esomeprazole, or a pharmaceutically acceptable salt thereof, is released at a pH of from about 0 to about 2.

16. The method according to any one of claims 13-15, wherein at least a portion of said esomeprazole, or a pharmaceutically acceptable salt thereof, is not coated with an enteric coating.

17. The method according to any one of claims 13-16, wherein said first layer is an enteric coating.

18. The method according to any one of claims 13-17, wherein said multi-layer tablet is substantially free of sodium bicarbonate.

19. The method according to any one of claims 13-18, wherein said first layer begins to release the naproxen, or a pharmaceutically acceptable salt thereof, when the pH of the surrounding medium is at about 4.0 or greater.

20. The method according to any one of claims 13-18, wherein said first layer begins to release the naproxen, or a pharmaceutically acceptable salt thereof, when the pH of the surrounding medium is at about 4.5 or greater.

21. The method according to any one of claims 1-20, wherein the amount of esomeprazole, or a pharmaceutically acceptable salt thereof, sufficient to raise the gastric pH is 20 mg.

22. The method according to any one of claims 1-20, wherein the therapeutically effective amount of naproxen, or a pharmaceutically acceptable salt thereof, is selected from 375 mg and 500 mg.

23. The method according to claim 22, wherein the therapeutically effective amount of naproxen, or a pharmaceutically acceptable salt thereof, is 375 mg.

24. The method according to claim 22, wherein the therapeutically effective amount of naproxen, or a pharmaceutically acceptable salt thereof, is 500 mg.

25. A method comprising: treating a disease or disorder in a patient at risk of developing an NSAID-associated ulcer by administering to the patient a pharmaceutical composition in unit dosage form suitable for oral administration comprising:

    (a) esomeprazole or a pharmaceutically acceptable salt thereof, that is immediately soluble when the dosage form is placed in an aqueous medium, independent of pH, in an amount effective to raise the gastric pH of the patient to at least 3.5 upon administration of one or more of the unit dosage forms, and

    (b) naproxen or pharmaceutically acceptable salt thereof, wherein the naproxen or a pharmaceutically acceptable salt thereof is surrounded by a coating that is substantially insoluble in an aqueous medium at a pH below 3.5 and at a temperature of about 37°C; and

    wherein said pharmaceutical composition in unit dose form decreases the risk of said patient developing an ulcer.

26. The method of claim 25, wherein the risk is associated with chronic NSAID treatment.

27. The method of claim 25, wherein the risk is associated with age of the patient.

28. The method of claim 25, wherein the risk is associated with chronic NSAID treatment and administration of low dose aspirin prior to or during NSAID treatment.
29. The method of any one of claims 25-28, wherein the method decreases the risk of the occurrence of a gastroduodenal ulcer.
30. The method of any one of claims 25-28, wherein the method decreases the risk of the occurrence of a duodenal ulcer.
31. The method of any one of claims 25-30, wherein the patient is treated for a disease or disorder selected from pain, inflammation, osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and combinations thereof.
32. The method of any one of claims 25-31, wherein the esomeprazole or a pharmaceutically acceptable salt thereof is present in an amount effective to raise the pH of the gastric fluid of the patient to at least 3.5 when the dosage form is administered orally to the patient.
33. The method of any one of claims 25-32, wherein the esomeprazole or a pharmaceutically acceptable salt thereof is present in an amount of from 10 mg to 50 mg.
34. The method of any one of claims 25-32, wherein the esomeprazole or a pharmaceutically acceptable salt thereof is present in an amount of 20 mg.
35. The method of any one of claims 25-34, wherein the amount of naproxen, or a pharmaceutically acceptable salt thereof, is from 200 mg to 600 mg.
36. The method of any one of claims 25-34, wherein the amount of naproxen, or a pharmaceutically acceptable salt thereof, is 375 mg.
37. The method of any one of claims 25-34, wherein the amount of naproxen, or a pharmaceutically acceptable salt thereof, is 500 mg.
38. The method of any one of claims 25-37, wherein the pharmaceutical composition is formulated to be administered to a patient twice daily.
39. The method according to any one of claims 25-38, wherein said pharmaceutical composition in unit dose form is administered to said patient twice a day for at least about 1 month.
40. The method according to any one of claims 25-38, wherein said pharmaceutical composition in unit dose form is administered to said patient twice a day for at least about 3 months.

41. The method according to any one of claims 25-38, wherein said pharmaceutical composition in unit dose form is administered to said patient twice a day for at least about 6 months.

42. The method of any one of claims 25-41, wherein the unit dosage form is a tablet.

43. The method of any one of claims 25-41, wherein the unit dosage form is a capsule containing beads or minitablets.

44. The method of claim 25-42, wherein the unit dosage form is a tablet comprising a core and two or more layers, in which

    (a) the naproxen, or a pharmaceutically acceptable salt thereof, is in the core;

    (b) a first layer surrounds the core and is a coating substantially insoluble in aqueous medium at a pH below 3.5 and at a temperature of about 37°C; and

    (c) at least one second layer comprising the esomeprazole, or a pharmaceutically acceptable salt thereof, surrounds the coating of the first layer.

45. The method of any one of claims 25-42, wherein the unit dosage form is a multilayer tablet comprising a core and at least a first layer enclosing the core, and a second layer enclosing the first layer, wherein:

    (a) the core comprises naproxen, or a pharmaceutically acceptable salt thereof;

    (b) the first layer is a coating that releases less than 10% of the naproxen or a pharmaceutically acceptable salt thereof after 2 hours when tested using the USP Paddle Method in 1000 ml of 0.1N HCl at 75 rpm at 37°C. + -0.5°C; and

    (c) the second layer comprises esomeprazole, or a pharmaceutically acceptable salt thereof and at least one excipient, wherein the second layer is at least 95% soluble after 30 minutes when tested using the USP Paddle Method in 1000 ml of 0.1N HCl for two hours at 75 rpm at 37°C. + -0.5°C.

46. The method of any one of claims 25-44, wherein the unit dosage form further comprises a pharmacologically inert, water soluble coating or film surrounding the outermost layer of the unit dosage form.

47. The method of claim 47, wherein the inert coating or film comprises a water soluble sugar.

48. The method of any one of claims 25-47, wherein administration of the unit dosage form is more effective at reducing the risk of ulcer than treatment with enteric coated naproxen or a pharmaceutically acceptable salt thereof.

49. A method comprising improving compliance in a patient who requires frequent daily dosages of naproxen or a pharmaceutically acceptable salt thereof by administering the unit dosage form of claim 1.

50. A method comprising improving compliance in a patient who requires long-term daily dosages of naproxen or a pharmaceutically acceptable salt thereof by administering the unit dosage form of claim 1.

51. A method comprising: treating a disease or disorder in a patient at risk of developing an NSAID-associated ulcer by administering to the patient a pharmaceutical composition in unit dosage form suitable for oral administration comprising:

(a) esomeprazole, or a pharmaceutically acceptable salt thereof, that is immediately soluble when the dosage form is placed in an aqueous medium, independent of pH, in an amount effective to raise the gastric pH of the patient to at least 3.5 upon administration of one or more of the unit dosage forms, and

(b) naproxen, or a pharmaceutically acceptable salt thereof, wherein the naproxen, or a pharmaceutically acceptable salt thereof, is surrounded by a coating substantially insoluble in an aqueous medium at a pH below 3.5 and at a temperature of about 37°C; and

wherein said pharmaceutical composition in unit dose form reduces said patient's heartburn associated symptoms.

52. The method of claim 51, wherein administration of the unit dosage form reduces said patient's heartburn associated symptoms more than treating said patient with enteric coated naproxen, or a pharmaceutically acceptable salt thereof.

53. The method of claims 51 or 52, wherein said pharmaceutical composition in unit dose form is administered to said patient twice a day for at least about 1 month.

54. The method of claims 51 or 52, wherein said pharmaceutical composition in unit dose form is administered to said patient twice a day for at least about 3 months.

55. The method of claims 51 or 52, wherein said pharmaceutical composition in unit dose form is administered to said patient twice a day for at least about 6 months.

56. A method comprising: treating a disease or disorder in a patient at risk of developing an NSAID-associated ulcer by administering to the patient a pharmaceutical composition in unit dosage form suitable for oral administration comprising:

(a) esomeprazole, or a pharmaceutically acceptable salt thereof, that is immediately soluble when the dosage form is placed in an aqueous medium, independent of pH, in an amount effective to raise the gastric pH of the patient to at least 3.5 upon administration of one or more of the unit dosage forms, and

(b) naproxen, or a pharmaceutically acceptable salt thereof, wherein the naproxen or a pharmaceutically acceptable salt thereof is surrounded by a coating substantially insoluble in an aqueous medium at a pH below 3.5 and at a temperature of about 37°C; and

wherein the pharmaceutical composition reduces said patient's dyspepsia associated symptoms.

57. The method of claim 56, wherein administration of the unit dosage form to the patient reduces the patient's dyspepsia associated symptoms more than treating said patient with enteric coated naproxen, or a pharmaceutically acceptable salt thereof.

58. The method of claims 55 or 56, wherein said pharmaceutical composition in unit dose form is administered to said patient twice a day for at least about 1 month.

59. The method of claims 55 or 56, wherein said pharmaceutical composition in unit dose form is administered to said patient twice a day for at least about 3 months.

60. The method of claims 55 or 56, wherein said pharmaceutical composition in unit dose form is administered to said patient twice a day for at least about 6 months.

61. The method according to claim 1, wherein said ulcer is a gastric ulcer, said patient is ≥ 60 years of age, and administration of said unit dose form to said patient results in an 70 to 100% relative risk reduction of said patient developing a gastric ulcer than a patient ≥ 60 years of age who is treated with enteric coated naproxen, or a pharmaceutically acceptable salt thereof.

62. The method according to 25, wherein said ulcer is a gastric ulcer, said patient is ≥ 60 years of age, and administration of said unit dosage form to said patient results in an 70 to 100% relative risk reduction of said patient developing a gastric ulcer than a patient ≥ 60 years of age who is treated with enteric coated naproxen, or a pharmaceutically acceptable salt thereof.

63. The method according to claims 61 or 62, wherein the administration of said unit dose form to said patient results in an 89.2% relative risk reduction of said patient developing a gastric ulcer than a patient ≥ 60 years of age who is treated with enteric coated naproxen, or a pharmaceutically acceptable salt thereof.

Abstract

The present disclosure is directed to a method for treating a disease or disorder in a patient at risk of developing an NSAID-associated ulcer by administering to said patient in need thereof a pharmaceutical composition in unit dose form comprising naproxen, or pharmaceutically acceptable salt thereof, and esomeprazole, or pharmaceutically acceptable salt thereof to said at risk patient and thereby decreasing the patient's risk of developing an ulcer.

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer
First Named Inventor/Applicant Name:	Brian Ault
Filer:	Jacqueline Marie Cohen/Elizabeth Ashton
Attorney Docket Number:	103786-1 US/NS

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility application filing	1011	1	330	330
Utility Search Fee	1111	1	540	540
Utility Examination Fee	1311	1	220	220
Pages:				
Claims:				
Claims in excess of 20	1202	48	52	2496
Independent claims in excess of 3	1201	1	220	220
Multiple dependent claims	1203	1	390	390

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**4196**

Electronic Acknowledgement Receipt

EFS ID:	7885900
Application Number:	12822612
International Application Number:	
Confirmation Number:	6136
Title of Invention:	Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer
First Named Inventor/Applicant Name:	Brian Ault
Customer Number:	22466
Filer:	Jacqueline Marie Cohen/Elizabeth Ashton
Filer Authorized By:	Jacqueline Marie Cohen
Attorney Docket Number:	103786-1 US/NS
Receipt Date:	24-JUN-2010
Filing Date:	
Time Stamp:	15:16:46
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$4196
RAM confirmation Number	2483
Deposit Account	260166
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal of New Application	103786US_UtilityTrans.pdf	1078888 31b01b09087b0e4a704abb5ed2a6b2f8b607e908	no	2
Warnings:					
Information:					
2	Application Data Sheet	103786US_ADS.pdf	1351294 59e88506beb2c7e846b744b756f86ef589dc1ed2	no	6
Warnings:					
Information:					
3		103786US_PrelimAmend2.pdf	133830 a98eafa9d7d4b295954758c5f9a054bedbc6c8f1	yes	11

Multipart Description/PDF files in .zip description

Document Description	Start	End
Preliminary Amendment	1	1
Specification	2	2
Claims	3	10
Applicant Arguments/Remarks Made in an Amendment	11	11

Warnings:					
Information:					
4		103786US_Spec.pdf	270795 68c5723740e12c04a9c6c057b56f1a41a321e101	yes	44

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	35
Claims	36	43
Abstract	44	44

Warnings:

Information:					
5	Fee Worksheet (PTO-875)	fee-info.pdf	39827 0c157325833394fde61f2f92d5508da1c772168d	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	2874634	

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

New Applications Under 35 U.S.C. 111

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

National Stage of an International Application under 35 U.S.C. 371

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

New International Application Filed with the USPTO as a Receiving Office

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

PTO/SB/07 (07-06)

Approved for use through 1/31/2007. OMB 0651-0032

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

Substitute for Form PTO-1360

(For use with Form PTO/SB/06)

Application Number	Filing Date
12/822,612	06/24/2010

Applicant(s)

* May be used for additional claims or amendments

CLAIMS	AS FILED		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT	
	Indep	Depend	Indep	Depend	Indep	Depend
1			1			
2				1		
3				1		
4				1		
5				1		
6				1		
7				1		
8				1		
9				1		
10				1		
11				1		
12				1		
13				1		
14				1		
15				1		
16				3		
17				1		
18				1		
19				1		
20				1		
21				1		
22				2		
23				2		
24				2		
25			1			
26				1		
27				1		
28				1		
29				1		
30				1		
31				1		
~~32~~		Cancelled				
~~33~~				1		
~~34~~				1		
~~35~~				1		
~~36~~				1		
~~37~~				1		
38				1		
39				1		
40				1		
41				1		
42				1		
43				1		
44				1		
45				1		
46				1		
47				1		
48				1		
49				1		
50				1		
Total Indep			4			
Total Depend			64			
Total Claims			68			

CLAIMS	AS FILED		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT	
	Indep	Depend	Indep	Depend	Indep	Depend
51			1			
52				1		
53				1		
54				1		
55				1		
56			1			
57				1		
58				1		
59				1		
~~60~~ 59				1		
~~61~~ 60				1		
~~62~~ 61				1		
~~63~~ 62				2		
64						
65						
66						
67						
68						
69						
70						
71						
72						
73						
74						
75						
76						
77						
78						
79						
80						
81						
82		47				
83						
84						
85						
86						
87						
88						
89						
90						
91						
92						
93						
94						
95						
96						
97						
98						
99						
100						
Total Indep						
Total Depend			12			

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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

PTO/SB/06 (12-04)

Date: **06/24/10**

Approved for use through 7/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD
Substitute for Form PTO-875

Application or Docket Number
12/822,612

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	**330**
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	**540**
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	**220**
TOTAL CLAIMS (37 CFR 1.16(i))	**68** minus 20 =	**48**	x$26		OR	x$52	**2496**
INDEPENDENT CLAIMS (37 CFR 1.16(h))	**4** minus 3 =	* **1**	x$110			x$220	**220**
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $260 ($130 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR						
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))			195			390	**390**
			TOTAL			TOTAL	**4196**

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

APPLICATION AS AMENDED – PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					N/A		OR	N/A	
						TOTAL ADD'T FEE		OR	TOTAL ADD'T FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	RATE ($)	ADDITIONAL FEE ($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					N/A		OR	N/A	
						TOTAL ADD'T FEE		OR	TOTAL ADD'T FEE	

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

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 12/822,612	Filing Date 06/24/2010	☐ To be Mailed

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	06/24/2010	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 67	Minus	** 68	= 0	X $ =		OR	X $52=	0
	Independent (37 CFR 1.16(h))	* 4	Minus	***4	= 0	X $ =		OR	X $220=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/VIOLA ROGERS/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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