

LITE DEPALMA GREENBERG & RIVAS, LLC

Allyn Z. Lite
Michael E. Patunas
Mayra V. Tarantino
Two Gateway Center, 12th Floor
Newark, New Jersey 07102-5003
(973) 623-3000

Of Counsel:

KENYON & KENYON LLP

James Galbraith
Anita Pamintuan Fusco
Huiya Wu
One Broadway
New York, NY 10004
(212) 425-7200

Attorneys for Plaintiff Ivax Pharmaceuticals, Inc.

**UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY**

IVAX PHARMACEUTICALS, INC.,

Plaintiff,

v.

ASTRAZENECA AB and
MERCK & CO., INC.,

Defendants.

Civil Action No. _____

COMPLAINT FOR DECLARATORY JUDGMENT

Plaintiff IVAX Pharmaceuticals, Inc., (“IVAX Pharma”) for its Complaint against AstraZeneca AB and Merck & Co., Inc. (collectively “defendants”), alleges as follows:

THE PARTIES

1. IVAX Pharma is a Florida corporation with its principal place of business at 4400 Biscayne Boulevard, Miami, FL 33137. IVAX Pharma develops, manufactures, and markets generic pharmaceutical products in the United States.

2. On information and belief, defendant AstraZeneca AB (“AstraZeneca”) is a company organized and existing under the laws of Sweden, having its principal place of business at Södertälje, SE-151 85, Sweden. AstraZeneca AB was a corporate name change from Astra Aktiebolaget.

3. On information and belief, defendant Merck & Co., Inc. (“Merck”) is a New Jersey corporation, having its principal place of business at One Merck Drive, Whitehouse Station, New Jersey 08889.

4. On information and belief, AstraZeneca owns U.S. Patent No. 5,690,960 (“the ‘960 patent”), entitled “Pharmaceutical Formulation of Omeprazole,” a copy of which is attached hereto as Exhibit A.

5. On information and belief, AstraZeneca owns U.S. Patent No. 5,900,424 (“the ‘424 patent”), entitled “Omeprazole Magnesium Salt Form,” a copy of which is attached hereto as Exhibit B.

6. On information and belief, Merck owns U.S. Patent No. 6,147,103 (“the ‘103 patent”), entitled “Omeprazole Process and Compositions Thereof,” a copy of which is attached hereto as Exhibit C.

7. On information and belief, Merck owns U.S. Patent No. 6,166,213 (“the ‘213 patent”), entitled “Omeprazole Process and Compositions Thereof,” a copy of which is attached hereto as Exhibit D.

8. On information and belief, Merck owns U.S. Patent No. 6,191,148 (“the ’148 patent”), entitled “Omeprazole Process and Compositions Thereof,” a copy of which is attached hereto as Exhibit E.

JURISDICTION AND VENUE

9. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a), in that it involves substantial claims arising under the United States Patent Act, 35 U.S.C. § 1 *et seq.*

10. This Court may declare the rights and other legal relations of the parties pursuant to 21 U.S.C. § 355(j)(5)(C) and 28 U.S.C. §§ 2201 and 2202 because this is a case of actual controversy within the Court’s jurisdiction which seeks a declaratory judgment that the ’960, ’424, ’103, ’213 and ’148 patents are invalid and would not be infringed.

11. The Court has personal jurisdiction over AstraZeneca because of its continuous and systematic contacts with the state of New Jersey, including its conducting of substantial and regular business therein through the marketing and sales of its pharmaceutical products in New Jersey.

12. The Court has personal jurisdiction over Merck because of its continuous and systematic contacts with the state of New Jersey, including its maintaining a principal place of business in this District.

13. Venue is proper in this judicial district based on 28 U.S.C. § 1400(b) and/or 28 U.S.C. § 1391(b), (c) and (d).

BACKGROUND

14. On information and belief, AstraZeneca or an affiliated entity is the owner of approved New Drug Application (“NDA”) No. 21-153 for esomeprazole magnesium in capsule form, 20 mg and 40 mg.

15. On information and belief, defendants, by themselves or through affiliated entities, market NEXIUM[®] esomeprazole magnesium 20 mg and 40 mg capsules throughout the United States under NDA No. 21-153.

16. AstraZeneca has informed the United States Food and Drug Administration (“FDA”) of the following unexpired patents “with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of [esomeprazole magnesium capsules]”: the ’960, ’424, ’103, ’213 and ’148 patents, and U.S. Patent Nos. 5,714,504 (“the ’504 patent”); 5,877,192 (“the ’192 patent”); 6,875,872 (“the ’872 patent”); 6,428,810 (“the ’810 patent”), and 6,369,085 (“the ’085 patent”). *See* 21 U.S.C. § 355(b)(1), (c)(2). The FDA listed these patents in a publication entitled “Approved Drug Products with Therapeutic Equivalence Evaluations,” commonly known as the “Orange Book,” in connection with NDA No. 21-153. *See* 21 U.S.C. § 355(j)(2)(A)(i).

17. IVAX Pharma holds Abbreviated New Drug Application (“ANDA”) No. 78-003, filed November 23, 2005, for 20 mg and 40 mg esomeprazole magnesium capsules. This

ANDA, which has been accepted for review by the FDA, seeks approval to market generic versions of NEXIUM[®] 20 mg and 40 mg esomeprazole magnesium capsules.

18. IVAX Pharma seeks to market esomeprazole magnesium capsules before the expiration of the patents listed in the Orange Book covering those drug products, and filed a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (a “Paragraph IV certification”) certifying that the patents listed in the Orange Book are either invalid or will not be infringed by the manufacture, use, or sale of IVAX Pharma’s proposed esomeprazole magnesium capsules.

19. In connection with its filing of its Paragraph IV certification, IVAX Pharma provided Defendants with an offer of confidential access to its ANDA in accordance with 21 U.S.C. §§ 355(j)(5)(C)(i)(I)(cc) and (III).

20. On March 8, 2006, AstraZeneca sued IVAX Pharma, alleging, *inter alia*, infringement of the ’504, ’192, ’872, ’810 and ’085 patents; it did not allege infringement of the ’960, ’424, ’103, ’213 and ’148 patents. *See AstraZeneca AB et al. v. IVAX Corporation et al.*, Civil Action No. 06-1057 (D.N.J.). The 45-day period following defendants’ receipt of IVAX Pharma’s notice of Paragraph IV certification has expired.

THE CONTROVERSY

21. Because defendants did not assert the ’960, ’424, ’103, ’213 and ’148 patents within the 45 days following receipt of IVAX Pharma’s notice of Paragraph IV certification, IVAX Pharma faces uncertainty and great potential risk if AstraZeneca should assert any of the ’960, ’424, ’103, ’213 and ’148 patents after IVAX Pharma begins commercially marketing its esomeprazole magnesium capsules.

22. Accordingly, there is an actual, substantial, and continuing justiciable case and controversy between IVAX Pharma and Defendants regarding the validity and infringement of the '960, '424, '103, '213 and '148 patents, over which this Court can and should exercise jurisdiction and declare the rights of the parties. IVAX Pharma is therefore entitled to bring and maintain this action for declaratory judgment. 21 U.S.C. § 355(j)(5)(C).

COUNT I

DECLARATORY JUDGMENT OF NONINFRINGEMENT

23. IVAX Pharma's commercial manufacture, use, offer for sale, sale, or importation of its generic equivalents of NEXIUM[®] or the active ingredient thereof would not infringe the '960 patent.

COUNT II

DECLARATORY JUDGMENT OF NONINFRINGEMENT

24. IVAX Pharma's commercial manufacture, use, offer for sale, sale, or importation of its generic equivalents of NEXIUM[®] or the active ingredient thereof would not infringe the '424 patent.

COUNT III

DECLARATORY JUDGMENT OF NONINFRINGEMENT

25. IVAX Pharma's commercial manufacture, use, offer for sale, sale, or importation of its generic equivalents of NEXIUM[®] or the active ingredient thereof would not infringe the '103 patent.

**COUNT IV
DECLARATORY JUDGMENT OF NONINFRINGEMENT**

26. IVAX Pharma's commercial manufacture, use, offer for sale, sale, or importation of its generic equivalents of NEXIUM[®] or the active ingredient thereof would not infringe the '213 patent.

**COUNT V
DECLARATORY JUDGMENT OF NONINFRINGEMENT**

27. IVAX Pharma's commercial manufacture, use, offer for sale, sale, or importation of its generic equivalents of NEXIUM[®] or the active ingredient thereof would not infringe the '148 patent.

**COUNT VI
DECLARATORY JUDGMENT OF PATENT INVALIDITY**

28. The claims of the '960 patent are invalid under 35 U.S.C. § 101 *et seq.*

**COUNT VII
DECLARATORY JUDGMENT OF PATENT INVALIDITY**

29. The claims of the '424 patent are invalid under 35 U.S.C. § 101 *et seq.*

**COUNT VIII
DECLARATORY JUDGMENT OF PATENT INVALIDITY**

30. The claims of the '103 patent are invalid under 35 U.S.C. § 101 *et seq.*

**COUNT IX
DECLARATORY JUDGMENT OF PATENT INVALIDITY**

31. The claims of the '213 patent are invalid under 35 U.S.C. § 101 *et seq.*

**COUNT X
DECLARATORY JUDGMENT OF PATENT INVALIDITY**

32. The claims of the '148 patent are invalid under 35 U.S.C. § 101 *et seq.*

PRAYER FOR RELIEF

WHEREFORE, IVAX Pharma respectfully requests the Court enter judgment against AstraZeneca and Merck to include:

A. a declaration that IVAX Pharma's manufacture, use or sale of its generic equivalents of NEXIUM[®] or the active ingredient thereof will not infringe United States Patent No. 5,690,960;

B. a declaration that IVAX Pharma's manufacture, use or sale of its generic versions of NEXIUM[®] or the active ingredient thereof will not infringe United States Patent No. 5,900,424;

C. a declaration that IVAX Pharma's manufacture, use or sale of its generic versions of NEXIUM[®] or the active ingredient thereof will not infringe United States Patent No. 6,147,103;

D. a declaration that IVAX Pharma's manufacture, use or sale of its generic equivalents of NEXIUM[®] or the active ingredient thereof will not infringe United States Patent No. 6,166,213;

E. a declaration that IVAX Pharma's manufacture, use or sale of its generic equivalents of NEXIUM[®] or the active ingredient thereof will not infringe United States Patent No. 6,191,148;

F. a declaration that United States Patent No. 5,690,960 is invalid;

G. a declaration that United States Patent No. 5,900,424 is invalid;

H. a declaration that United States Patent No. 6,147,103 is invalid;

I. a declaration that United States Patent No. 6,166,213 is invalid;

I. a declaration that United States Patent No. 6,191,148 is invalid;

J. an award of IVAX Pharma's reasonable costs and attorneys' fees in connection with this action; and

K. all such other and further relief as the Court may deem just and proper.

LITE DEPALMA GREENBERG & RIVAS, LLC

Dated: April 30, 2008

/s/ Michael E. Patunas

Allyn Z. Lite

Michael E. Patunas

Mayra V. Tarantino

Two Gateway Center, 12th Floor

Newark, New Jersey 07102-5003

(973) 623-3000

Of Counsel:

KENYON & KENYON LLP

James Galbraith

Anita Pamintuan Fusco

Huiya Wu

One Broadway

New York, NY 10004

Tel.: (212) 425-7200

Fax: (212) 425-5288

LOCAL CIVIL RULE 11.2 CERTIFICATION

Plaintiff, by its attorneys, hereby certifies that to the best of its knowledge the specific matters in controversy herein are not the subject any action pending in any court, or of any pending arbitration or administrative proceeding. Plaintiff hereby provides notice of pendency in this District of actions related to this case. Specifically, *AstraZeneca AB, et al. v. IVAX Corporation, et al.*, original Civil Action No. 06cv01057-JAP-TJB, consolidated with Civil Action No. 05cv05553-JAP-TJB, and *AstraZeneca AB, et al. v. Dr. Reddy's Laboratories, et al.*, Civil Action No. 08cv00328-JAP-TJB, relate to claims of infringement of other patents arising out of Abbreviated New Drug Applications concerning generic esomeprazole magnesium capsules, the product at issue in this action.

I hereby certify that the following statements made by me are true. I am aware that if any of the foregoing statements made by me are willfully false, I am subject to punishment.

Dated: April 30, 2008

/s/ Michael E. Patunas

Michael E. Patunas

EXHIBIT A



US005690960A

United States Patent [19]
Bengtsson et al.

[11] **Patent Number:** **5,690,960**
 [45] **Date of Patent:** **Nov. 25, 1997**

[54] **PHARMACEUTICAL FORMULATION OF OMEPRAZOLE**

[75] **Inventors:** **Inga Siv Bengtsson, Göteborg; Kurt Ingmar Lövgren, Mölnlycke, both of Sweden**

[73] **Assignee:** **Astra Aktiebolag, Sodertalje, Sweden**

[21] **Appl. No.:** **313,036**

[22] **PCT Filed:** **Jul. 8, 1994**

[86] **PCT No.:** **PCT/SE94/00681**

§ 371 Date: **Sep. 27, 1994**

§ 102(e) Date: **Sep. 27, 1994**

[87] **PCT Pub. No.:** **WO95/01783**

PCT Pub. Date: **Jan. 19, 1995**

[30] **Foreign Application Priority Data**

Jul. 9, 1993 [SE] Sweden 9302395

[51] **Int. Cl.⁶** **A61K 9/32; A61K 9/36**

[52] **U.S. Cl.** **424/480; 424/474; 424/482; 424/494; 424/497**

[58] **Field of Search** **424/480, 474, 424/482, 494, 497**

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,738,974 4/1988 Brandstrom 514/338
 4,786,505 11/1988 Lovgren et al. 424/468

FOREIGN PATENT DOCUMENTS

0005129 4/1981 European Pat. Off. .
 0124495 11/1984 European Pat. Off. .
 0342522 11/1989 European Pat. Off. .
 0247983 12/1990 European Pat. Off. .
 9501783 8/1994 WIPO .

OTHER PUBLICATIONS

Pilbrant et al., "Development of an oral formulation of omeprazole," Scand J Gastroenterol 1985; vol. 20 (Suppl 108) : 113-120.

Primary Examiner—Thurman K. Page

Assistant Examiner—James M. Spear

Attorney, Agent, or Firm—White & Case

[57] **ABSTRACT**

A new oral pharmaceutical formulation containing a novel physical form of a magnesium salt of omeprazole, a method for the manufacture of such a formulation, and the use of such a formulation in medicine.

22 Claims, No Drawings

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PHARMACEUTICAL FORMULATION OF OMEPRAZOLE

This application is a 371 of PCT/SE 94/00681 filed Jul. 8, 1994.

FIELD OF THE INVENTION

The present invention is related to a new pharmaceutical formulation containing a novel physical form of a magnesium salt of omeprazole, to a method for the manufacture of such a formulation, and to the use of such a formulation in medicine.

BACKGROUND OF THE INVENTION

The compound known under the generic name omeprazole, 5-methoxy-2-(((4-methoxy-3,5-dimethyl-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole, is described i.a. in EP-A 0 005 129.

Omeprazole is useful for inhibiting gastric acid secretion and has gastric mucosa protective activity. In a more general sense, omeprazole may be used for prevention and treatment of gastric acid related disorders in mammals and man, including e.g. gastroesophageal reflux disease, gastritis, gastric ulcer and duodenal ulcer. Omeprazole is susceptible to degradation/transformation in acid reacting and neutral media. The half-life of degradation of omeprazole in water solutions at pH-values less than four is shorter than ten minutes. Also at neutral pH-values degradation proceeds rapidly, e.g. at pH=7 the half-life of omeprazole is about 14 hours, while at higher pH-values the stability in solution is much better (Pilbrant and Cederberg, Scand. J. Gastroenterology 1985; 20 (suppl. 108) p. 113-120). Omeprazole also in the solid state is susceptible to degradation and is stabilized in mixtures with alkaline reacting compounds. The stability of omeprazole is also affected by moisture, heat, organic solvents and to some degree by light.

From what is said about the stability properties of omeprazole, it is obvious that an oral dosage form of omeprazole must be protected from contact with the acid reacting gastric juice and the active substance must be transferred in intact form to that part of the gastrointestinal tract where pH is near neutral and where rapid absorption of omeprazole can occur.

A pharmaceutical oral solid dosage form of omeprazole must be protected from contact with acidic gastric juice by an enteric coating. In U.S. Pat. No. 4,786,505 is described an enteric coated omeprazole preparation containing a separating subcoat between the core material and the enteric coating. Said preparation contains an alkaline core comprising omeprazole, a subcoating and an enteric coating.

Certain salts of omeprazole including alkaline reacting salts of omeprazole are described in EP-A 0 124 495. In said patent specification the requirements and importance regarding storage stability of omeprazole for incorporation in pharmaceutical preparations are emphasized.

There is however, a demand for the development of new enteric preparations of omeprazole with enhanced stability and for environmental aspects there is also a strong desire for the use of water based processes in production of pharmaceutical products.

The isolation and purification in full manufacturing scale of the magnesium omeprazole salts described in EP-A 0 124 495 presents one major problem in that the magnesium omeprazole salt particles are very fragile making pharmaceutical manufacturing processes utilising this product less

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attractive in full scale production. Performing the process without crystallization of the magnesium omeprazole gives a product which is less suitable as a pharmaceutical substance.

In order to use the magnesium salt of omeprazole, in this specification denoted magnesium omeprazole, in full manufacturing scale in preparing pharmaceutical formulations primarily for oral administration, such as tablets, it is necessary that said magnesium omeprazole possesses a combination of properties which makes such full scale manufacturing feasible.

The combination of physical properties of the novel magnesium omeprazole product described in the present specification with respect to the degree of crystallinity, particle diameter, density, hygroscopicity, low water content and low content of other solvents is favorable and permits the manufacture of magnesium omeprazole in a form which is useful for the manufacture of the new pharmaceutical formulation.

The novel form of magnesium omeprazole can be formulated into different dosage forms for oral and rectal administration. Examples of such formulations are tablets, granules, pellets, capsules, suppositories and suspensions.

SUMMARY OF THE INVENTION

One object of the present invention is to provide a pharmaceutical formulation of magnesium omeprazole.

Another object of the present invention is to provide a process for full scale production of pharmaceutical formulations of omeprazole, especially an enteric coated dosage form of omeprazole, which is resistant to dissolution in acid media and which dissolves rapidly in neutral to alkaline media and has a good stability during long-term storage.

Yet another object of the invention is to provide an environment friendly completely water-based process for the manufacture of pharmaceutical formulations of omeprazole.

The new dosage form is characterized in the following way. Core material in the form of pellets, granules or tablets containing the novel form of a magnesium salt of omeprazole, optionally together with an alkaline reacting compound, and on said core material one or more subcoating layers optionally comprising tablet excipients which are soluble or insoluble but disintegrating in water, or polymeric, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the core and an outer layer, which is an enteric coating. This/these inner layer/layers separates/separate the core material from the outer layer being an enteric coating.

The process of forming the enteric coated dosage form is preferably water-based. Also the enteric coating process step, which usually is carried out using an organic solvent, can be carried out using a water-based process which is desirable both for the working environment inside the pharmaceutical plant and for global environmental reasons.

It has been found that a magnesium omeprazole having a degree of crystallinity which is higher than 70% is useful in the manufacture of the pharmaceutical formulations of omeprazole according to the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The new pharmaceutical formulation is defined in claims 1-8, a process for the manufacture of the pharmaceutical formulation according to the present invention is defined in

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claims 9-10 and the use of the formulation in medicine is defined in claims 11-17.

Magnesium Omeprazole

Magnesium omeprazole feasible for the manufacturing of the claimed formulation has the following properties:

- a) Crystalline form, with a degree of crystallinity of not less than 70%, preferably higher than 75% as determined by X-ray powder diffraction

It is desirable that the product also exhibits the following properties;

- b) Particle size measured as mean mass diameter (MMD) less than 30 μm , preferably less than 20 μm as determined by laser diffraction technique.
- c) Density between 1.33 g/cm^3 and 1.35 g/cm^3 as determined by powder pycnometer.
- d) Hygroscopicity not exceeding 2% increase of weight upon storage for one month up to 94% relative atmospheric humidity as determined gravimetrically.
- e) A content of water of between 5% and 10% by weight as determined by titration according to Karl Fischer.
- f) A content of methanol less than 0.1% preferably less than 0.05% by weight as determined by gas chromatography, in case methanol is used as solvent.

The process for producing the novel form of magnesium omeprazole is characterized by the following consecutive steps

- 1) treating omeprazole or a salt thereof with magnesium alcoholate in a solution
- 2) separating inorganic salts from the reaction mixture
- 3) crystallizing magnesium omeprazole
- 4) isolating the obtained crystalline magnesium omeprazole and, optionally
- 5) purifying and drying the crystalline magnesium omeprazole using conventional methods.

The process for manufacturing the novel magnesium omeprazole can be described in the following way:

A lower alcohol, such as methanol, ethanol, n-propanol or iso-propanol, preferably methanol, is treated in a solution of polar solvents with a weighed amount of magnesium at temperatures between 0° C. and reflux temperature. The temperature should preferably be between 10° and 30° C. After addition of the magnesium to the solution the temperature can, in a second step be raised further to between 0° C. and reflux temperature, preferably 20°-50° C. After termination of the reaction the temperature is reduced to 0°-40° C., preferably 10°-25° C. Omeprazole or a salt of omeprazole is then added to the solution and after termination of the reaction the mixture is cooled to -10° C. to +20° C., preferably -5° C. to +5° C. The solvent is then evaporated to 40-60% of the initial volume, which makes the inorganic salts precipitate. The precipitate is separated from the reaction solution for example by centrifugation or filtration and the solution is heated to 5° C. to 30° C. whereafter the solution is seeded with magnesium omeprazole crystals. An amount of water, which is approximately equal to the volume of the solution, is added to start the crystallization. The solution is cooled to -10° to +20° C., preferably 0°-10° C. to complete the crystallization. The crystals are then separated from the mother liquid for example by centrifugation or filtration and washed with polar solvents preferably an aqueous lower alcohol such as aqueous methanol. Finally, the crystals are dried preferably under reduced pressure and heating.

Pharmaceutical formulations containing the novel magnesium omeprazole described above are manufactured as described herein below.

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Core Material

The novel magnesium salt of omeprazole, herein referred to as magnesium omeprazole, is mixed with inert, preferably water soluble, conventional pharmaceutical constituents to obtain the preferred concentration of omeprazole in the final mixture. Optionally the magnesium omeprazole may be mixed with an alkaline reacting, otherwise inert, 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 coprecipitate; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$, $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$, $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$ or similar compounds; organic pH-buffering substances such as trihydroxymethylaminomethane, basic amino acids and their salts or other similar, pharmaceutically acceptable pH-buffering substances.

The powder mixture is then formulated into pellets, granules or tablets, by conventional pharmaceutical procedures. The pellets, granules or tablets are used as core material for further processing.

Separating Layer—Subcoating

The cores containing magnesium omeprazole and optionally alkaline reacting substances are separated from the enteric coating polymer(s). The subcoating layer, in the following defined as the separating layer, serves as a pH-buffering zone in which hydrogen ions diffusing from the outside in towards the core can react with hydroxyl ions diffusing from the core towards the surface of the coated particles. The pH-buffering properties of the separating layer can be further strengthened by introducing in the layer 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, for instance $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$, $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$, $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$, 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 or salts thereof.

The separating layer may consist of one or more layers.

The separating layer(s) can be applied to the core material—pellets, granules or tablets—by conventional coating procedures in a suitable coating pan, centrifugal fluidized coating-granulator, or in a fluidized bed apparatus using water and/or conventional organic solvents for the coating solution. The material for the separating layer is chosen among pharmaceutically acceptable, inert compounds or polymers used for film-coating applications such as, for instance, sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxymethyl cellulose or hydroxypropyl methylcellulose. The separating layer, "subcoating", applied to the core material may constitute from approximately 0.5 to 25% by weight of the core weight, preferably 2.0-10.0%, and more preferably 2.5-5.0%.

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In the case of a tablet formulation another method to apply the separating layer(s) can be performed by drycoating technique. First a tablet containing magnesium omeprazole is formulated as described above. Around this tablet one or more layers are compressed using a suitable tableting machine. The separating layer(s) consists of pharmaceutically acceptable, soluble or insoluble but in water disintegrating tablet excipients. The separating layer(s) has preferably a thickness of not less than approximately 1 mm.

Ordinary plasticizers, colorants, pigments, titanium dioxide, talc and other additives may also be included into one or more of the separating layer(s).

Enteric Coating Layer

The enteric coating layer is applied in one or more layers onto the subcoated core material by conventional coating techniques such as, for instance, pan coating or fluidized bed coating using solutions of polymers in water, or by using latex suspensions of said polymers or optionally using polymer solutions in suitable organic solvents. As enteric coating polymers can be used one or more of the following, for example solutions or dispersions of acrylates (methacrylic acid/methacrylic acid methylester copolymer), cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylcellulose, shellac or other suitable enteric coating polymer(s). Preferably water-based polymer dispersions such as for example compounds known under the trade names Aquateric® (FMC Corporation), Eudragit® (Röhm Pharma), Acoat™ (Shin-Etsu Chemical), Opadry™ (Colorcon) or similar compounds are used to obtain enteric coatings. The enteric coating layer can optionally contain a pharmaceutically acceptable plasticizer for example cetanol, triacetin, citric acid esters such as, those known under the trade name Citrofex® (Pfizer), phthalic acid esters, dibutyl succinate, polyethylene glycol (PEG) or similar plasticizers. The amount of plasticizer is usually optimized for each enteric coating polymer(s) and is usually in the range of 1-50% of the enteric coating polymer(s). Dispersants such as talc, colorants and pigments may also be included into the enteric coating layer or sprayed onto the enteric coated material as an overcoat.

The thickness of the enteric coating may vary widely without influencing the in vitro release of omeprazole in test solutions which mimic in vivo conditions in man. To protect the acid susceptible omeprazole compound and to obtain an acceptable acid resistance, the enteric coating constitutes at least an amount of 1.0% by weight of the core weight, preferably at least 3.0% and especially at least 6.0%. The upper amount of the applied enteric coating is normally only limited by processing conditions. This possibility to vary the thickness of the enteric coating without deleterious influence on the release of omeprazole is especially desirable in large scale processes. The enteric coating layer(s) may be applied on the pre-processed formulation containing subcoating layer(s) without exactly controlling the thickness of the applied coating layer(s).

Thus, the formulation according to the invention consists of core material containing magnesium omeprazole optionally mixed with alkaline reacting compound(s). The addition of alkaline reacting material is not necessary, in any sense, but such a substance may further enhance the stability of omeprazole. The core material is coated with an enteric coating rendering the dosage form insoluble in acid media, but disintegrating/dissolving in neutral to alkaline media

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such as, for instance the liquids present in the proximal part of the small intestine, the site where dissolution is wanted. The core material is further coated with an soluble or insoluble but in water disintegrating coating, optionally containing one or more pH-buffering substances, which separate the core material from the enteric coating.

Final Dosage Form

The final dosage form is either an enteric coated tablet or capsule or in the case of enteric coated pellets or granules, these pellets or granules dispensed in hard gelatin capsules or sachets. The final dosage form may further be coated with an additional layer containing pigment(s) and/or colorant(s). It is essential for the long term stability during storage that the water content of the final dosage form containing magnesium omeprazole (enteric coated tablets, capsules, granules or pellets) is kept low.

Process

A process for the manufacture of a dosage form according to the present invention represents a further aspect of the invention. After the forming of the core material, said material is first coated with the separating layer(s) and then with the enteric coating layer(s). The coating(s) are carried out as described above. Further another aspect of the invention is that the pharmaceutical processes can be completely water-based.

The preparation according to the invention is especially advantageous in reducing gastric acid secretion. It is administered one to several times a day. The typical daily dose of the active substance varies and will depend on various factors such as the individual requirements of the patients, the mode of administration and the disease. In general the daily dose will be in the range of 1-400 mg of omeprazole.

The invention is illustrated in detail by the following examples. Example 1 discloses the preparation of the novel magnesium omeprazole product, which product is suitable in manufacturing of the pharmaceutical formulations according to the present invention. Example 2 discloses compositions of different enteric coated tablets containing magnesium omeprazole and results from acid resistance test and in vitro dissolution test. Examples 3 discloses tablet formulations with different thickness of the enteric coating, the obtained gastric acid resistance of said formulations and the in vitro release rate of omeprazole. Example 4 discloses an enteric coated pellet formulation.

EXAMPLES

The following detailed Example 1 will serve to illustrate a process for manufacturing the magnesium omeprazole, which will be used in the pharmaceutical preparations according to the present invention.

Example 1

A reactor was filled with 2026 liters of methanol. The stirrer was started and the temperature was adjusted to 20° C. 3,90 kg of magnesium was added to the vessel and immediately thereafter 1,0 liter of CH₂Cl₂. The reactor was heated to 40° C. and kept at this temperature for 60 min. It was then cooled to 15° C. before the addition of 99,9 kg of omeprazole. The reactor was kept at this temperature for 60 min and then cooled to 0° C. The temperature was kept at this level for 30 minutes before 1000 L of methanol were evaporated under vacuum and the inorganic solid salt was separated from the liquid first by centrifugation and then by

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filtration. The liquid was heated to 10° C. and the liquid was seeded with magnesium omeprazole crystals whereafter the magnesium omeprazole salt was precipitated by addition of 900 L of water. The mixture was then cooled to 5° C. After the crystallization had been completed the magnesium omeprazole crystals were centrifuged off and then washed with a mixture of 50 L of methanol and 150 L of water. The produced magnesium omeprazole was dried under reduced pressure finally producing 92,5 kg of crystalline product corresponding to a yield of 81,4%.

The novel form of the magnesium salt of omeprazole according to Example 1 fulfills the properties defined above.

Example 2

Tablet formulations containing magnesium omeprazole.

Amount omeprazole Ingredient	10 (mg/tab)	20 (mg/tab)	40 (mg/tab)
<u>Tablet core</u>			
Magnesium omeprazole	11.2	22.5	45.0
Mannitol	68.7	57.4	34.9
Microcrystalline cellulose	25.0	25.0	25.0
Sodium starch glycolate	6.0	6.0	6.0
Hydroxypropyl methylcellulose	6.0	6.0	6.0
Talc	5.0	5.0	5.0
Sodium stearyl fumarate	2.5	2.5	2.5
Water purified	50.0	50.0	50.0
<u>Sub-coating layer</u>			
Hydroxypropyl methylcellulose	3.7	3.7	3.7
Hydrogen peroxide 30%	0.04	0.04	0.04
Water purified	34.0	34.0	34.0
<u>Enteric coating layer</u>			
Methacrylic acid copolymer	9.1	9.1	9.1
Polyethylene glycol	1.0	1.0	1.0
Titanium dioxide	0.82	1.1	0.51
Colour iron oxide, red-brown	0.04	0.13	0.43
Colour iron oxide, yellow	0.02	—	—
Water purified	45.0	45.0	45.0
Polish			
Paraffin powder	0.05	0.05	0.05

The tablets with an amount of 20 mg omeprazole/tablet have been manufactured both in a pilot scale of about 300 000 tablets and a large scale of about 2 million tablets.

Description of Manufacturing

Magnesium omeprazole, mannitol, hydroxypropyl methylcellulose, microcrystalline cellulose and sodium starch glycolate are dry-mixed, moistened with water and wet mixed. The wet mass is dried and milled and finally mixed with anti-adherent and lubricant substances. The milled granulate is compressed to tablets with a diameter of 7 mm. The tablets are sub-coated with a polymer film based on hydroxypropyl methylcellulose and enteric coated with a methacrylic acid copolymer film. Water used in the manufacture of the tablets is removed during subsequent processing.

Investigation of Acid-Resistance

Six individual tablets were exposed to artificial gastric fluid without enzymes, pH 1.2. After six hours the tablets were removed, washed and analysed for omeprazole content using HPLC. The amount of omeprazole is taken as acid resistance.

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Tablet Strength (mg)	Acid resistance (%)
10	95 (93-98)
20	100 (94-102)
40	100 (96-103)

Investigation of In-Vitro Dissolution

After exposure to acid environment, pH 1.2, as described above, the medium was switched to artificial intestinal fluid without enzymes, pH 6.8. The dissolved amount of omeprazole was determined by HPLC.

Tablet Strength (mg)	Dissolved amount of omeprazole (%) after (minutes)						
	0 (%)	5 (%)	10 (%)	15 (%)	20 (%)	25 (%)	30 (%)
10	0	2	78	92	93	94	94
20	0	0	75	93	96	96	97
40	0	9	71	86	91	91	94

All values of dissolved amount of omeprazole are mean values of 12 tablets.

Example 3

Tablet formulations containing magnesium omeprazole with different thickness of the enteric coating.

The composition of the tablets is the same as in Example 2 (20 mg omeprazole). The tablets (n=6) have been exposed in an artificial gastric juice (pH 1.2) during 2 hours and then analysed for remaining amount of omeprazole (acid resistance). The release of omeprazole was analysed on tablets (n=6) pre-exposed in gastric juice 2 hrs and thereafter exposed in a buffer solution (pH 6.8) during 30 min.

Experiment ^(*)	Enteric coating (% weight per tablet)	Acid resistance (% residue after 2 h; pH 1.2)	Release (% after 30 min; pH 6.8)
A	8	101 (98-105)	94 (93-96)
B	8	100 (98-102)	95 (85-98)
C	16		98 (96-100)

^(*)A manufactured in large scale

B manufactured in pilot scale

C manufactured in laboratory scale

Example 4

Enteric coated pellet formulation containing magnesium omeprazole.

Pellet core

Magnesium omeprazole	225 g
Mannitol	1425 g
Hydroxypropyl cellulose	60 g
Microcrystalline cellulose	40 g
Lactose anhydrous	80 g
Sodium lauryl sulphate	5 g

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-continued

Disodium hydrogen phosphate dihydrate	8 g
Water purified	350 g
<u>Subcoating layer (I)</u>	
Hydroxypropyl methylcellulose	70 g
Water purified	1450 g
<u>Enteric-coating layer (II)</u>	
Methacrylic acid copolymer	430 g
Polyethylene glycol	40 g
Water purified	1890 g
<u>Polish</u>	
Magnesium stearate	5 g

The dry ingredients given above were mixed well in a mixer. Addition of granulation liquid was made and the mixture was kneaded and granulated to a proper consistency. The wet mass was pressed through an extruder and the granules were converted to spherical form in a spheronizer. The pellets were dried and classified into suitable particle size ranges, e.g. 0.5–1.5 mm.

The polymer solution (I) was sprayed on the uncoated pellets in a fluidized bed apparatus under conditions suitable for the equipment used.

The polymer dispersion (II) was sprayed on the subcoated pellets in a fluidized bed apparatus. The enteric-coated pellets were classified, polishing material was admixed and the pellets were filled into hard gelatin capsules in an amount corresponding to 20 mg of omeprazole, using a capsule filling machine.

Biopharmaceutical Tests

The enteric coated formulations according to Example 2 have been tested in humans with good results.

We claim:

1. A stable oral formulation comprising:

a core containing a magnesium salt of omeprazole said salt having more than 70% crystallinity as determined by x-ray powder diffraction;

a subcoating layer; and

an enteric coating layer, whereby the thickness of the enteric coating layer does not effect the release of omeprazole into solution at the pH predominantly present in the small intestine.

2. A formulation according to claim 1, wherein the formulation is a tablet formulation.

3. A formulation according to claim 1, wherein the formulation is a pellet formulation.

4. A formulation according to claim 1, wherein the enteric coating comprising an enteric coating material, optionally containing one or more pharmaceutically acceptable plasticizers, dispersants, colorants and pigments.

5. A formulation according to claim 4, wherein the enteric coating comprises water-based polymer solutions or dispersions of acrylates, hydroxypropyl methylcellulose acetate succinate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, cellulose acetate trimellitate and/or cellulose acetate phthalate.

6. A formulation according to claim 1, wherein the enteric coating constitutes from 1.0% by weight of the weight of the core material.

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7. A formulation according to claim 6, wherein the enteric coating constitutes at least 3.0% by weight of the weight of the core material.

8. A formulation according to claim 1 wherein the subcoating layer(s) comprise polymeric, filmforming compounds or tablet excipients which are soluble or insoluble but disintegrating in water, and optionally containing pH-buffering, alkaline compounds.

9. A formulation according to claim 1 wherein the produced enteric coated formulation contains an overcoat, optionally comprising one or more pharmaceutically acceptable plasticizers, dispersants, colorants and pigments.

10. A process for the manufacture of a formulation of a pharmaceutical composition for the oral administration of magnesium omeprazole comprising the steps of:

(a) forming a core material containing magnesium omeprazole salt said salt having at least 70% crystallinity as determined by x-ray powder diffraction;

(b) applying in the presence of water at least one subcoating layer onto the core;

(c) further applying in the presence of water at least one enteric coating layer onto the subcoated core; and drying the prepared formulation.

11. A process according to claim 10, wherein the subcoating layer(s) is applied on the core material by a dry-coating process.

12. The oral formulation according to claim 8 or 1 wherein the core is coated with more than one subcoating layer.

13. The oral formulation according to any one of the claim 1, 4-7 or 9 wherein the enteric coating comprises more than one layer.

14. The oral formulation according to claim 1 wherein the crystalline magnesium omeprazole has a mean mass particle size diameter of less than 30 μm .

15. The oral formulation according to claim 1 wherein the crystalline magnesium omeprazole has a hygroscopicity of less than 2% by weight.

16. The formulation according to claim 1, wherein the core material is in the form of pellets, granules or tablets.

17. A method for inhibiting gastric acid secretion in mammals and man by administering to a host in need thereof a therapeutically effective dose of an enteric coated formulation according to any of claims 1 to 9.

18. A method for the treatment of gastric acid related diseases in mammals and man by administering to a host in need thereof a therapeutically effective dose of an enteric coated formulation according to any of claims 1 to 9.

19. The formulation according to claim 1, wherein the core further comprises an alkaline reacting compound.

20. The process according to claim 10, wherein the core material further comprises an alkaline reacting compound.

21. A pharmaceutical composition produced in accordance with the process of claim 10.

22. An improved oral pharmaceutical composition containing a core of omeprazole salt with a subcoating and an enteric coating wherein the improvement comprises magnesium omeprazole salt having more than 70% crystallinity as determined by x-ray powder diffraction.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 5,690,960
DATED : November 25, 1997
INVENTOR(S) : Bengtsson et al.

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

col. 9, line 43 (claim 1, line 7), change "effect" to
--significantly affect--;

col. 10, line 22, change "pittance" to --presence--;

col. 10, lines 31, change "claim" to --claims--.

Signed and Sealed this
Second Day of June, 1998

Attest:



BRUCE LEHMAN

Attesting Officer

Commissioner of Patents and Trademarks

EXHIBIT B



US005900424A

United States Patent [19]**Källström et al.**[11] **Patent Number:** **5,900,424**[45] **Date of Patent:** **May 4, 1999**[54] **OMEPRAZOLE MAGNESIUM SALT FORM**[75] Inventors: **Lars Åke Källström; Monica Annelie Nygren**, both of Södertälje, Sweden[73] Assignee: **Astra Aktiebolag**, Sodertälje, Sweden[21] Appl. No.: **08/313,342**[22] PCT Filed: **Jul. 8, 1994**[86] PCT No.: **PCT/SE94/00680**§ 371 Date: **Sep. 27, 1994**§ 102(e) Date: **Sep. 27, 1994**[87] PCT Pub. No.: **WO95/01977**PCT Pub. Date: **Jan. 19, 1995**[30] **Foreign Application Priority Data**

Jul. 9, 1993 [SE] Sweden 9302396

[51] **Int. Cl.⁶** **C07D 401/12; A61K 31/44**[52] **U.S. Cl.** **514/338; 546/273.7**[58] **Field of Search** **546/273.7; 514/338**[56] **References Cited****FOREIGN PATENT DOCUMENTS**

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Primary Examiner—Jane Fan*Attorney, Agent, or Firm*—White & Case L.L.P.[57] **ABSTRACT**

A novel compound form of magnesium omeprazole useful in the manufacture of pharmaceutical formulations, the use of the product and the process for its production are described.

22 Claims, 1 Drawing Sheet

U.S. Patent

May 4, 1999

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Fig. 1

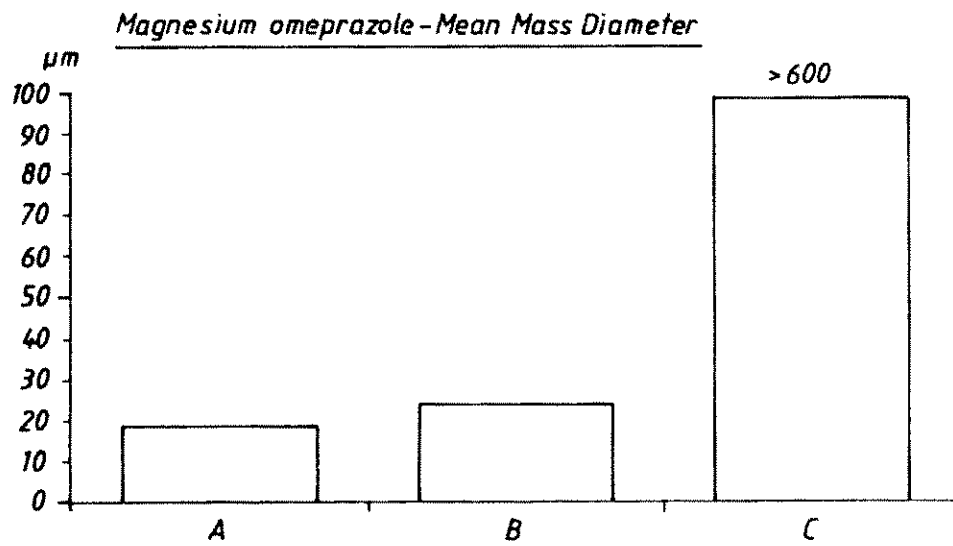
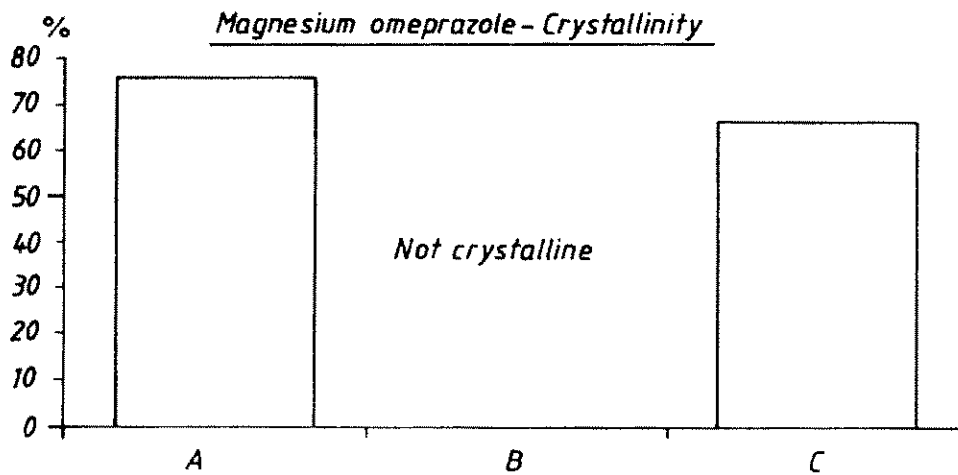


Fig. 2



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OMEPRAZOLE MAGNESIUM SALT FORM

This is a 371 of PCT/SE94/00680 filed Jul. 8, 1994, now WO 95/01977.

FIELD OF THE INVENTION

The present invention relates to a novel process for manufacturing the magnesium salt of omeprazole; the magnesium salt of omeprazole in a novel physical form, especially the magnesium salt as a product of the novel process; the use of the novel form of the magnesium salt of omeprazole in the manufacture of pharmaceutical formulations; and to the use of the novel form of the magnesium salt of omeprazole in medicine.

BACKGROUND OF THE INVENTION

The compound known under the generic name omeprazole is described i.a. in European patent specification 0005129.

Omeprazole is useful for inhibiting gastric acid secretion and has gastric mucosa protective activity in mammals and man. In a more general sense, omeprazole may be used for prevention and treatment of gastric acid related disorders and gastrointestinal inflammatory diseases in mammal and man, including e.g. gastritis, gastric ulcer and duodenal ulcer.

The term "omeprazole" as used in this specification designates the neutral form of the compound, that is the form without a salt forming cation present.

Certain salts of omeprazole are described in European patent specification 0124495. In said patent specification the requirements and importance regarding storage stability of pharmaceutical preparations are emphasized. Salts possessing superior properties with regard i.a. to storage stability are described in the said European patent specification. In EP 0124495; examples 5 and 6 disclose the synthesis of a magnesium salt of omeprazole.

The isolation and purification in full manufacturing scale of the described magnesium omeprazole salts presents one major problem in that magnesium omeprazole salt crystals are very fragile making processes utilising such crystals less attractive in full scale production. Performing the process without crystallization of the magnesium omeprazole gives a product which is less suitable as a pharmaceutical substance.

In order to use the magnesium salt of omeprazole, in this specification denoted magnesium omeprazole, in full manufacturing scale in preparing pharmaceutical formulations primarily for oral administration, such as tablets, it is necessary that said magnesium omeprazole possesses a combination of properties which makes such full scale manufacturing feasible. One object of the present invention is to provide a process for full scale production of magnesium omeprazole. A further object of the present invention is to provide a novel form of the magnesium salt of omeprazole which can be used in full scale manufacturing of pharmaceutical formulations, such as tablets.

The combination of physical properties of the novel magnesium omeprazole product of the present invention with respect to the degree of crystallinity, particle diameter, density, hygroscopicity, water content and content of other solvents are favorable and permit the manufacture of magnesium omeprazole in a form which possesses the desired properties.

The novel form of magnesium omeprazole can also be formulated into other forms for oral administration and other

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types of administration such as rectal administration. Examples of formulations are tablets, pellets, granules, capsules, suspensions and suppositories.

The invention

5 We now provide a novel form of the magnesium salt of omeprazole exhibiting the desired combination of physical properties. This makes full scale production of magnesium omeprazole as well as full scale production of pharmaceutical formulations thereof feasible.

10 The novel process for the manufacture of magnesium omeprazole also circumvents the above described manufacturing problems and renders possible the recovery and work-up of the magnesium omeprazole substance in traditional chemical process equipment.

15 It has been found that the following property is significant to obtain such product:

a) Crystalline form, with a degree of crystallinity of not less than 70%, preferably higher than 75% as determined by X-ray powder diffraction

20 It is desirable that the product also exhibits the following properties;

b) Particle size measured as mean mass diameter (MMD) less than 30 μm , preferably less than 20 μm as determined by laser diffraction technique.

25 c) Density between 1.33 g/cm³ and 1.35 g/cm³ as determined by powder pycnometer.

d) Hygroscopicity not exceeding 2% increase of weight upon storage for one month up to 94% relative atmospheric humidity as determined gravimetrically.

30 e) A content of water of between 5% and 10% by weight as determined by titration according to Karl Fischer.

f) A content of methanol less than 0.1% preferably less than 0.05% by weight as determined by gas chromatography, in case methanol is used as solvent.

35 In a further aspect, the invention also relates to a process for manufacturing the novel form of magnesium omeprazole. This process is described in more detail below.

The invention relates to all of the aspects given under Field of the invention.

40 The process for producing the novel form of magnesium omeprazole is characterized by the following consecutive steps

a) treating omeprazole or a salt thereof with magnesium alcoholate in a solution

45 b) separating inorganic salts from the reaction mixture

c) crystallizing magnesium omeprazole

d) isolating the obtained crystalline magnesium omeprazole and, optionally,

50 e) purifying and drying the crystalline magnesium omeprazole using conventional methods.

The process for manufacturing the new product can be described in the following way.

A lower alcohol, such as methanol, ethanol, n-propanol or iso-propanol, preferably methanol, is treated in a solution of 55 polar solvents with a weighed amount of magnesium at temperatures between 0° C. and reflux temperature. The temperature should preferably be between 10 and 30° C. After addition of the magnesium to the solution the temperature can, in a second step be raised further to between 0° C. and reflux temperature, preferably 20–50° C. After termination of the reaction the temperature is reduced to 0–40° C., preferably 10–25° C. Omeprazole or a salt of omeprazole is then added to the solution and after termination of the reaction the mixture is cooled to –10° C. to +20° 60 C., preferably –5° C. to +5° C. The solvent is then evaporated to 40–60% of the initial volume, which makes the inorganic salts precipitate. The precipitate is separated from

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the reaction solution for example by centrifugation or filtration and the solution is heated to 5° C. to 30° C. whereafter the solution is seeded with magnesium omeprazole crystals. An amount of water, which is approximately equal to the volume of the solution, is added to start the crystallization. The solution is cooled to -10 to +20° C., preferably 0-10° C. to complete the crystallization. The crystals are then separated from the mother liquid for example by centrifugation or filtration and washed with polar solvents preferably an aqueous lower alcohol such as aqueous methanol. Finally, the produced crystals are dried preferably under reduced pressure and heating.

The process for manufacturing the new form of magnesium omeprazole differs from the earlier known processes in that the product is recovered after a controlled crystallization step in aqueous alcohol, preferably methanol by, first, separating the inorganic salts from the mother liquor. The crystallinity resulting from this step is, unexpectedly, higher and the product possesses a higher degree of purity and is more stable to decomposition from uptake of moisture. The drying step can be performed without caking. The new process is possible to perform in conventional chemical process equipment and gives a product with a higher yield than the processes hitherto known.

The following detailed Example 1 will serve to more fully illustrate the process for manufacturing magnesium omeprazole in full scale according to the present invention. In FIGS. 1 and 2 sample A is manufactured according to this example.

EXAMPLE 1

A reactor was filled with 2026 liters of methanol. The stirrer was started and the temperature was adjusted to 20° C. 3.90 kg of magnesium was added to the vessel and immediately thereafter 1.0 liter of CH₂Cl₂. The reactor was heated to 40° C. and kept at this temperature for 60 min. It was then cooled to 15° C. before the addition of 99.9 kg of omeprazole. The reactor was kept at this temperature for 60 min and then cooled to 0° C. The temperature was kept at this level for 30 minutes before 1000 l of methanol were evaporated under vacuum and the inorganic solid salt was separated from the liquid first by centrifugation and then by filtration. The liquid was heated to 10° C. and the liquid was seeded with magnesium omeprazole crystals whereafter the magnesium omeprazole salt was precipitated by addition of 900 l of water. The mixture was then cooled to 5° C. After the crystallization had been completed the magnesium omeprazole crystals were centrifuged off and then washed with a mixture of 50 l of methanol and 150 l of water. The produced magnesium omeprazole was dried under reduced pressure finally producing 92.5 kg of crystalline product corresponding to a yield of 81.4%.

The novel form of the magnesium salt of omeprazole according to Example 1 possesses the following properties:

- a) Crystalline form, with a degree of crystallinity of 76%, as determined by X-ray powder diffraction.
- b) Particle size measured as mean mass diameter (MMD) of 19 μ m as determined by laser diffraction technique.
- c) Density of 1.342 g/cm³ as determined by powder pycnometer.
- d) Hygroscopicity of 1.62% increase of weight upon storage for one month at 94% relative atmospheric humidity as determined gravimetrically.
- e) Content of moisture water of 7.6 by weight as determined by titration according to Karl Fischer.
- f) Content of methanol of 0.006% by weight as determined by gas chromatography.

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A comparison between two different samples of the novel form of magnesium omeprazole of the present invention obtained from two laboratory scale experiments by prior art methods and magnesium omeprazole goes forth from diagrams 1 and 2. In these diagrams sample A represents the novel form of the present invention as manufactured in full scale process equipment. Sample B represents the product of preparation via synthesis by treatment of omeprazole with Mg(OCH₃)₂. Sample C represents the product of preparation via treatment of sodium omeprazole with MgCl₂.

FIG. 1 shows in diagram 1 that the particle size measured as mean mass diameter of the product of method A is 19 μ m which is smaller than the corresponding particle size for the products of method B which is 25 μ m and of method C which is greater than 600 μ m.

FIG. 2 shows in diagram 2 that the degree of crystallinity of the particles of the product of method A is 76% which is higher than the corresponding figure for the product of sample B, which is 0% and also higher than the corresponding figure of sample C, which 67%.

What is claimed is:

1. An omeprazole magnesium salt having a degree of crystallinity which is higher than 70% as determined by x-ray powder diffraction.
2. The omeprazole magnesium salt according to claim 1 wherein the degree of crystallinity is higher than 75%.
3. The omeprazole magnesium salt according to claim 1 wherein the mean particle diameter as determined by laser diffraction technique is less than 30 μ m, and preferably less than 20 μ m.
4. The omeprazole magnesium salt according to claim 1 wherein the density is between 1.33 g/cm³ and 1.35 g/cm³ as determined by powder pycnometer.
5. The omeprazole magnesium salt according to claim 1 wherein the water content is between 5% and 10% by weight as determined by titration according to Karl Fischer.
6. The omeprazole magnesium salt according to claim 1 having a solvent content less than 0.1% by weight of solvent as determined by gas chromatography.
7. The omeprazole magnesium salt according to claim 1 having a solvent content less than 0.05% by weight of solvent as determined by gas chromatography.
8. The omeprazole magnesium salt of claim 6 or 7, wherein the solvent is an aqueous alcohol.
9. The omeprazole magnesium salt of claim 6 or 7, wherein the solvent is methanol.
10. The omeprazole magnesium salt according to claim 1 wherein the hygroscopicity is less than 2% increase of weight upon storage for one month at up to 94% relative atmospheric humidity as determined by gravimetry.
11. A process for the manufacture of magnesium omeprazole according to claim 1 comprising in consecutive steps
 - a) treating omeprazole or salt thereof with magnesium alcoholate in a solution,
 - b) separating inorganic salts from the reaction mixture,
 - c) crystallizing magnesium omeprazole by the addition of water, and
 - d) isolating the obtained crystalline magnesium omeprazole.
12. A process according to claim 11 wherein the magnesium alcoholate is magnesium methyl alcoholate.
13. A process according to claim 11 wherein the solvent is methanol.
14. A process according to claim 11 wherein the isolation of the magnesium omeprazole is performed by centrifugal separation of the crystals.

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15. A process according to claim 11 wherein the isolation of the magnesium omeprazole is performed by crystallization followed by filtration of the crystals.

16. The process according to claim 11, further comprising the steps of purifying and drying the crystalline magnesium omeprazole. 5

17. A process according to claim 16 wherein the purification of the magnesium omeprazole crystals is performed by washing the crystals with a solution of polar solvents.

18. A process according to claim 16 wherein the magnesium omeprazole crystals are dried under reduced pressure. 10

19. A process according to claim 16 wherein the drying of the magnesium omeprazole crystals is performed by evaporating the remaining solvent by heating.

20. In a process for the manufacture of a crystalline magnesium salt comprising, (a) treating omeprazole or a salt thereof with magnesium alcoholate in a solution, (b) crys- 15

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tallizing magnesium omeprazole and (c) isolating the obtained crystalline magnesium omeprazole, wherein the improved process comprises separating inorganic salts from the reaction mixture prior to the crystallization step by the addition of water.

21. A method for inhibiting gastric acid secretion in mammals and man comprising administering to a host in need thereof a therapeutically effective dose of magnesium omeprazole according to any of claims 1 to 4, 6-8 and 10.

22. A method for the treatment of gastric acid related diseases in mammals and man comprising administering to a host in need thereof a therapeutically effective dose of magnesium omeprazole according to any of claims 1 to 4, 6-8 and 10.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 5,900,424

DATED : May 4, 1999

INVENTOR(S) : Kallstrom et al.

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

In claim 21, col. 6, line 9, delete "claims 1 to 4, 6-8" and insert therefor -- claims 1-7 --.

In claim 22, col. 6, lines 13-14, delete "claims 1 to 4, 6-8" and insert therefor -- claims 1-7 --.

Signed and Sealed this
Twenty-eighth Day of September, 1999

Attest:



Q. TODD DICKINSON

Attesting Officer

Acting Commissioner of Patents and Trademarks

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 5,900,424

DATED : May 4, 1999

INVENTOR(S) : Kallstrom et al.

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

On the title page:-

After "[56] References Cited," insert

-- U.S. PATENT DOCUMENTS

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5,714,504	3/1998	514/338--

Signed and Sealed this
Fourth Day of January, 2000

Attest:



Attesting Officer

Acting Commissioner of Patents and Trademarks

EXHIBIT C



US006147103A

United States Patent [19]**Anousis et al.**[11] **Patent Number:** **6,147,103**[45] **Date of Patent:** **Nov. 14, 2000**[54] **OMEPRAZOLE PROCESS AND COMPOSITIONS THEREOF**

[75] Inventors: **Nick Anousis; James W. McManus; Benjamin Newton Banks**, all of Albany, Ga.; **Lingwen Zhou**, North Brunswick, N.J.

[73] Assignee: **Merck & Co., Inc.**, Rahway, N.J.

[21] Appl. No.: **09/387,945**

[22] Filed: **Sep. 1, 1999**

Related U.S. Application Data

[62] Division of application No. 09/169,231, Oct. 9, 1998.
[60] Provisional application No. 60/096,037, Aug. 11, 1998.

[51] **Int. Cl.⁷** **A61K 31/415**
[52] **U.S. Cl.** **514/394; 514/395**
[58] **Field of Search** 514/394, 395

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WO 98/40378	9/1998	WIPO .
WO 98/09962	12/1998	WIPO .

Primary Examiner—Kevin E. Weddington
Attorney, Agent, or Firm—Philippe L. Durette; Melvin Winokur

[57] **ABSTRACT**

The present invention describes an improved process for the preparation, isolation, and purification of the anti-ulcer agent omeprazole whereby the sulfide precursor pyrmetazole is reacted subsurface with exactly one molar equivalent of meta-chloroperoxybenzoic acid in methylene chloride or toluene solution; residual organic solvent is removed from the aqueous layer by vacuum distillation; crude product is obtained by reactive crystallization with an alkyl formate and seeding; and pure product is isolated by recrystallization in methanol-water containing aqueous NaOH by subsurface addition of aqueous acetic acid to pH 9.0, seeding, filtration, washing, and drying. Compositions of omeprazole containing no chromatographically detectable levels of residual non-alcoholic organic reaction solvent are also described.

8 Claims, No Drawings

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OMEPRAZOLE PROCESS AND COMPOSITIONS THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a divisional of Ser. No. 09/169,231, filed Oct. 9, 1998, which in turn is related to U.S. provisional application Ser. No. 60/096,037 filed Aug. 11, 1998, the contents of which are hereby incorporated by reference.

FIELD OF THE INVENTION

The present invention provides a novel improved process for the preparation, isolation, and purification of the anti-ulcer agent omeprazole. Compositions of omeprazole containing no chromatographically detectable levels of residual non-alcoholic organic reaction solvent are also disclosed.

BACKGROUND OF THE INVENTION

Omeprazole, the generic name for 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (denoted as Formula I below) is a well-described gastric proton-pump inhibitor and is on the market as LOSEC® or PRILOSEC® for the treatment of gastric and duodenal ulcers, gastritis, duodenitis, and reflux esophagitis (see Merck Index, 12th Ed., entry 6977, and references cited therein). Omeprazole is commercially prepared via a multi-step sequence, the last step of which is oxidation of the sulfide intermediate, 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]methylthio]-1H-benzimidazole (denoted as Formula II below), known generically as pyrimetazole, which is typically effected with a peroxy acid, such as meta-chloroperoxybenzoic acid (hereinafter referred to as MCPBA) (U.S. Pat. Nos. 4,255, 431 and 5,386,032), magnesium monoperoxyphthalate (MMPP) (U.S. Pat. No. 5,391,752), or peroxyacetic acid (WO 98/09962), in a suitable non-alcoholic organic reaction solvent. The preferred oxidizing agent is usually MCPBA, and suitable non-alcoholic organic reaction solvents include aromatic hydrocarbon solvents, such as benzene and toluene, and chlorinated aliphatic hydrocarbon solvents, such as chloroform and methylene chloride, in admixture with an alcoholic solvent, such as methanol, ethanol, isopropanol, or 1-butanol. The preferred non-alcoholic organic reaction solvents are usually methylene chloride and toluene, and the preferred alcoholic solvent is ethanol.

Prior processes to omeprazole have numerous disadvantages that limit both the yield and the purity of the final product.

A significant drawback of such prior methods is incomplete oxidative conversion of pyrimetazole into omeprazole as well as non-chemoselective oxidation. Two aspects of chemoselectivity are important in the oxidation of pyrimetazole. First, pyrimetazole contains two tertiary amino groups which can compete with the sulfide group for the oxidizing agent. Although these amino groups are less reactive than the desired sulfide, they can nevertheless undergo quantitative oxidation with MCPBA below ambient temperature. Second, the product omeprazole (a sulfoxide) can also react with MCPBA to form a sulfone by-product. Non-chemoselectivity and over-oxidation, characteristic of the previous methods, arise from ineffective control over the amount of the oxidizing agent as well as the manner in which the oxidizing agent is charged into the reaction vessel. Prior methods do not use accurately determined amounts of the oxidizing agent and do not provide for careful control of its addition to the reaction mixture. Non-chemoselective, over-, and under-oxidation all contribute to high impurities and loss of yield of the final desired product.

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Another disadvantage of prior procedures is the considerable loss of product in the purification and isolation steps due to solubility of omeprazole in the mother liquors and solvent washes.

A further drawback concerns diminished product quality resulting from occlusion of residual solvents and reaction by-products during the crystallization steps. It is desirable to eliminate residual levels of organic reaction solvent and recrystallization solvent impurities in the final crystalline product for toxicity/safety reasons.

It is therefore an object of the present invention to provide an improved process for the preparation, purification, and isolation of omeprazole that overcomes the yield and product purity limitations of prior methods.

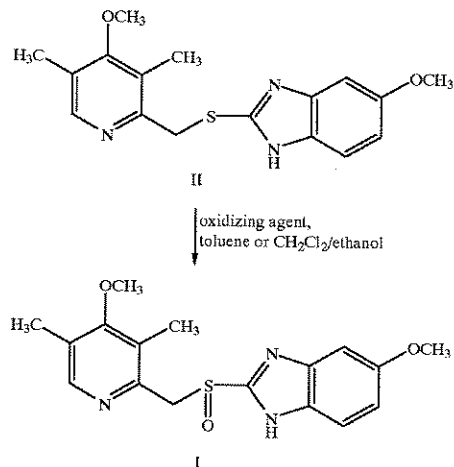
It is also an object of the invention to provide compositions of omeprazole having lower levels of residual non-alcoholic organic reaction solvent after the initial crude reactive crystallization step.

It is a further object of the present invention to provide final compositions of omeprazole that contain no residual non-alcoholic organic reaction solvent within the limits of chromatographic detection and less than 20 p.p.m. of residual crystallization solvent.

SUMMARY OF THE INVENTION

The present invention provides an improved process for the preparation, purification, and isolation of omeprazole of the Formula I.

The last chemical transformation in the preparation of omeprazole is the oxidative conversion of the sulfide intermediate pyrimetazole of the Formula II into its sulfoxide derivative omeprazole of the Formula I.



In one embodiment of the improved process, the oxidizing agent is meta-chloroperoxybenzoic acid (MCPBA), and the non-alcoholic organic reaction solvent is methylene chloride or toluene in admixture with an alcoholic solvent, such as methanol, ethanol, isopropanol, or 1-butanol, in particular, ethanol. In this embodiment, the completeness and chemoselectivity of the oxidation have been optimized by careful control of the amount of MCPBA charged to the reaction vessel. The use of one molar equivalent of MCPBA relative to the number of moles of pyrimetazole prevents non-chemoselective, over-, and under-oxidation resulting in fewer impurities and higher yields. In another embodiment

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of the present invention, the concentration of MCPBA in the charging solution is calculated using a novel analytical method based upon MCPBA oxidation of 3-methylisoquinoline to its N-oxide derivative and subsequent HPLC quantitation. Without this assay there exists no practical way to avoid either over-oxidation or incomplete conversion of pyrimetazole into omeprazole.

In a further embodiment of the present invention, control over localized over-oxidation is achieved by subsurface addition of MCPBA, providing for entry of the oxidizing solution into the reaction vessel at the tip of the agitator blades, with simultaneous control of the reaction temperature. Incorporation of these novel features into the process ensures complete conversion of pyrimetazole into omeprazole with no formation of sulfone by-products.

In another embodiment of the present invention, the isolation of the crude product has been improved by vacuum distillation of the crude aqueous phase after extraction of the reaction mixture prior to crystallization to remove most of the entrained methylene chloride or toluene from the oxidation step. The alcoholic solvent, in particular ethanol, concentration is re-adjusted in order to promote good crystal growth during the crude crystallization step. The crystallization step involves a two-stage neutralization with a C₁₋₃ alkyl formate, preferably methyl formate, which is added subsurface through a dip tube located near and directed perpendicular to the impeller tip. This mode of addition of the methyl formate ensures rapid dispersion of the neutralizing agent, which promotes crystal growth over spontaneous nucleation. In so doing, occlusion of mother liquors in the crystals is minimized. Lowering the concentration of ammonia, relative to that used in prior procedures, in the ammonia-water wash, necessary to remove color impurities in the crude product, provides for further improvement in the yield of omeprazole.

A further embodiment of the present invention concerns the final purification step. A methanol-water mixture is used for the crystallization step which is initiated by subsurface addition of aqueous acetic acid and subsequent seeding with omeprazole. The same methanol-water mixture is employed as a displacement wash to remove mother liquors and dissolved impurities while suppressing solubility losses. In this fashion, significant yield improvements are obtained with no adverse impact on product quality.

Crystalline omeprazole is thus obtained with significant improvement in yield and purity. The isolated material contains no chromatographically detectable levels of residual non-alcoholic organic reaction solvent and less than 20 p.p.m. of residual methanol as the crystallization solvent.

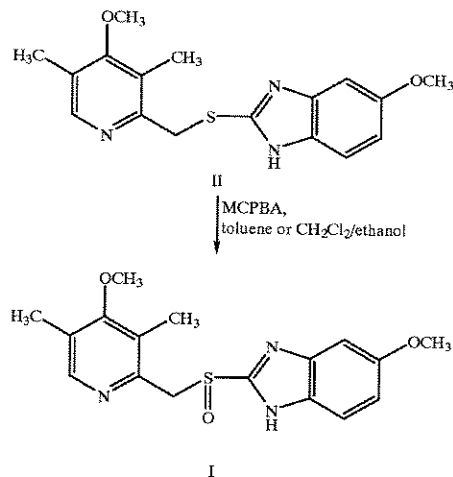
BRIEF DESCRIPTION OF THE DRAWINGS

Not Applicable

DETAILED DESCRIPTION OF THE INVENTION

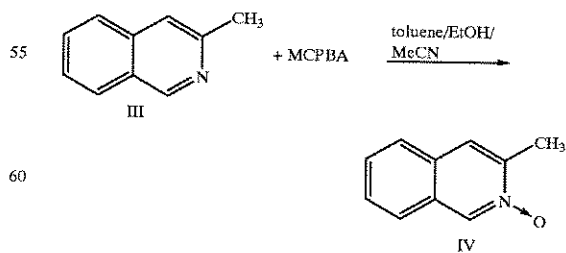
The instant invention relates to an improved process for the preparation, purification, and isolation of the proton-pump inhibitor omeprazole and to novel compositions thereof. Omeprazole, having formula I, is prepared by reacting a solution of pyrimetazole, having Formula II, cooled to about -5 to +5° C. and buffered to a pH of about 5 to 6,

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with one molar equivalent of an oxidizing agent, relative to the number of moles of pyrimetazole, dissolved in a non-alcoholic organic reaction solvent in admixture with an alcoholic solvent. The alcoholic solvent is selected from methanol, ethanol, isopropanol, and 1-butanol.

In one embodiment of the instant improved process, the buffered solution comprises potassium bicarbonate, the oxidizing agent is meta-chloroperoxybenzoic acid, and the non-alcoholic organic reaction solvent is methylene chloride or toluene, either in admixture with ethanol. The reaction is carried out such that both completeness and chemoselectivity of the oxidation are optimized. To force the reaction to proceed in a near quantitative fashion, it is necessary that any excess of the oxidizing agent, MCPBA, be minimized. Hence, the solution containing the oxidizing agent is accurately assayed so that an exact amount of reagent will be charged to the reaction vessel. In prior methods, the amount of MCPBA added was based on the commercial supplier's assay number. Since MCPBA solid contains about 15–25% water for safety reasons, the solid is not homogeneous. Therefore, the manufacturer can provide only the average assay results of MCPBA. If MCPBA from different containers and different suppliers is used, an inaccurate charge of MCPBA will result. A novel analytical method has therefore been developed to quantify MCPBA in the charging solution in order to deliver an accurate amount of the oxidizing agent. According to the assay, an excess amount of 3-methylisoquinoline (III) is reacted with CPBA in toluene/ethanol solution to form 3-methylisoquinoline N-oxide (IV), according to the equation:



The reaction is fast and quantitative. The remaining tertiary amine in the reaction mixture is quantitated by reverse-phase high-performance liquid chromatography (RP-HPLC). The

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amount of the amine consumed during the reaction is used to calculate the concentration of the MCPBA solution.

It is also important that no excess oxidizing agent accumulate during addition of the reagent. This is best accomplished by subsurface addition of MCPBA, such that the solution enters the batch through a diptube located near and directed perpendicular to the agitator blades. This mode of addition provides for immediate dispersion of the oxidant, thus limiting localized over-oxidation.

Chemoselectivity and extent of oxidation are also enhanced by controlling the reaction temperature without crystallization of the oxidizing agent. The optimum temperature range is about 0–5° C. for the solution of the oxidizing agent and about –5 to +5° C. for the reaction mixture throughout the addition process. Higher temperatures of either the MCPBA solution or the reaction mixture will result in some sulfone formation. Likewise, much lower temperatures temporarily suppress the oxidation reaction, which results in a localized accumulation of the oxidizing agent that can lead to over-oxidation products.

After addition of the solution containing the oxidizing agent, aqueous base, for example 50% NaOH or KOH, is added, the solution allowed to age for about 0.5–1.0 hours at 0–5° C., and the aqueous phase separated from the organic phase. To minimize residual levels of the non-alcoholic organic reaction solvent, in particular toluene or methylene chloride, in the crude product, which translates into higher levels of volatile non-alcoholic organic reaction solvent in the pure product, it is important to remove as much entrained toluene or methylene chloride as possible from the crude aqueous phase. The source of residual toluene or methylene chloride is an emulsion that forms when the crude batch is extracted from toluene or methylene chloride with aqueous base. Removal of residual solvent may be accomplished by vacuum distillation of the aqueous phase at a pressure of about 25–70 mm Hg and temperature of about 15–35° C. for about 1–4 hours. In further exemplification, the distillation is carried out at about 50 mm Hg and about 15° C. for 2 hours. The vacuum distillation procedure reduces the pre-crystallization levels of toluene or methylene chloride to less than 400 p.p.m. Other options to break up the emulsion and effect better phase separation are less effective; these include filtration of the crude aqueous phase through a bed of Celite™, increasing the settling time, and addition of a strong electrolyte.

Since the distillation process also results in removal of the alcohol, in particular ethanol, its concentration must be re-adjusted to approximately 15%, in order to facilitate crystal growth during the crude crystallization process. A lower level of the alcoholic solvent, in particular ethanol, produces finer crystals which are more likely to dissolve during subsequent washes thereby diminishing yields of the crude product.

At this point, the reactive crystallization of omeprazole is initiated and maintained under controlled conditions. Approximately 40% of a C₁₋₃-alkyl formate charge, preferably methyl formate, is added over the first 30 minutes to bring the batch from a pH of about 13.5 to near supersaturation at a pH of about 10.6 to 10.8. The methyl formate addition is accomplished through a diptube which is narrowed at one end to create a fine stream and which is located near and perpendicular to the impeller tip. This technique ensures rapid dispersion of the methyl formate so that occlusion of impurities is minimized. When a pH of about 10.6–10.8 is attained, the methyl formate addition is discontinued, and the batch is aged for ten to twenty minutes to allow the temperature to cool to approximately 20° C.

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prior to seeding. It is important to seed between pH 10.6 and 10.8. Below 10.6 spontaneous nucleation will occur with little crystal growth, if a sufficient seed bed is not present. Seeding is effected with pure, milled omeprazole (100% by HPLC), and the rest of the methyl formate is added subsurface over 6–8 hours to adjust the pH to about 9.0–9.3. This crystallization procedure improves both the yield and purity of the product. Without being held to a specific mechanism, it is believed that the purity enhancement is mainly due to preventing occlusion of mother liquors by promoting crystal growth over nucleation. Crude omeprazole at this stage contains less than 100 p.p.m. of residual toluene or methylene chloride, as determined by gas-liquid chromatographic analysis.

The crude crystallized product is then filtered, washed with 0.01–1.0%, preferably 0.1%, ammonia-water, and then methanol.

The crude wet omeprazole is then purified by dissolving it in 2:1–0.5–1 (v/v) methanol-water solution containing aqueous base, preferably 50% NaOH or KOH, at 20° C., cooling the basic solution to about 0–5° C., reducing the pH from >11.0 to approximately 10.5 by subsurface addition through a narrowed end diptube (configuration of apparatus same as in crude isolation step) of aqueous acetic acid, preferably 25% aqueous acetic acid, over a 30-minute period, while maintaining the temperature at 0–5° C. At this point the batch is seeded with pure omeprazole (100% by HPLC), and the subsurface addition of 25% aqueous acetic acid is continued over a 2–4 hour period until a pH of about 9.0 is attained. The batch is then aged for 0.5–1.0, preferably 0.5, hours. Following the aging period, the product is filtered, washed with the same methanol-water mixture to displace the mother liquors containing the impurities, and finally with cold methanol. Pure omeprazole is obtained after vacuum drying with a nitrogen purge at 30–50 mm Hg and 30–35° C.

The optimal methanol-water ratio in this final purification step is 1:1. Previous methods used a higher methanol to water ratio. Lowering the proportion of methanol in the solvent mixture used in the displacement wash minimizes solubility losses and provides the purification demands, thereby improving the yield of the final product without compromising product quality.

Crystalline omeprazole obtained using the improved process of the instant invention has an HPLC purity of 100% with no detectable levels of entrained residual toluene or methylene chloride from the crude step as measured by gas-liquid chromatography, the detection limit being 3 p.p.m. Prior methods have afforded omeprazole containing 30–100 p.p.m. of residual non-alcoholic organic reaction solvent, namely toluene or methylene chloride. The pure product contains less than 20 p.p.m. of residual methanol as the crystallization solvent.

For the preparation of pharmaceutical compositions in the form of dosage units for oral administration, omeprazole prepared according to the process of the present invention may be mixed with a solid, pulverulent carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives or gelatin, as well as an antifriction agent such as magnesium stearate, calcium stearate, and polyethyleneglycol waxes. The mixture is then pressed into tablets. If coated tablets are desired, the above-prepared core may be coated with a concentrated solution of sugar, which may contain gum arabic, gelatin, talc, titanium dioxide, or with a lacquer dissolved in volatile organic solvent or mixture of solvents. To this coating various dyes may be added in order to distinguish among tablets with different amounts of active compound present.

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Soft gelatin capsules may be prepared which contain a mixture of pure omeprazole prepared according to the process of the present invention and vegetable oil. Hard gelatin capsules may contain granules of the active compound in combination with a solid, pulverulent carrier, such as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives, or gelatin.

Pharmaceutical tablets for oral use are prepared in the following manner. The solid substances are ground or sieved to a certain particle size, and the binding agent is homogenized and suspended in a suitable solvent. The solid omeprazole prepared according to the process of the present invention and auxiliary agents are mixed with the binding agent solution. The resulting mixture is moistened to form a uniform suspension having the consistency of wet snow. The moistening causes the particles to aggregate slightly, and the resulting mass is pressed through a stainless steel sieve having a mesh size of about 1 millimeter. The layers of the mixture are dried in carefully controlled drying cabinets for approximately ten hours to obtain the desired particle size and consistency. The granules of the dried mixture are sieved to remove any powder. To this mixture, disintegrating, antifriction, and antiadhesive agents are added. Finally, the mixture is pressed into tablets using a machine with the appropriate punches and dies to obtain the desired tablet size. The pressure applied affects the size of the tablet, its strength and ability to dissolve in water. The compression pressure used should be in the range of 0.5 to 5 tons. The tablets, especially those which are rough or bitter, may be coated with a layer of sugar or some other palatable substance. They are then packaged by machines having electronic counting devices.

The following examples illustrate the process of the present invention and are not intended to limit the scope of the invention set forth in the claims appended thereto.

EXAMPLE 1

HPLC Assay of MCPBA Charging Solution

Step A. HPLC Operating Parameters

High-performance liquid chromatography was performed using a Waters μ Bondapak C-18 column (4.6x300 mm, 10 μ m particle size) with the following additional parameters: Mobile phase: A=acetonitrile; B=0.1% H_3PO_4 Mode: isocratic 25%A/75%B at a flow rate of 1.0 mL/min Injection size: 10 μ L

Detector wavelength: 254 nm

Run time: 32 min.

Method of quantitation: Area by electronic integration

Approximate retention times: 3-methylisoquinoline: 3.5 mins.

3-methylisoquinoline N-oxide: 5.7 mins.

MCPBA: 11.4 mins.

Toluene: 25.1 mins.

Step B.	Reagents
	Acetonitrile (MeCN): HPLC Grade
	Water: HPLC Grade
	Phosphoric Acid: HPLC Grade
	3-Methylisoquinoline: 98%
	Sample Diluent: 50/50 (MeCN/0.1% H_3PO_4)

Step C. Preparation of 3-Methylisoquinoline Standard

20 \pm 5 mg of 3-methylisoquinoline (98%) was transferred into a 10 mL volumetric flask and dissolved in 1.0 mL of

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MeCN. 1.0 mL of MCPBA after warming to room temperature was carefully pipetted into the flask, and the sides of the flask were washed with 1.0 mL of MeCN. The flask was then wrapped with parafilm and sonicated for 5 minutes. After cooling, the sides of the flask were washed with 1.0 mL of MeCN and the flask sonicated for an additional minute. The mixture was carefully diluted to the mark with acetonitrile. 1.0 mL of this solution was transferred by pipet to a 25-mL volumetric flask and diluted to the mark with the sample diluent from Step B.

Step D. Procedures

The HPLC system was equilibrated for at least 10 minutes at the mobile phase condition given in Step A. The standard preparation from Step C was injected twice, and the average area response for the 3-methylisoquinoline peaks should agree within $\pm 1\%$ of their average. The sample preparation was injected once.

Step E. Calculations

The concentration (mg/mL) of the MCPBA solution was calculated using the following equation:

$$\text{mg/mL of MCPBA solution} = (w - (A/As) \times Cs \times 250) \times \frac{172.57}{143.19}$$

where:

A=area response of the 3-methylisoquinoline for the Sample Solution

B=weight (mg) of the 3-methylisoquinoline in the Sample Preparation

As=average area response of the 3-methylisoquinoline for the Standard Solution

Cs=concentration of the 3-methylisoquinoline Standard Preparation

172.57=formula weight for 3-methylisoquinoline

143.19=formula weight for MCPBA

As an illustration of the assay, an MCPBA sample from Spectrum (Lot# LF0102, 72.7% MCPBA) was assayed, and a value of 72.8% (wt. %) for MCPBA was obtained.

EXAMPLE 2

Preparation of Omeprazole with Methylene Chloride as Solvent

A solution of potassium bicarbonate (14.0 g, 0.140 mol, 1.2 equivalents) in deionized water (115 mL) was added to a solution of pyrimetazole (0.114 mol) in methylene chloride (170 mL) in a one-liter, three-necked round-bottom flask, and the mixture was cooled to 0° C. A solution of meta-chloroperoxybenzoic acid (MCPBA) (28 g, 0.114 mol, 1.0 equivalent) in methylene chloride (51 mL) and ethanol (13.3 mL) was prepared and assayed by the 3-methylisoquinoline/HPLC procedure described in Example 1 to ensure that exactly one molar equivalent of MCPBA is used. The solution is then cooled between 0–5° C. and added, subsurface directed at the tip of the impeller, to the rapidly agitated solution of pyrimetazole over a 2-hour period. The oxidation conversion was 99.8% with no over-oxidation to sulfone or N-oxides, as determined by HPLC analysis. Cold deionized water (115 mL, 5° C.) and 50% NaOH (15 mL) were then added to the reaction mixture. The solution was allowed to stand at 0–5° C. for thirty minutes and the phases separated. The methylene chloride layer was discarded and the aqueous layer concentrated under vacuum (50 mm Hg) for 2 hours at 15° C. to remove the bulk of the residual methylene chloride. The ethanol level was then re-adjusted

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to 15% v/v. At this point the residual methylene chloride level was less than 200 p.p.m., as determined by gas-liquid chromatographic analysis.

The crude product was then isolated by reactive crystallization by subsurface addition of methyl formate. Approximately 40% of the methyl formate charge (approximately 6 mL) was added during the first thirty minutes to adjust the pH from about 13.5 to 10.8. The mixture was allowed to stand for about twenty minutes to allow the internal temperature to cool back down to approximately 20° C. The mixture was seeded with pure omeprazole (0.5 g), and the remainder of the methyl formate (approximately 9 mL) was added subsurface over a 7-hour period to a pH of 9.0. The crude product was filtered, washed with 0.1% ammonia-water (50 mL) followed by methanol (40 mL).

The crude product was dissolved in 1:1 methanol-water (270 mL) and 50% NaOH (4 mL) in a 500-mL, three-necked, round-bottomed flask at 20° C. The solution was then cooled to 0–5° C. and the pH adjusted from >11.0 to approximately 10.5 by subsurface addition of 25% acetic acid over a 30-minute period, maintaining the temperature at 5° C. The batch was seeded with pure omeprazole (0.5 g), and the subsurface addition of 25% acetic acid was continued over a 4-hour period until pH 9.0 was achieved. After thirty minutes, the resulting solid was filtered, washed with 1:1 methanol-water (30 mL), and finally with cold (5° C.) methanol (30 mL). Pure omeprazole (100% as determined by HPLC analysis) was obtained after vacuum drying (50 mm Hg, 30–35° C.). The overall yield was 92.7%. The residual methanol level was 10 ppm, as determined by gas-liquid chromatography, with no detectable levels of methylene chloride (detection limit of 3 p.p.m.).

EXAMPLE 3

Preparation of Omeprazole with Toluene as Solvent

A solution of potassium bicarbonate (14.0 g, 0.140 mol, 1.2 equivalents) in deionized water (115 mL) was added to a solution of pyrimetazole (0.114 mol) in toluene (310 mL) in a one-liter, three-necked round-bottom flask, and the mixture was cooled to 0° C. Following the bicarbonate addition, a solution of meta-chloroperoxybenzoic acid (0.114 mol, 1 equivalent) in toluene (53 mL) and ethanol (20 mL) was assayed and charged to the pyrimetazole solution as in Example 2. The oxidation conversion was 99.8% with no over-oxidation to sulfone or N-oxides. Cold deionized water (145 mL, 5° C.) and 50% NaOH (12 mL) were then added to the reaction mixture. The solution was allowed to stand at 0–5° C. for thirty minutes and the phases separated. The toluene layer was discarded and the aqueous layer concentrated under vacuum (50 mm Hg) for 2 hours at 15° C. to remove the bulk of the residual toluene. The ethanol level was then adjusted to 15% v/v. At this point the residual toluene level was less than 400 p.p.m., as determined by gas-liquid chromatographic analysis.

The crude product was then isolated by reactive crystallization by subsurface addition of methyl formate as in Example 2. It was filtered, washed with 0.1% ammonia-water (50 mL) followed by methanol (40 mL). The wet crude product was then processed to pure omeprazole as in Example 2. The overall yield was 93.8% with an HPLC purity of 100%. The residual methanol level was 10 ppm, as determined by gas-liquid chromatography, with no detectable levels of toluene (detection limit 3 p.p.m.).

EXAMPLE 4

A pharmaceutical composition containing omeprazole prepared according to the process of the present invention as the active ingredient is illustrated in the following formulation.

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Capsules containing 30 mg of omeprazole of the present invention were prepared from the following ingredients:

Compound of Example 2 or 3	300 grams
Lactose	700 grams
Microcrystalline cellulose	40 grams
Hydroxypropyl cellulose, low substituted	62 grams
Disodium hydrogenphosphate	2 grams
Purified water	q.s.

The omeprazole of Example 2 or 3 was mixed with the dry ingredients and granulated with a solution of disodium hydrogenphosphate. The wet mass was forced through an extruder and spheronized and dried in a fluidized bed dryer. 500 Grams of the pellets were coated with a solution of hydroxypropyl methylcellulose (30 grams) in water (750 mL) using a fluidized bed coater. After drying, the pellets were coated with a second coating as follows:

Coating solution:	
Hydroxypropyl methylcellulose phthalate	70 grams
Cetyl alcohol	4 grams
Acetone	200 grams
Ethanol	600 grams

The final coated pellets were filled into capsules.

What is claimed is:

1. A composition comprising 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (omeprazole) having less than three parts per million of residual aromatic hydrocarbon solvent and less than 20 p.p.m. of residual methanol relative to omeprazole.

2. A composition comprising 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (omeprazole) having less than three parts per million of residual chlorinated aliphatic hydrocarbon solvent and less than 20 p.p.m. of residual methanol relative to omeprazole.

3. The composition according to claim 1 wherein the aromatic hydrocarbon solvent is toluene.

4. The composition according to claim 2 wherein the chlorinated aliphatic hydrocarbon solvent is methylene chloride.

5. A pharmaceutical composition comprising 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (omeprazole) having less than three parts per million of residual aromatic hydrocarbon solvent and less than 20 p.p.m. of residual methanol relative to omeprazole, and a pharmaceutically acceptable excipient.

6. A pharmaceutical composition comprising 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (omeprazole) having less than three parts per million of residual chlorinated aliphatic hydrocarbon solvent and less than 20 p.p.m. of residual methanol relative to omeprazole, and a pharmaceutically acceptable excipient.

7. The pharmaceutical composition according to claim 5 wherein the aromatic hydrocarbon solvent is toluene.

8. The pharmaceutical composition according to claim 6 wherein the chlorinated aliphatic hydrocarbon solvent is methylene chloride.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,147,103

Page 1 of 1

DATED : November 14, 2000

INVENTOR(S) : Nick Anousis, James W. Mc Manus, Benjamin Newton Banks, Lingwen Zhou

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

Claims.

Claim 1.

Lines 4-5, cancel "less than 20" and substitute therefor "10-20".

Claims 2, 5 and 6.

Line 5, in each, cancel "less than 20" and substitute therefor "10-20".

Signed and Sealed this

Sixth Day of November, 2001

Attest:

Nicholas P. Godici

Attesting Officer

NICHOLAS P. GODICI
Acting Director of the United States Patent and Trademark Office

EXHIBIT D



US006166213A

United States Patent [19]**Anousis et al.**[11] **Patent Number:** **6,166,213**[45] **Date of Patent:** **Dec. 26, 2000**[54] **OMEPRAZOLE PROCESS AND COMPOSITIONS THEREOF**[75] Inventors: **Nick Anousis; James W. McManus; Benjamin Newton Banks**, all of Albany, Ga.; **Lingwen Zhou**, North Brunswick; **Hui Liu**, Greenbrook, both of N.J.[73] Assignee: **Merck & Co., Inc.**, Rahway, N.J.[21] Appl. No.: **09/169,231**[22] Filed: **Oct. 9, 1998****Related U.S. Application Data**

[60] Provisional application No. 60/096,037, Aug. 11, 1998.

[51] **Int. Cl.⁷** **C07D 401/12**[52] **U.S. Cl.** **546/273.7**[58] **Field of Search** **546/273.7**[56] **References Cited****U.S. PATENT DOCUMENTS**

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WO 98/40378 9/1998 WIPO .*Primary Examiner*—Patricia L. Morris
Attorney, Agent, or Firm—Philippe L. Durette; Melvin Winokur[57] **ABSTRACT**

The present invention describes an improved process for the preparation, isolation, and purification of the anti-ulcer agent omeprazole whereby the sulfide precursor pyrmetazole is reacted subsurface with exactly one molar equivalent of meta-chloroperoxybenzoic acid in methylene chloride or toluene solution; residual organic solvent is removed from the aqueous layer by vacuum distillation; crude product is obtained by reactive crystallization with an alkyl formate and seeding; and pure product is isolated by recrystallization in methanol-water containing aqueous NaOH by subsurface addition of aqueous acetic acid to pH 9.0, seeding, filtration, washing, and drying. Compositions of omeprazole containing no chromatographically detectable levels of residual non-alcoholic organic reaction solvent are also described.

29 Claims, No Drawings

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OMEPRAZOLE PROCESS AND COMPOSITIONS THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

The present invention is related to U.S. provisional application Ser. No. 60/096,037 filed Aug. 11, 1998, the contents of which are hereby incorporated by reference.

FIELD OF THE INVENTION

The present invention provides a novel improved process for the preparation, isolation, and purification of the anti-ulcer agent omeprazole. Compositions of omeprazole containing no chromatographically detectable levels of residual non-alcoholic organic reaction solvent are also disclosed.

BACKGROUND OF THE INVENTION

Omeprazole, the generic name for 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (denoted as Formula I below) is a well-described gastric proton-pump inhibitor and is on the market as LOSEC® or PRILOSEC® for the treatment of gastric and duodenal ulcers, gastritis, duodenitis, and reflux esophagitis (see Merck Index, 12th Ed., entry 6977, and references cited therein). Omeprazole is commercially prepared via a multi-step sequence, the last step of which is oxidation of the sulfide intermediate, 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]methylthio]-1H-benzimidazole (denoted as Formula II below), known generically as pyrimetazole, which is typically effected with a peroxy acid, such as meta-chloroperoxybenzoic acid (hereinafter referred to as MCPBA) (U.S. Pat. Nos. 4,255, 431 and 5,386,032), magnesium monoperoxyphthalate MMPP (U.S. Pat. No. 5,391,752), or peroxyacetic acid (WO 98/09962), in suitable non-alcoholic organic reaction solvent. The preferred oxidizing agent is usually MCPBA, and suitable non-alcoholic organic reaction solvents include aromatic hydrocarbon solvents, such as benzene and toluene, and chlorinated aliphatic hydrocarbon solvents, such as chloroform and methylene chloride, in admixture with an alcoholic solvent, such as methanol, ethanol, isopropanol, or 1-butanol. The preferred non-alcoholic organic reaction solvents are usually methylene chloride and toluene, and the preferred alcoholic solvent is ethanol.

Prior processes to omeprazole have numerous disadvantages that limit both the yield and the purity of the final product.

A significant drawback of such prior methods is incomplete oxidative conversion of pyrimetazole into omeprazole as well as non-chemoselective oxidation. Two aspects of chemoselectivity are important in the oxidation of pyrimetazole. First, pyrimetazole contains two tertiary amino groups which can compete with the sulfide group for the oxidizing agent. Although these amino groups are less reactive than the desired sulfide, they can nevertheless undergo quantitative oxidation with MCPBA below ambient temperature. Second, the product omeprazole (a sulfoxide) can also react with MCPBA to form a sulfone by-product. Non-chemoselectivity and over-oxidation, characteristic of the previous methods, arise from ineffective control over the amount of the oxidizing agent as well as the manner in which the oxidizing agent is charged into the reaction vessel. Prior methods do not use accurately determined amounts of the oxidizing agent and do not provide for careful control of its addition to the reaction mixture. Non-chemoselective,

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over-, and under-oxidation all contribute to high impurities and loss of yield of the final desired product.

Another disadvantage of prior procedures is the considerable loss of product in the purification and isolation steps due to solubility of omeprazole in the mother liquors and solvent washes.

A further drawback concerns diminished product quality resulting from occlusion of residual solvents and reaction by-products during the crystallization steps. It is desirable to eliminate residual levels of organic reaction solvent and recrystallization solvent impurities in the final crystalline product for toxicity/safety reasons.

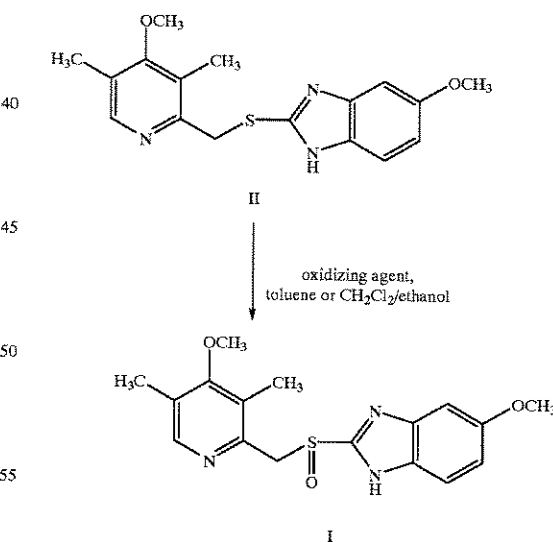
It is therefore an object of the present invention to provide an improved process for the preparation, purification, and isolation of omeprazole that overcomes the yield and product purity limitations of prior methods.

It is also an object of the invention to provide compositions of omeprazole having lower levels of residual non-alcoholic organic reaction solvent after the initial crude reactive crystallization step.

It is a further object of the present invention to provide final compositions of omeprazole that contain no residual non-alcoholic organic reaction solvent within the limits of chromatographic detection and less than 20 p.p.m. of residual crystallization solvent.

SUMMARY OF THE INVENTION

The present invention provides an improved process for the preparation, purification, and isolation of omeprazole of the Formula I. The last chemical transformation in the preparation of omeprazole is the oxidative conversion of the sulfide intermediate pyrimetazole of the Formula II into its sulfoxide derivative omeprazole of the Formula I.



In one embodiment of the improved process, the oxidizing agent is meta-chloroperoxybenzoic acid (MCPBA), and the non-alcoholic organic reaction solvent is methylene chloride or toluene in admixture with an alcoholic solvent, such as methanol, ethanol, isopropanol, or 1-butanol, in particular, ethanol. In this embodiment, the completeness and chemoselectivity of the oxidation have been optimized by careful control of the amount of MCPBA charged to the

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reaction vessel. The use of one molar equivalent of MCPBA relative to the number of moles of pyrimetazole prevents non-chemoselective, over-, and under-oxidation resulting in fewer impurities and higher yields. In another embodiment of the present invention, the concentration of MCPBA in the charging solution is calculated using a novel analytical method based upon MCPBA oxidation of 3-methylisoquinoline to its N-oxide derivative and subsequent HPLC quantitation. Without this assay there exists no practical way to avoid either over-oxidation or incomplete conversion of pyrimetazole into omeprazole.

In a further embodiment of the present invention, control over localized over-oxidation is achieved by subsurface addition of MCPBA, providing for entry of the oxidizing solution into the reaction vessel at the tip of the agitator blades, with simultaneous control of the reaction temperature. Incorporation of these novel features into the process ensures complete conversion of pyrimetazole into omeprazole with no formation of sulfone by-products.

In another embodiment of the present invention, the isolation of the crude product has been improved by vacuum distillation of the crude aqueous phase after extraction of the reaction mixture prior to crystallization to remove most of the entrained methylene chloride or toluene from the oxidation step. The alcoholic solvent, in particular ethanol, concentration is re-adjusted in order to promote good crystal growth during the crude crystallization step. The crystallization step involves a two-stage neutralization with a C₁₋₃ alkyl formate, preferably methyl formate, which is added subsurface through a dip tube located near and directed perpendicular to the impeller tip. This mode of addition of the methyl formate ensures rapid dispersion of the neutralizing agent, which promotes crystal growth over spontaneous nucleation. In so doing, occlusion of mother liquors in the crystals is minimized. Lowering the concentration of ammonia, relative to that used in prior procedures, in the ammonia-water wash, necessary to remove color impurities in the crude product, provides for further improvement in the yield of omeprazole.

A further embodiment of the present invention concerns the final purification step. A methanol-water mixture is used for the crystallization step which is initiated by subsurface addition of aqueous acetic acid and subsequent seeding with omeprazole. The same methanol-water mixture is employed as a displacement wash to remove mother liquors and dissolved impurities while suppressing solubility losses. In this fashion, significant yield improvements are obtained with no adverse impact on product quality.

Crystalline omeprazole is thus obtained with significant improvement in yield and purity. The isolated material contains no chromatographically detectable levels of residual non-alcoholic organic reaction solvent and less than 20 p.p.m. of residual methanol as the crystallization solvent.

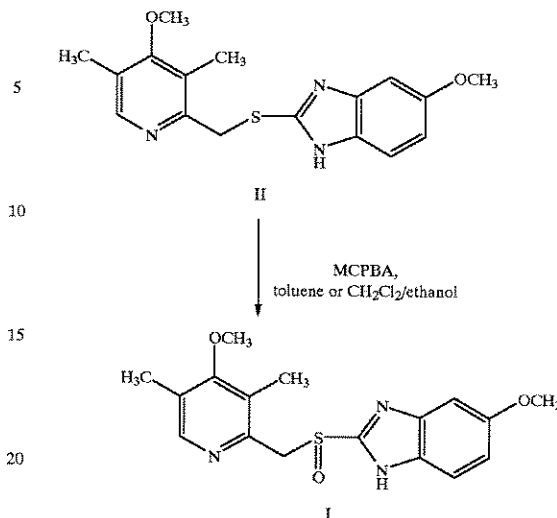
BRIEF DESCRIPTION OF THE DRAWINGS

Not Applicable

DETAILED DESCRIPTION OF THE INVENTION

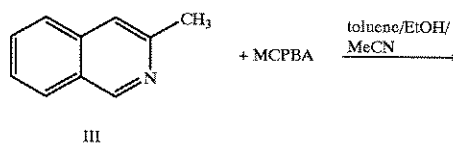
The instant invention relates to an improved process for the preparation, purification, and isolation of the proton-pump inhibitor omeprazole and to novel compositions thereof. Omeprazole, having formula I, is prepared by reacting a solution of pyrimetazole, having Formula II, cooled to about -5 to +5° C. and buffered to a pH of about 5 to 6,

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with one molar equivalent of an oxidizing agent, relative to the number of moles of pyrimetazole, dissolved in a non-alcoholic organic reaction solvent in admixture with an alcoholic solvent. The alcoholic solvent is selected from methanol, ethanol, isopropanol, and 1-butanol.

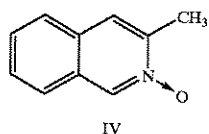
In one embodiment of the instant improved process, the buffered solution comprises potassium bicarbonate, the oxidizing agent is meta-chloroperoxybenzoic acid, and the non-alcoholic organic reaction solvent is methylene chloride or toluene, either in admixture with ethanol. The reaction is carried out such that both completeness and chemoselectivity of the oxidation are optimized. To force the reaction to proceed in a near quantitative fashion, it is necessary that any excess of the oxidizing agent, MCPBA, be minimized. Hence, the solution containing the oxidizing agent is accurately assayed so that an exact amount of reagent will be charged to the reaction vessel. In prior methods, the amount of MCPBA added was based on the commercial supplier's assay number. Since MCPBA solid contains about 15–25% water for safety reasons, the solid is not homogeneous. Therefore, the manufacturer can provide only the average assay results of MCPBA. If MCPBA from different containers and different suppliers is used, an inaccurate charge of MCPBA will result. A novel analytical method has therefore been developed to quantify MCPBA in the charging solution in order to deliver an accurate amount of the oxidizing agent. According to the assay, an excess amount of 3-methylisoquinoline (III) is reacted with MCPBA in toluene/ethanol solution to form 3-methylisoquinoline N-oxide (IV), according to the equation:



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The reaction is fast and quantitative. The remaining tertiary amine in the reaction mixture is quantitated by reverse-phase high-performance liquid chromatography (RP-HPLC). The amount of the amine consumed during the reaction is used to calculate the concentration of the MCPBA solution.

It is also important that no excess oxidizing agent accumulate during addition of the reagent. This is best accomplished by subsurface addition of MCPBA, such that the solution enters the batch through a diptube located near and directed perpendicular to the agitator blades. This mode of addition provides for immediate dispersion of the oxidant, thus limiting localized over-oxidation.

Chemoselectivity and extent of oxidation are also enhanced by controlling the reaction temperature without crystallization of the oxidizing agent. The optimum temperature range is about 0–5° C. for the solution of the oxidizing agent and about –5 to +5° C. for the reaction mixture throughout the addition process. Higher temperatures of either the MCPBA solution or the reaction mixture will result in some sulfone formation. Likewise, much lower temperatures temporarily suppress the oxidation reaction, which results in a localized accumulation of the oxidizing agent that can lead to over-oxidation products.

After addition of the solution containing the oxidizing agent, aqueous base, for example 50% NaOH or KOH, is added, the solution allowed to age for about 0.5–1.0 hours at 0–5° C., and the aqueous phase separated from the organic phase. To minimize residual levels of the non-alcoholic organic reaction solvent, in particular toluene or methylene chloride, in the crude product, which translates into higher levels of volatile non-alcoholic organic reaction solvent in the pure product, it is important to remove as much entrained toluene or methylene chloride as possible from the crude aqueous phase. The source of residual toluene or methylene chloride is an emulsion that forms when the crude batch is extracted from toluene or methylene chloride with aqueous base. Removal of residual solvent may be accomplished by vacuum distillation of the aqueous phase at a pressure of about 25–70 mm Hg and temperature of about 15–35° C. for about 1–4 hours. In further exemplification, the distillation is carried out at about 50 mm Hg and about 15° C. for 2 hours. The vacuum distillation procedure reduces the pre-crystallization levels of toluene or methylene chloride to less than 400 p.p.m. Other options to break up the emulsion and effect better phase separation are less effective; these include filtration of the crude aqueous phase through a bed of Celite™, increasing the settling time, and addition of a strong electrolyte.

Since the distillation process also results in removal of the alcohol, in particular ethanol, its concentration must be re-adjusted to approximately 15%, in order to facilitate crystal growth during the crude crystallization process. A lower level of the alcoholic solvent, in particular ethanol, produces finer crystals which are more likely to dissolve during subsequent washes thereby diminishing yields of the crude product.

At this point, the reactive crystallization of omeprazole is initiated and maintained under controlled conditions. Approximately 40% of a C₁₋₃-alkyl formate charge, prefer-

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ably methyl formate, is added over the first 30 minutes to bring the batch from a pH of about 13.5 to near supersaturation at a pH of about 10.6 to 10.8. The methyl formate addition is accomplished through a diptube which is narrowed at one end to create a fine stream and which is located near and perpendicular to the impeller tip. This technique ensures rapid dispersion of the methyl formate so that occlusion of impurities is minimized. When a pH of about 10.6–10.8 is attained, the methyl formate addition is discontinued, and the batch is aged for ten to twenty minutes to allow the temperature to cool to approximately 20° C. prior to seeding. It is important to seed between pH 10.6 and 10.8. Below 10.6 spontaneous nucleation will occur with little crystal growth, if a sufficient seed bed is not present. Seeding is effected with pure, milled omeprazole (100% by HPLC), and the rest of the methyl formate is added subsurface over 6–8 hours to adjust the pH to about 9.0–9.3. This crystallization procedure improves both the yield and purity of the product. Without being held to a specific mechanism, it is believed that the purity enhancement is mainly due to preventing occlusion of mother liquors by promoting crystal growth over nucleation. Crude omeprazole at this stage contains less than 100 p.p.m. of residual toluene or methylene chloride, as determined by gas-liquid chromatographic analysis.

The crude crystallized product is then filtered, washed with 0.01–1.0%, preferably 0.1%, ammonia-water, and then methanol.

The crude wet omeprazole is then purified by dissolving it in 2:1–0.5–1 (v/v) methanol-water solution containing aqueous base, preferably 50% NaOH or KOH, at 20° C., cooling the basic solution to about 0–5° C., reducing the pH from >11.0 to approximately 10.5 by subsurface addition through a narrowed end diptube (configuration of apparatus same as in crude isolation step) of aqueous acetic acid, preferably 25% aqueous acetic acid, over a 30-minute period, while maintaining the temperature at 0–5° C. At this point the batch is seeded with pure omeprazole (100% by HPLC), and the subsurface addition of 25% aqueous acetic acid is continued over a 2–4 hour period until a pH of about 9.0 is attained. The batch is then aged for 0.5–1.0, preferably 0.5, hours. Following the aging period, the product is filtered, washed with the same methanol-water mixture to displace the mother liquors containing the impurities, and finally with cold methanol. Pure omeprazole is obtained after vacuum drying with a nitrogen purge at 30–50 mm Hg and 30–35° C.

The optimal methanol-water ratio in this final purification step is 1:1. Previous methods used a higher methanol to water ratio. Lowering the proportion of methanol in the solvent mixture used in the displacement wash minimizes solubility losses and provides the purification demands, thereby improving the yield of the final product without compromising product quality.

Crystalline omeprazole obtained using the improved process of the instant invention has an HPLC purity of 100% with no detectable levels of entrained residual toluene or methylene chloride from the crude step as measured by gas-liquid chromatography, the detection limit being 3 p.p.m. Prior methods have afforded omeprazole containing 30–100 p.p.m. of residual non-alcoholic organic reaction solvent, namely toluene or methylene chloride. The pure product contains less than 20 p.p.m. of residual methanol as the crystallization solvent.

For the preparation of pharmaceutical compositions in the form of dosage units for oral administration, omeprazole prepared according to the process of the present invention

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may be mixed with a solid, pulverulent carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives or gelatin, as well as an antifriction agent such as magnesium stearate, calcium stearate, and polyethyleneglycol waxes. The mixture is then pressed into tablets. If coated tablets are desired, the above-prepared core may be coated with a concentrated solution of sugar, which may contain gum arabic, gelatin, talc, titanium dioxide, or with a lacquer dissolved in volatile organic solvent or mixture of solvents. To this coating various dyes may be added in order to distinguish among tablets with different amounts of active compound present.

Soft gelatin capsules may be prepared which contain a mixture of pure omeprazole prepared according to the process of the present invention and vegetable oil. Hard gelatin capsules may contain granules of the active compound in combination with a solid, pulverulent carrier, such as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives, or gelatin.

Pharmaceutical tablets for oral use are prepared in the following manner. The solid substances are ground or sieved to a certain particle size, and the binding agent is homogenized and suspended in a suitable solvent. The solid omeprazole prepared according to the process of the present invention and auxiliary agents are mixed with the binding agent solution. The resulting mixture is moistened to form a uniform suspension having the consistency of wet snow. The moistening causes the particles to aggregate slightly, and the resulting mass is pressed through a stainless steel sieve having a mesh size of about 1 millimeter. The layers of the mixture are dried in carefully controlled drying cabinets for approximately ten hours to obtain the desired particle size and consistency. The granules of the dried mixture are sieved to remove any powder. To this mixture, disintegrating, antifriction, and antiadhesive agents are added. Finally, the mixture is pressed into tablets using a machine with the appropriate punches and dies to obtain the desired tablet size. The pressure applied affects the size of the tablet, its strength and ability to dissolve in water. The compression pressure used should be in the range of 0.5 to 5 tons. The tablets, especially those which are rough or bitter, may be coated with a layer of sugar or some other palatable substance. They are then packaged by machines having electronic counting devices.

The following examples illustrate the process of the present invention and are not intended to limit the scope of the invention set forth in the claims appended thereto.

EXAMPLE 1

HPLC Assay of MCPBA Charging Solution

Step A. HPLC Operating Parameters

High-performance liquid chromatography was performed using a Waters μ Bondapak C-18 column (4.6x300 mm, 10 μ m particle size) with the following additional parameters:

Mobile phase: A=acetonitrile; B=0.1% H_3PO_4

Mode: isocratic 25%A/75%B at a flow rate of 1.0 mL/min

Injection size: 10 μ L

Detector wavelength: 254 nm

Run time: 32 min.

Method of quantitation: Area by electronic integration

Approximate retention times:

3-methylisoquinoline: 3.5 mins.

3-methylisoquinoline N-oxide: 5.7 mins.

MCPBA: 11.4 mins.

Toluene: 25.1 mins.

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Step B. Reagents

Acetonitrile (MeCN): HPLC Grade

Water: HPLC Grade

Phosphoric Acid: HPLC Grade

3-Methylisoquinoline: 98%

Sample Diluent: 50/50 (MeCN/0.1% H_3PO_4)

Step C. Preparation of 3-Methylisoquinoline Standard

20 \pm 5 mg of 3-methylisoquinoline (98%) was transferred into a 10 mL volumetric flask and dissolved in 1.0 mL of MeCN. 1.0 mL of MCPBA after warming to room temperature was carefully pipetted into the flask, and the sides of the flask were washed with 1.0 mL of MeCN. The flask was then wrapped with parafilm and sonicated for 5 minutes. After cooling, the sides of the flask were washed with 1.0 mL of MeCN and the flask sonicated for an additional minute. The mixture was carefully diluted to the mark with acetonitrile. 1.0 mL of this solution was transferred by pipet to a 25-mL volumetric flask and diluted to the mark with the sample diluent from Step B.

Step D. Procedures

The HPLC system was equilibrated for at least 10 minutes at the mobile phase condition given in Step A. The standard preparation from Step C was injected twice, and the average area response for the 3-methylisoquinoline peaks should agree within $\pm 1\%$ of their average. The sample preparation was injected once.

Step E. Calculations

The concentration (mg/mL) of the MCPBA solution was calculated using the following equation:

$$\text{mg/mL of MCPBA solution} = (w - (A / A_s) \times C_s \times 250) \times \frac{172.57}{143.19}$$

where:

A=area response of the 3-methylisoquinoline for the Sample Solution

B=weight (mg) of the 3-methylisoquinoline in the Sample Preparation

As=average area response of the 3-methylisoquinoline for the Standard Solution

Cs=concentration of the 3-methylisoquinoline Standard Preparation

172.57=formula weight for 3-methylisoquinoline

143.19=formula weight for MCPBA

As an illustration of the assay, an MCPBA sample from Spectrum (Lot# LF0102, 72.7% MCPBA) was assayed, and a value of 72.8% (wt.%) for MCPBA was obtained.

EXAMPLE 2

Preparation of Omeprazole with Methylene Chloride as Solvent

A solution of potassium bicarbonate (14.0 g, 0.140 mol, 1.2 equivalents) in deionized water (115 mL) was added to a solution of pyrimetazole (0.114 mol) in methylene chloride (170 mL) in a one-liter, three-necked round-bottom flask, and the mixture was cooled to 0° C. A solution of meta-chloroperoxybenzoic acid (MCPBA) (28 g, 0.114 mol, 1.0 equivalent) in methylene chloride (51 mL) and ethanol (13.3 mL) was prepared and assayed by the 3-methylisoquinoline/HPLC procedure described in Example 1 to ensure that exactly one molar equivalent of MCPBA is used. The solution is then cooled between 0–5° C. and added, subsonically directed at the tip of the impeller, to the rapidly agitated solution of pyrimetazole over a 2-hour period. The

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oxidation conversion was 99.8% with no over-oxidation to sulfone or N-oxides, as determined by HPLC analysis. Cold deionized water (115 mL, 5° C.) and 50% NaOH (15 mL) were then added to the reaction mixture. The solution was allowed to stand at 0–5° C. for thirty minutes and the phases separated. The methylene chloride layer was discarded and the aqueous layer concentrated under vacuum (50 mm Hg) for 2 hours at 15° C. to remove the bulk of the residual methylene chloride. The ethanol level was then re-adjusted to 15% v/v. At this point the residual methylene chloride level was less than 200 p.p.m., as determined by gas-liquid chromatographic analysis.

The crude product was then isolated by reactive crystallization by subsurface addition of methyl formate. Approximately 40% of the methyl formate charge (approximately 6 mL) was added during the first thirty minutes to adjust the pH from about 13.5 to 10.8. The mixture was allowed to stand for about twenty minutes to allow the internal temperature to cool back down to approximately 20° C. The mixture was seeded with pure omeprazole (0.5 g), and the remainder of the methyl formate (approximately 9 mL) was added subsurface over a 7-hour period to a pH of 9.0. The crude product was filtered, washed with 0.1% ammonia-water (50 mL) followed by methanol (40 mL).

The crude product was dissolved in 1:1 methanol-water (270 mL) and 50% NaOH (4 mL) in a 500-mL, three-necked, round-bottomed flask at 20° C. The solution was then cooled to 0–5° C. and the pH adjusted from >11.0 to approximately 10.5 by subsurface addition of 25% acetic acid over a 30-minute period, maintaining the temperature at 5° C. The batch was seeded with pure omeprazole (0.5 g), and the subsurface addition of 25% acetic acid was continued over a 4-hour period until pH 9.0 was achieved. After thirty minutes, the resulting solid was filtered, washed with 1:1 methanol-water (30 mL), and finally with cold (5° C.) methanol (30 mL). Pure omeprazole (100% as determined by HPLC analysis) was obtained after vacuum drying (50 mm Hg, 30–35° C.). The overall yield was 92.7%. The residual methanol level was 10 ppm, as determined by gas-liquid chromatography, with no detectable levels of methylene chloride (detection limit of 3 p.p.m.).

EXAMPLE 3

Preparation of Omeprazole with Toluene as Solvent

A solution of potassium bicarbonate (14.0 g, 0.140 mol, 1.2 equivalents) in deionized water (115 mL) was added to a solution of pyrimetazole (0.114 mol) in toluene (310 mL) in a one-liter, three-necked round-bottom flask, and the mixture was cooled to 0° C. Following the bicarbonate addition, a solution of meta-chloroperoxybenzoic acid (0.114 mol, 1 equivalent) in toluene (53 mL) and ethanol (20 mL) was assayed and charged to the pyrimetazole solution as in Example 2. The oxidation conversion was 99.8% with no over-oxidation to sulfone or N-oxides. Cold deionized water (145 mL, 5° C.) and 50% NaOH (12 mL) were then added to the reaction mixture. The solution was allowed to stand at 0–5° C. for thirty minutes and the phases separated. The toluene layer was discarded and the aqueous layer concentrated under vacuum (50 mm Hg) for 2 hours at 15° C. to remove the bulk of the residual toluene. The ethanol level was then adjusted to 15% v/v. At this point the residual toluene level was less than 400 p.p.m., as determined by gas-liquid chromatographic analysis.

The crude product was then isolated by reactive crystallization by subsurface addition of methyl formate as in

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Example 2. It was filtered, washed with 0.1% ammonia-water (50 mL) followed by methanol (40 mL). The wet crude product was then processed to pure omeprazole as in Example 2. The overall yield was 93.8% with an HPLC purity of 100%. The residual methanol level was 10 ppm, as determined by gas-liquid chromatography, with no detectable levels of toluene (detection limit 3 p.p.m.).

EXAMPLE 4

A pharmaceutical composition containing omeprazole prepared according to the process of the present invention as the active ingredient is illustrated in the following formulation.

Capsules containing 30 mg of omeprazole of the present invention were prepared from the following ingredients:

Compound of Example 2 or 3	300 grams
Lactose	700 grams
Microcrystalline cellulose	40 grams
Hydroxypropyl cellulose, low-substituted	62 grams
Disodium hydrogenphosphate	2 grams
Purified water	q.s.

The omeprazole of Example 2 or 3 was mixed with the dry ingredients and granulated with a solution of disodium hydrogenphosphate. The wet mass was forced through an extruder and spheronized and dried in a fluidized bed dryer.

500 Grams of the pellets were coated with a solution of hydroxypropyl methylcellulose (30 grams) in water (750 mL) using a fluidized bed coater. After drying, the pellets were coated with a second coating as follows:

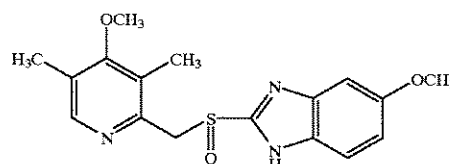
Coating Solution:

Hydroxypropyl methylcellulose phthalate	70 grams
Cetyl alcohol	4 grams
Acetone	200 grams
Ethanol	600 grams

The final coated pellets were filled into capsules.

What is claimed is:

1. A process for the preparation of omeprazole, having the formula I,

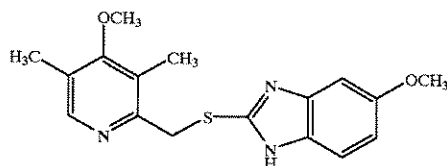


which comprises:

(a) treating, at about –5 to +5° C., a buffered solution of pyrimetazole, having the formula II, in a non-alcoholic organic

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reaction solvent, with one equivalent, relative to the number of moles of said pyrimetazole, of meta-chloroperoxybenzoic dissolved in the non-alcoholic organic reaction solvent in admixture with an alcoholic solvent at about 0–5° C. followed by aging in the presence of an aqueous base;

(b) separating the aqueous phase of the aged reaction mixture from the organic phase; and

(c) removing residual non-alcoholic organic reaction solvent from said aqueous phase followed by re-adjusting the alcoholic solvent concentration to about 15% v/v.

2. The process according to claim 1 wherein the alcoholic solvent is selected from methanol, ethanol, isopropanol, and 1-butanol.

3. The process according to claim 2 wherein the alcoholic solvent is ethanol.

4. The process according to claim 1 which further comprises:

(a) crystallizing crude product from said aqueous phase by subsurface addition of a C₁₋₃ alkyl formate to adjust the pH from about 13.5 to about 10.6–10.8, aging for about 10–20 minutes, allowing the temperature to reach about 20° C., seeding, and adding remainder of said alkyl formate over 6–8 hours to adjust the pH to about 9.0–9.3; and

(b) isolating crude product by filtration and washing with ammonia-water and methanol.

5. The process according to claim 4 which further comprises:

(a) recrystallizing crude product in methanol-water containing aqueous sodium hydroxide by cooling to about 0–5° C., adjusting the pH to about 10.5 by subsurface addition of 25% aqueous acetic acid, seeding, adding 25% aqueous acetic acid to a pH of about 9.0, and aging for about 0.5 hours; and

(b) isolating pure product by filtration, washing with methanol-water and cold methanol, and vacuum drying.

6. The process according to claim 1 wherein residual non-alcoholic organic reaction solvent is removed from the aqueous phase by vacuum distillation at about 25–70 mm Hg and about 15–35° C. for about 1–4 hours.

7. The process according to claim 1 wherein the non-alcoholic organic reaction solvent is selected from an aromatic hydrocarbon solvent and a chlorinated aliphatic hydrocarbon solvent.

8. The process according to claim 7 wherein the aromatic hydrocarbon solvent is toluene.

9. The process according to claim 7 wherein the chlorinated aliphatic hydrocarbon solvent is selected from methylene chloride, 1,2-dichloroethane, and chloroform.

10. The process according to claim 9 wherein the chlorinated aliphatic hydrocarbon solvent is methylene chloride.

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11. The process according to claim 1 wherein the aging is allowed to proceed at about 0–5° C. for about 0.5–1.0 hours.

12. The process according to claim 1 wherein the buffer comprises aqueous sodium bicarbonate or aqueous potassium bicarbonate.

13. The process according to claim 1 wherein the aqueous base comprises aqueous sodium hydroxide or aqueous potassium hydroxide.

14. The process according to claim 4 wherein the C₁₋₃ alkyl formate in Step (a) is methyl formate.

15. The process according to claim 5 wherein the volume ratio of methanol to water in Steps (a) and (b) is 2:1 to 0.5–1.

16. The process according to claim 15 wherein the volume ratio of methanol to water is 1:1.

17. The process according to claim 6 wherein the vacuum distillation is performed at a pressure of about 50 mm Hg and a temperature of about 15–25° C.

18. The process according to claim 4 wherein the concentration of ammonia-water in Step (b) is 0.01–1.0%(v/v).

19. The process according to claim 18 wherein the concentration of ammonia-water is 0.1%(v/v).

20. The process according to claim 1 wherein the molar amount of oxidizing agent to be added to said pyrimetazole solution is calculated by means of a high-performance liquid chromatographic assay which quantifies the extent of oxidation of an excess of 3-methylisoquinoline to 3-methylisoquinoline-N-oxide.

21. The process according to claim 1 wherein the oxidizing agent is added subsurface such that the solution enters the reaction mixture at the tip of the agitator blades.

22. 5-Methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (omeprazole) obtained by the process of claim 5 containing less than 100 parts per million of residual aromatic hydrocarbon solvent.

23. 5-Methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (omeprazole) obtained by the process of claim 5 containing less than 100 parts per million of residual chlorinated aliphatic hydrocarbon solvent.

24. 5-Methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (omeprazole) according to claim 22 wherein the aromatic hydrocarbon solvent is toluene.

25. 5-Methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (omeprazole) according to claim 23 wherein the chlorinated aliphatic hydrocarbon solvent is methylene chloride.

26. 5-Methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (omeprazole) containing less than three parts per million of residual aromatic hydrocarbon solvent and 10–20 p.p.m. of residual methanol.

27. 5-Methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (omeprazole) containing less than three parts per million of residual chlorinated aliphatic hydrocarbon solvent and 10–20 p.p.m. of residual methanol.

28. 5-Methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (omeprazole) according to claim 26 wherein the aromatic hydrocarbon solvent is toluene.

29. 5-Methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (omeprazole) according to claim 27 wherein the chlorinated aliphatic hydrocarbon solvent is methylene chloride.

* * * * *

EXHIBIT E



US006191148B1

(12) **United States Patent**
McManus et al.

(10) **Patent No.:** **US 6,191,148 B1**

(45) **Date of Patent:** **Feb. 20, 2001**

(54) **OMERAZOLE PROCESS AND COMPOSITIONS THEREOF**

(75) Inventors: **James W. McManus; Nick Anousis; Benjamin Newton Banks**, all of Albany, GA (US); **Hui Liu**, Greenbrook; **Lingwen Zhou**, North Brunswick, both of NJ (US)

(73) Assignee: **Merck & Co., Inc.**, Rahway, NJ (US)

(*) Notice: Under 35 U.S.C. 154(b), the term of this patent shall be extended for 0 days.

(21) Appl. No.: **09/461,605**

(22) Filed: **Dec. 15, 1999**

Related U.S. Application Data

(63) Continuation-in-part of application No. 09/169,231, filed on Oct. 9, 1998.

(60) Provisional application No. 60/096,037, filed on Aug. 11, 1998.

(51) **Int. Cl.⁷** **A61K 31/4439; C07D 401/12**

(52) **U.S. Cl.** **514/341; 546/273.7**

(58) **Field of Search** **546/273.7; 514/341**

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Primary Examiner—Patricia L. Morris

(74) *Attorney, Agent, or Firm*—Philippe L. Durette; Melvin Winokur

(57) **ABSTRACT**

The present invention describes an improved process for the preparation, isolation, and purification of the anti-ulcer agent omeprazole whereby the sulfide precursor pyrimetazole is reacted subsurface with exactly one molar equivalent of meta-chloroperoxybenzoic acid in a chlorinated aliphatic hydrocarbon or aromatic hydrocarbon solvent, such as methylene chloride or toluene; residual organic solvent is removed from the aqueous layer by vacuum distillation; crude product is obtained by reactive crystallization with an alkyl formate or formic acid solution and seeding; and pure product is isolated by recrystallization in methanol-water containing aqueous NaOH by subsurface addition of aqueous acetic acid to pH 9.0, seeding, filtration, washing, and drying. Omeprazole and compositions of omeprazole containing no chromatographically detectable levels of residual non-alcoholic organic reaction solvent and diminished levels of alcoholic solvent are also described.

16 Claims, No Drawings

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**OMERAZOLE PROCESS AND
COMPOSITIONS THEREOF****CROSS-REFERENCE TO RELATED
APPLICATIONS**

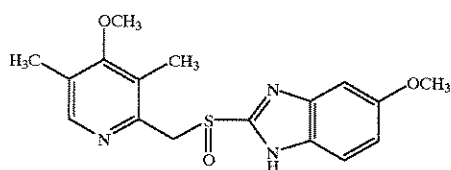
The present application is a continuation-in-part of application Ser. No. 09/169,231, filed Oct. 9, 1998, which is related to U.S. provisional application Serial No. 60/096,037, filed Aug. 11, 1998, the contents of both of which are hereby incorporated by reference.

FIELD OF THE INVENTION

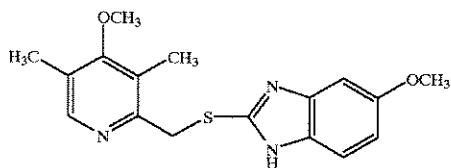
The present invention provides a novel improved process for the preparation, isolation, and purification of the anti-ulcer agent omeprazole. Omeprazole and compositions of omeprazole containing no chromatographically detectable levels of residual non-alcoholic organic reaction solvent and diminished levels of alcoholic solvent are also disclosed.

BACKGROUND OF THE INVENTION

Omeprazole, the generic name for 5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfonyl]-1H-benzimidazole (denoted as Formula I below) is a well-described gastric proton-pump inhibitor and is on the market as LOSEC® or PRILOSEC® for the treatment of gastric and duodenal ulcers, gastritis, duodenitis, and reflux esophagitis (see Merck Index, 12th Ed., entry 6977, and references cited therein). Omeprazole is commercially prepared via a multi-step sequence, the last step of which is oxidation of the sulfide intermediate, 5-methoxy-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole (denoted as Formula II below), known generically as pyrimetazole, which is typically effected with a peroxy acid, such as meta-chloroperoxybenzoic acid (hereinafter referred to as MCPBA) (U.S. Pat. Nos. 4,255,431; 5,386,032; and EPO 484,265), magnesium monoperoxyphthalate (MMPP) (U.S. Pat. No. 5,391,752), or peroxyacetic acid (WO 98/09962), in a suitable non-alcoholic organic reaction solvent.



(I)



(II)

Oxidants other than peroxyacids have also been used for the oxidation of pyrimetazole to omeprazole. EPO 302,720 utilizes aqueous hydrogen peroxide in the presence of a vanadium catalyst, Spanish application No. ES 550,070 discloses periodate as the oxidant, and Spanish applications No. ES 539,793 and ES 540,147 describe iodosobenzene and 3-methyliodosobenzene, respectively. A photooxidative method is disclosed in GB 2,239,453.

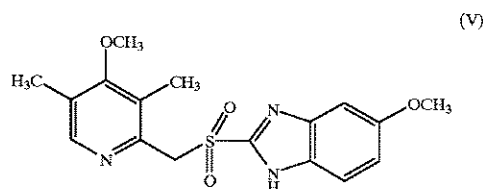
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Reduction of omeprazole-N-oxide to omeprazole is described in WO 98/40377 and WO 98/40378.

The preferred oxidizing agent is usually MCPBA, and suitable non-alcoholic organic reaction solvents include aromatic hydrocarbon solvents, such as benzene and toluene or a mixture thereof, and chlorinated aliphatic hydrocarbon solvents, such as chloroform, 1,2-dichloroethane, and methylene chloride or a mixture thereof, in admixture with an alcoholic solvent, such as methanol, ethanol, isopropanol, or 1-butanol. The preferred non-alcoholic organic reaction solvent is usually chloroform, methylene chloride, or toluene, and the preferred alcoholic solvent is ethanol.

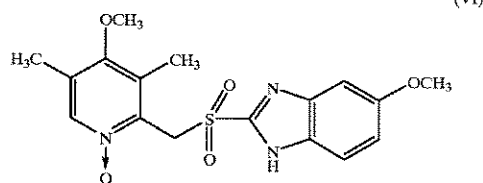
Prior processes to omeprazole have numerous disadvantages that limit both the yield and the purity of the final product.

A significant drawback of such prior methods is incomplete oxidative conversion of pyrimetazole into omeprazole as well as over-oxidation. Two such by-products of over-oxidation are the sulfone of structural formula V and the sulfone-N-oxide of structural formula VI. Incomplete and over-oxidation, characteristic of the previous methods, arise from ineffective control over the amount of the oxidizing agent as well as the manner in which the oxidizing agent is charged into the reaction vessel. Prior methods do not use accurately determined amounts of the oxidizing agent and do not provide for careful control of its addition to the reaction mixture. Incomplete and over-oxidation both contribute to the presence of impurities and loss of yield of the final desired product.



(V)

5-Methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfonyl]-1H-benzimidazole[sulfone]



(VI)

5-Methoxy-2-[[[(4-methoxy-3,5-dimethyl-1-oxo-2-pyridinyl)methyl]sulfonyl]-1H-benzimidazole [sulfone-N-oxide]

Another disadvantage of prior procedures is the considerable loss of product in the purification and isolation steps due to solubility of omeprazole in the mother liquors and solvent washes.

A further drawback concerns diminished product quality resulting from occlusion of residual solvents and reaction by-products during the crystallization steps. It is desirable to eliminate residual levels of organic reaction solvent and recrystallization solvent impurities in the final crystalline product for toxicity/safety reasons.

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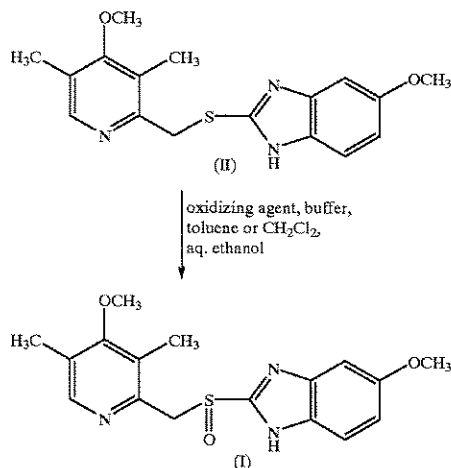
It is therefore an object of the present invention to provide an improved process for the preparation, purification, and isolation of omeprazole that overcomes the yield and product purity limitations of prior methods.

It is also an object of the invention to provide omeprazole and compositions of omeprazole having lower levels of residual non-alcoholic organic reaction solvent after the initial crude reactive crystallization step.

It is a further object of the present invention to provide omeprazole and compositions of omeprazole that contain no residual non-alcoholic organic reaction solvent within the limits of chromatographic detection and lower levels of residual alcoholic solvent.

SUMMARY OF THE INVENTION

The present invention provides an improved process for the preparation, purification, and isolation of omeprazole of the Formula 1. The last chemical transformation in the preparation of omeprazole is the oxidative conversion of the sulfide intermediate pyrmatazole of the Formula II into its sulfoxide derivative omeprazole of the Formula 1.



In one embodiment of the improved process, the oxidizing agent is meta-chloroperoxybenzoic acid (MCPBA), and the non-alcoholic organic reaction solvent is a chlorinated aliphatic hydrocarbon solvent or an aromatic hydrocarbon solvent in admixture with an alcoholic solvent, such as methanol, ethanol, isopropanol, or 1-butanol, in particular, ethanol. In a class of this embodiment, the chlorinated aliphatic hydrocarbon solvent is chloroform, 1,2-dichloroethane, or methylene chloride or a mixture thereof, and the aromatic hydrocarbon solvent is benzene or toluene or a mixture thereof. In a subclass of this class, the chlorinated aliphatic hydrocarbon solvent is methylene chloride, and the aromatic hydrocarbon solvent is toluene. In this embodiment, oxidative conversion of pyrmatazole to omeprazole has been optimized by careful control of the amount of MCPBA charged to the reaction vessel. The use of one molar equivalent of MCPBA relative to the number of moles of pyrmatazole minimizes over-oxidation to the sulfone V and sulfone-N-oxide VI, and incomplete reaction to give back pyrmatazole II, resulting in fewer impurities and higher yields. In another embodiment of the present invention, the concentration of MCPBA in the charging solution is calculated using a novel analytical method based upon MCPBA oxidation of 3-methylisoquinoline to its N-oxide derivative

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and subsequent HPLC quantitation. Without this assay there exists no practical way to avoid either over-oxidation or incomplete conversion of pyrmatazole into omeprazole.

In a further embodiment of the present invention, control over localized over-oxidation is achieved by subsurface addition of MCPBA, providing for entry of the oxidizing solution into the reaction vessel slightly above the agitator blades and directed perpendicular to the flow from the impeller, with simultaneous control of the reaction temperature. Incorporation of these novel features into the process ensures complete conversion of pyrmatazole into omeprazole with minimal formation of over-oxidized by-products V and VI.

In another embodiment of the present invention, the isolation of the crude product has been improved by vacuum distillation of the crude aqueous phase after extraction of the reaction mixture prior to crystallization to remove most of the entrained chlorinated aliphatic hydrocarbon solvent or aromatic hydrocarbon solvent from the oxidation step. The concentration of the alcoholic solvent, in particular ethanol, is then re-adjusted in order to promote good crystal growth during the crude crystallization step. The crystallization step involves a two-stage neutralization with a C₁₋₃ alkyl formate, preferably methyl formate, or a solution of formic acid in aqueous methanol or ethanol, which is added subsurface through a dip tube slightly above the agitator blades and directed perpendicular to the flow from the impeller. This mode of addition of the methyl formate or formic acid solution ensures rapid dispersion of the neutralizing agent, which promotes crystal growth over spontaneous nucleation. In so doing, occlusion of mother liquors in the crystals is minimized. Lowering the concentration of ammonia, relative to that used in prior procedures, in the ammonia-water wash, necessary to remove color impurities in the crude product, provides for further improvement in the yield of omeprazole.

A further embodiment of the present invention concerns the final purification step. A methanol-water mixture is used for the crystallization step which is initiated by subsurface addition of aqueous acetic acid and subsequent seeding with omeprazole. The same methanol-water mixture is employed as a displacement wash to remove mother liquors and dissolved impurities while suppressing solubility losses. In this fashion, significant yield improvements are obtained with no adverse impact on product quality.

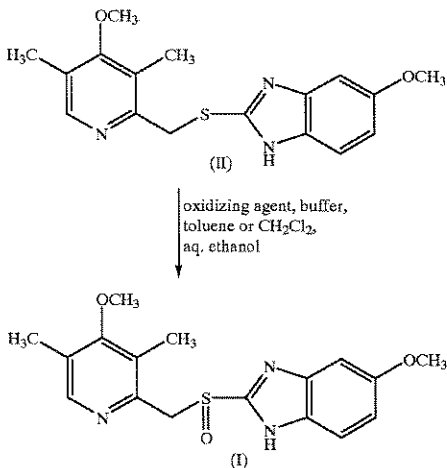
Crystalline omeprazole is thus obtained with significant improvement in yield and purity. The isolated material contains no chromatographically detectable levels of residual non-alcoholic organic reaction solvent and ethanol, and less than 30 p.p.m. of residual methanol.

DETAILED DESCRIPTION OF THE INVENTION

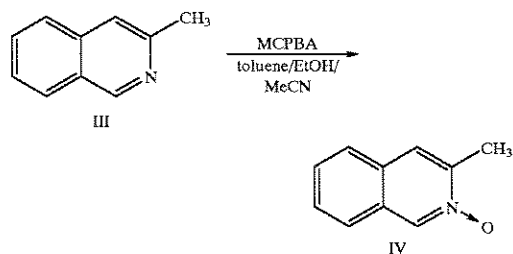
The instant invention relates to an improved process for the preparation, purification, and isolation of the proton-pump inhibitor omeprazole and to novel compositions thereof. Omeprazole, having formula I, is prepared by reacting a solution of pyrmatazole, having Formula II, cooled to about -5 to +5° C. and buffered to a pH of about 6 to 8, with one molar equivalent of an oxidizing agent, relative to the number of moles of pyrmatazole, dissolved in a non-alcoholic organic reaction solvent in admixture with an alcoholic solvent. The alcoholic solvent is selected from methanol, ethanol, isopropanol, and 1-butanol.

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In one embodiment of the instant improved process, the buffered solution comprises potassium bicarbonate, the oxidizing agent is meta-chloroperoxybenzoic acid, and the non-alcoholic organic reaction solvent is chloroform, methylene chloride, or a mixture thereof, or toluene, in admixture with ethanol. The reaction is carried out such that both the completeness and the extent of the oxidation are optimized. To force the reaction to proceed in a near quantitative fashion, it is necessary that any excess of the oxidizing agent, MCPBA, be minimized. Hence, the solution containing the oxidizing agent is accurately assayed so that an exact amount of reagent will be charged to the reaction vessel. In prior methods, the amount of MCPBA added was based on the commercial supplier's assay number. Since MCPBA solid contains about 15–25% water for safety reasons, the solid is not homogeneous. Therefore, the manufacturer can provide only the average assay results of MCPBA. If MCPBA from different containers and different suppliers is used, an inaccurate charge of MCPBA will result. A novel analytical method has therefore been developed to quantify MCPBA in the charging solution in order to deliver an accurate amount of the oxidizing agent. According to the assay, an excess amount of 3-methylisoquinoline (III) is reacted with MCPBA in toluene/ethanol solution to form 3-methylisoquinoline N-oxide (IV), according to the equation:



The reaction is fast and quantitative. The remaining tertiary amine in the reaction mixture is quantitated by reverse-phase high-performance liquid chromatography (RP-HPLC). The amount of the amine consumed during the reaction is used to calculate the concentration of the MCPBA solution.

It is also important that no excess oxidizing agent accumulate during addition of the reagent. This is best accom-

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plished by subsurface addition of MCPBA, such that the solution enters the batch through a dip tube slightly above the agitator blades and directed perpendicular to the flow from the impeller. This mode of addition provides for immediate dispersion of the oxidant, thus limiting localized over-oxidation.

Completeness and extent of oxidation are also enhanced by controlling the reaction temperature without crystallization of the oxidizing agent. The optimum temperature range is about 0–5° C. for the solution of the oxidizing agent and about –5 to +5° C. for the reaction mixture throughout the addition process. Higher temperatures of either the MCPBA solution or the reaction mixture will result in some formation of sulfone V and sulfone-N-oxide VI. Likewise, much lower temperatures temporarily suppress the oxidation reaction, which results in a localized accumulation of the oxidizing agent that can lead to over-oxidation products.

After addition of the solution containing the oxidizing agent, aqueous base, for example 50% NaOH or KOH, is added, the solution allowed to age for about 0.5–1.0 hours at 0–5° C., and the aqueous phase separated from the organic phase. To minimize residual levels of the non-alcoholic organic reaction solvent, in particular toluene, chloroform, or methylene chloride, in the crude product, which translates into higher levels of volatile non-alcoholic organic reaction solvent in the pure product, it is important to remove as much entrained toluene, chloroform, or methylene chloride as possible from the crude aqueous phase. The source of residual toluene, chloroform, or methylene chloride is an emulsion that forms when the crude batch is extracted from toluene, chloroform, or methylene chloride with aqueous base. Removal of residual solvent may be accomplished by vacuum distillation of the aqueous phase at a pressure of about 25–70 mm Hg and temperature of about 15–35° C. for about 1–4 hours. In further exemplification, the distillation is carried out at about 50 mm Hg and about 15° C. for 2 hours. The vacuum distillation procedure reduces the pre-crystallization levels of toluene, chloroform, or methylene chloride to less than 400 p.p.m. Other options to break up the emulsion and effect better phase separation are less effective; these include filtration of the crude aqueous phase through a bed of Celite™, increasing the settling time, and addition of a strong electrolyte.

Since the distillation process also results in removal of the alcohol, in particular ethanol, its concentration must be re-adjusted to approximately 15%, in order to facilitate crystal growth during the crude crystallization process. A lower level of the alcoholic solvent, in particular ethanol, produces finer crystals which are more likely to dissolve during subsequent washes thereby diminishing yields of the crude product.

At this point, the reactive crystallization of omeprazole is initiated and maintained under controlled conditions. Approximately 40% of a C₁₋₃-alkyl formate charge, preferably methyl formate, is added over the first 30 minutes to bring the batch from a pH of about 13.5 to near supersaturation at a pH of about 10.6 to 10.8. The methyl formate addition is accomplished through a dip tube which is narrowed at one end to create a fine stream and located slightly above the agitator blades and directed perpendicular to the flow from the impeller. This technique ensures rapid dispersion of the methyl formate so that occlusion of impurities is minimized. When a pH of about 10.6–10.8 is attained, the methyl formate addition is discontinued, and the batch is aged for ten to twenty minutes to allow the temperature to cool to approximately 20° C. prior to seeding. It is important to seed between pH 10.6 and 10.8. Below 10.6 spontaneous

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nucleation will occur with little crystal growth, if a sufficient seed bed is not present. Seeding is effected with pure, milled omeprazole (100% by HPLC), and the rest of the methyl formate is added subsurface over 6–8 hours to adjust the pH to about 9.0–9.3. This crystallization procedure improves both the yield and purity of the product. Without being held to a specific mechanism, it is believed that the purity enhancement is mainly due to preventing occlusion of mother liquors by promoting crystal growth over nucleation. Crude omeprazole at this stage contains less than 100 p.p.m. of residual toluene, chloroform, or methylene chloride, as determined by gas-liquid chromatographic analysis.

Reactive crystallization of crude omeprazole may also be carried out by neutralization of the aqueous basic solution of omeprazole with a solution of formic acid in aqueous methanol or ethanol, preferably a solution of 20% (v/v) formic acid in about 25% aqueous methanol, which is added in a subsurface manner as described in the previous paragraph. Enough formic acid solution is added in this fashion to adjust the pH from about 13.5 to near supersaturation at a pH of about 10.6 to 10.8. At this stage, seeding is effected with pure, milled omeprazole (100% by HPLC), and the rest of the formic acid solution is added subsurface over 6–8 hours to adjust the pH to about 9.0–9.3. This alternative neutralization procedure with formic acid solution in place of methyl formate produces crude crystalline omeprazole with larger, more uniform crystals. The average particle size of the omeprazole crystals obtained with formic acid neutralization is approximately 280 μm as contrasted to an average particle size of 180 μm obtained with methyl formate neutralization. The larger particle size translates into more efficient centrifugation or filtration leading to significantly enhanced productivity on a production scale.

The crude crystallized product is then filtered, washed with 0.01–1.0%, preferably 0.1%, ammonia-water, and then methanol.

The crude wet omeprazole is then purified by dissolving it in 2:1–0.5-(v/v) methanol-water solution containing aqueous base, preferably 50% NaOH or KOH, at 20° C., cooling the basic solution to about 0–5° C., reducing the pH from >11.0 to approximately 10.5 by subsurface addition through a narrowed end diptube (configuration of apparatus same as in crude isolation step) of aqueous acetic acid, preferably 25% aqueous acetic acid, over a 30-minute period, while maintaining the temperature at 0–5° C. At this point the batch is seeded with pure omeprazole (100% by HPLC), and the subsurface addition of 25% aqueous acetic acid is continued over a 2–4 hour period until a pH of about 9.0 is attained. The batch is then aged for 0.5–1.0, preferably 0.5 hours. Following the aging period, the product is filtered, washed with the same methanol-water mixture to displace the mother liquors containing the impurities, and finally with cold methanol. Pure omeprazole is obtained after vacuum drying with a nitrogen purge at 30–50 mm Hg and 30–35° C.

In one embodiment of the present invention, the methanol-water ratio in this final purification step is 1:1. Previous methods used a higher methanol to water ratio. Lowering the proportion of methanol in the solvent mixture used in the displacement wash minimizes solubility losses and provides the purification demands, thereby improving the yield of the final product without compromising product quality.

Crystalline omeprazole obtained using the improved process of the instant invention has an HPLC purity of greater than 99.94% (area percentage) with no detectable levels of residual toluene, chloroform, or methylene chloride, or a

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mixture thereof, entrained from the crude step as measured by gas-liquid chromatography, the detection limit being 3 p.p.m. Prior methods have afforded omeprazole containing 30–100 p.p.m. of residual non-alcoholic organic reaction solvent, namely toluene, chloroform, or methylene chloride. The pure product also contains less than 30 p.p.m. of methanol and no detectable levels of ethanol as measured by gas-liquid chromatography, the detection limit being 3 p.p.m. In one embodiment of the present invention, none of 5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole(pyrmetazole); 5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfonyl]-1H-benzimidazole (sulfone V); and 5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-1-oxo-2-pyridinyl)methyl]sulfonyl]-1H-benzimidazole(sulfone-N-oxide VI) is present to an extent greater than 0.04% .

For the preparation of pharmaceutical compositions in the form of dosage units for oral administration, omeprazole prepared according to the process of the present invention may be mixed with a solid, pulverulent carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives or gelatin, as well as an antifriction agent such as magnesium stearate, calcium stearate, and polyethyleneglycol waxes. The mixture is then pressed into tablets. If coated tablets are desired, the above-prepared core may be coated with a concentrated solution of sugar, which may contain gum arabic, gelatin, talc, titanium dioxide, or with a lacquer dissolved in volatile organic solvent or mixture of solvents. To this coating various dyes may be added in order to distinguish among tablets with different amounts of active compound present.

Soft gelatin capsules may be prepared which contain a mixture of pure omeprazole prepared according to the process of the present invention and vegetable oil. Hard gelatin capsules may contain granules of the active compound in combination with a solid, pulverulent carrier, such as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives, or gelatin.

Pharmaceutical tablets for oral use are prepared in the following manner. The solid substances are ground or sieved to a certain particle size, and the binding agent is homogenized and suspended in a suitable solvent. The solid omeprazole prepared according to the process of the present invention and auxiliary agents are mixed with the binding agent solution. The resulting mixture is moistened to form a uniform suspension having the consistency of wet snow. The moistening causes the particles to aggregate slightly, and the resulting mass is pressed through a stainless steel sieve having a mesh size of about 1 millimeter. The layers of the mixture are dried in carefully controlled drying cabinets for approximately ten hours to obtain the desired particle size and consistency. The granules of the dried mixture are sieved to remove any powder. To this mixture, disintegrating, antifriction, and antiadhesive agents are added. Finally, the mixture is pressed into tablets using a machine with the appropriate punches and dies to obtain the desired tablet size. The pressure applied affects the size of the tablet, its strength and ability to dissolve in water. The compression pressure used should be in the range of 0.5 to 5 tons. The tablets, especially those which are rough or bitter, may be coated with a layer of sugar or some other palatable substance. They are then packaged by machines having electronic counting devices.

The following examples illustrate the process of the present invention and are not intended to limit the scope of the invention set forth in the claims appended thereto.

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EXAMPLE 1

HPLC Assay of MCPBA Charging Solution

Step A

HPLC Operating Parameters

High-performance liquid chromatography was performed using a Waters μ Bondapak C-18 column (4.6x300 mm, 10 μ m particle size) with the following additional parameters:

Mobile phase: A=acetonitrile; B=0.1% H_3PO_4

Mode: isocratic 25% A/75% B at a flow rate of 1.0 mL/min

Injection size: 10 μ L

Detector wavelength: 254 nm

Run time: 32 min.

Method of quantitation: Area by electronic integration

Approximate retention times:

3-methylisoquinoline: 3.5 mins.

3-methylisoquinoline N-oxide: 5.7 mins.

MCPBA: 11.4 mins.

Toluene: 25.1 mins.

Step B

Reagents

Acetonitrile (MeCN): HPLC Grade

Water: HPLC Grade

Phosphoric Acid: HPLC Grade

3-Methylisoquinoline: 98%

Sample Diluent: 50/50 (MeCN/0.1% H_3PO_4)

Step C

Preparation of 3-Methylisoquinoline Standard

20 \pm 5 mg of 3-methylisoquinoline (98%) was transferred into a 10 mL volumetric flask and dissolved in 1.0 mL of MeCN. 1.0 mL of MCPBA after warming to room temperature was carefully pipetted into the flask, and the sides of the flask were washed with 1.0 mL of MeCN. The flask was then wrapped with parafilm and sonicated for 5 minutes. After cooling, the sides of the flask were washed with 1.0 mL of MeCN and the flask sonicated for an additional minute. The mixture was carefully diluted to the mark with acetonitrile. 1.0 mL of this solution was transferred by pipet to a 25-mL volumetric flask and diluted to the mark with the sample diluent from Step B.

Step D

Procedures

The HPLC system was equilibrated for at least 10 minutes at the mobile phase condition given in Step A. The standard preparation from Step C was injected twice, and the average area response for the 3-methylisoquinoline peaks should agree within $\pm 1\%$ of their average. The sample preparation was injected once.

Step E

Calculations

The concentration (mg/mL) of the MCPBA solution was calculated using, the following equation:

$$\text{mg/ml of MCPBA solution} = (B - (A/As) \times Cs \times 250) \times 172.57 / 143.19$$

where:

A=area response of the 3-methylisoquinoline for the Sample Solution

B=weight (mg) of the 3-methylisoquinoline in the Sample Preparation

As=average area response of the 3-methylisoquinoline for the Standard Solution

Cs=concentration of the 3-methylisoquinoline Standard Preparation

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172.57=formula weight for 3-methylisoquinoline

143.19=formula weight for MCPBA

As an illustration of the assay, an MCPBA sample from Spectrum (Lot# LF0102, 72.7% MCPBA) was assayed, and a value of 72.8% (wt. %) for MCPBA was obtained.

EXAMPLE 2

Preparation of Omeprazole With Methylene Chloride as Solvent

A solution of potassium bicarbonate (14.0 g, 0.140 mol, 1.2 equivalents) in deionized water (115 mL) was added to a solution of pyrimetazole (0.114 mol) in methylene chloride (170 mL) in a one-liter, three-necked round-bottom flask, and the mixture was cooled to 0° C. A solution of meta-chloroperoxybenzoic acid (MCPBA) (28 g, 0.114 mol, 1.0 equivalent) in methylene chloride (51 mL) and ethanol (13.3 mL) was prepared and assayed by the 3-methylisoquinoline/HPLC procedure described in Example 1 to ensure that exactly one molar equivalent of MCPBA is used. The solution is then cooled between 0–5° C. and added, subsurface directed at the tip of the impeller, to the rapidly agitated solution of pyrimetazole over a 2-hour period. The oxidation conversion was 99.8% with no over-oxidation to sulfone or N-oxides, as determined by HPLC analysis. Cold deionized water (115 mL, 5° C.) and 50% NaOH (15 mL) were then added to the reaction mixture. The solution was allowed to stand at 0–5° C. for thirty minutes and the phases separated. The methylene chloride layer was discarded and the aqueous layer concentrated under vacuum (50 mm Hg) for 2 hours at 15° C. to remove the bulk of the residual methylene chloride. The ethanol level was then re-adjusted to 15% v/v. At this point the residual methylene chloride level was less than 200 p.p.m., as determined by gas-liquid chromatographic analysis.

The crude product was then isolated by reactive crystallization by subsurface addition of methyl formate. Approximately 40% of the methyl formate charge (approximately 6 mL) was added during the first thirty minutes to adjust the pH from about 13.5 to 10.8. The mixture was allowed to stand for about twenty minutes to allow the internal temperature to cool back down to approximately 20° C. The mixture was seeded with pure omeprazole (0.5 g), and the remainder of the methyl formate (approximately 9 mL) was added subsurface over a 7-hour period to a pH of 9.0. The crude product was filtered, washed with 0.1% ammonia-water (50 mL) followed by methanol (40 mL).

The crude product was dissolved in 1:1 methanol-water (270 mL) and 50% NaOH (4 mL) in a 500-mL, three-necked, round-bottomed flask at 20° C. The solution was then cooled to 0–5° C. and the pH adjusted from >11.0 to approximately 10.5 by subsurface addition of 25% acetic acid over a 30-minute period, maintaining the temperature at 5° C. The batch was seeded with pure omeprazole (0.5 g), and the subsurface addition of 25% acetic acid was continued over a 4-hour period until pH 9.0 was achieved. After thirty minutes, the resulting solid was filtered, washed with 1:1 methanol-water (30 mL), and finally with cold (5° C.) methanol (30 mL). Omeprazole was obtained after vacuum drying (50 mm Hg, 30–35° C.). The overall yield was 92.7%. The residual methanol level was 10 ppm, as determined by gas-liquid chromatography, with no detectable levels of methylene chloride and ethanol (detection limit of 3 p.p.m.). The HPLC purity profile (area percentage) of the isolated omeprazole was found to be:

Omeprazole (I): 99.937

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Pyrimetazole (II): 0.022

Sulfone N-oxide (VI): 0.031

Sulfone (V): 0.010

using the following HPLC conditions:

Reagents and Solutions:

Methanol: HPLC Grade

Acetonitrile: HPLC Grade

Water: HPLC Grade

Disodium Hydrogen Phosphate (Na_2HPO_4 anhydrous):
HPLC GradeSodium Dihydrogen Phosphate ($\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$): HPLC
Grade0.5 M Disodium Hydrogen Phosphate (Na_2HPO_4
anhydrous) Solution—Dissolve 71.0 grams of Disodium
Hydrogen Phosphate in 1 liter of water.1.0 M Sodium Dihydrogen Phosphate ($\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$)
Solution—Dissolve 138.0 grams of Sodium Dihydrogen
Phosphate in 1 liter of water.pH 7.6 Phosphate Buffer Solution—Transfer 6.5 ml of the
1.0 M Sodium Dihydrogen Phosphate ($\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$)
solution and 79.0 ml of the 0.5 M Disodium Hydrogen
Phosphate (Na_2HPO_4 anhydrous) solution to a 5 liter (5000
ml) bottle and dilute to volume with water. Adjust pH to
7.6±0.1 with phosphoric acid if necessary. Note: If the pH is
not accurate, the retention time of the pyrimetazole will be
directly affected.

Sample Prep:

30–35 mg omeprazole is dissolved in 100 ml MeOH.
Chromatographic Conditions:

Column: Lichrospher RP 8.5, 5 micron, 12.5 cm × 4.0 mm.

Mobile Phase: A) MeCN and B) phosphate buffer (ionic
strength 0.025 at pH=7.6).

Mode: isocratic 30/70 A/B.

Flow rate: 1.5 mL/min.

Detector: photodiode array detector at 280 nm, bandwidth
32 nm, slit set to 16.

Run time: 20.0 mins.

Method of quantitation: Area by electronic integration.
Relative Retention Times:

Sulfone N-oxide (VI): 0.45 RRT

Sulfone (V): 0.65 RRT

Omeprazole (I): 1.00 RRT

Pyrimetazole (II): 3.67 RRT

EXAMPLE 3

Preparation of Omeprazole With Toluene as
Solvent

A solution of potassium bicarbonate (14.0 g, 0.140 mol, 1.2 equivalents) in deionized water (115 mL) was added to a solution of pyrimetazole (0.114 mol) in toluene (310 mL) in a one-liter, three-necked round-bottom flask, and the mixture was cooled to 0° C. Following the bicarbonate addition, a solution of meta-chloroperoxybenzoic acid (0.114 mol, 1 equivalent) in toluene (53 mL) and ethanol (20 mL) was assayed and charged to the pyrimetazole solution as in Example 2. The oxidation conversion was 99.8% with no over-oxidation to sulfone or N-oxides. Cold deionized water (145 mL, 5° C.) and 50% NaOH (12 mL) were then added to the reaction mixture. The solution was allowed to stand at 0–5° C. for thirty minutes and the phases separated. The toluene layer was discarded and the aqueous layer concentrated under vacuum (50 mm Hg) for 2 hours at 15° C. to

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remove the bulk of the residual toluene. The ethanol level was then adjusted to 15% v/v. At this point the residual toluene level was less than 400 p.p.m., as determined by gas-liquid chromatographic analysis.

The crude product was then isolated by reactive crystallization by subsurface addition of methyl formate as in Example 2. It was filtered, washed with 0.1% ammonia-water (50 mL) followed by methanol (40 mL). The wet crude product was then processed to pure omeprazole as in Example 2. The overall yield was 93.8%. The residual methanol level was 10 ppm, as determined by gas-liquid chromatography, with no detectable levels of toluene and ethanol (detection limit 3 p.p.m). The HPLC purity profile (area percentage) of the isolated omeprazole was determined using the HPLC conditions given in Example 2 and found to be as follows:

Omeprazole (I): 99.969

Pyrimetazole (II): 0

Sulfone N-oxide (VI): 0.021

Sulfone (V): 0.010

The HPLC purity profile of isolated omeprazole prepared according to the procedures of Examples 2, 3, or 4 in three additional separate experiments were as follows:

Omeprazole	Pyrimetazole	Sulfone	Sulfone-N-oxide
99.941	0.0268	0.0085	0.024
99.964	0.0076	0.0046	0.024
99.924	0.0229	0.0132	0.040

EXAMPLE 4

Isolation of Crude Omeprazole by Reactive
Crystallization With Formic Acid

The aqueous basic solution of omeprazole was prepared exactly as in Example 2 or 3 to the point of crystallization of the crude product. A solution of formic acid, methanol, and water in the ratio of 20:20:60 was then added to the aqueous solution of crude product in a subsurface manner at ambient temperature to effect crystallization. Approximately 40% of the formic acid solution was added over the first 30 minutes to adjust the pH from about 13.5 to about 10.8. The batch was then seeded with pure omeprazole (0.5 g), and the remainder of the formic acid solution was added subsurface over a seven-hour period to a pH of 9.0. The crude product was then filtered, washed with 0.1% ammonia-water (50 mL at 20° C.) followed by methanol (40 mL at 5° C.) and vacuum dried (50 mm Hg, 30–35° C.). The yield of the crude step was 95.4% with a purity of 99.9% (HPLC area percentage) and a median particle size of 285 μm .

EXAMPLE 5

A pharmaceutical composition containing omeprazole prepared according to the process of the present invention as the active ingredient is illustrated in the following formulation.

Capsules containing 30 mg of omeprazole of the present invention were prepared from the following ingredients:

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Compound of Example 2, 3, or 4	300 grams
Lactose	700 grams
Microcrystalline cellulose	40 grams
Hydroxypropyl cellulose, low-substituted	62 grams
Disodium hydrogenphosphate	2 grams
Purified water	q.s.

The omeprazole of Example 2, 3, or 4 was mixed with the dry ingredients and granulated with a solution of disodium hydrogenphosphate. The wet mass was forced through an extruder and spheronized and dried in a fluidized bed dryer. 500 Grams of the pellets were coated with a solution of hydroxypropyl methylcellulose (30 grams) in water (750 mL) using a fluidized bed coater. After drying, the pellets were coated with a second coating as follows:

Coating solution:

Hydroxypropyl methylcellulose phthalate	70 grams
Cetyl alcohol	4 grams
Acetone	200 grams
Ethanol	600 grams

The final coated pellets were filled into capsules.

What is claimed is:

1. 5-Methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole(omeprazole) of greater than 99.94% purity as determined by high-performance liquid chromatography and having less than 500 parts per million (p.p.m.) of residual ethanol relative to omeprazole.

2. Omeprazole according to claim 1 having less than 50 p.p.m. of residual ethanol relative to omeprazole.

3. Omeprazole according to claim 1 having less than 3 p.p.m. of residual ethanol relative to omeprazole.

4. Omeprazole according to claim 1 wherein none of 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole (pyrmetazole); 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfonyl]-1H-benzimidazole; and 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-1-oxo-2-pyridinyl)methyl]sulfonyl]-1H-benzimidazole is present to an extent greater than 0.04%.

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5. Omeprazole according to claim 1 further characterized by having less than 3 p.p.m. of residual chloroform or methylene chloride or a mixture thereof relative to omeprazole.

6. Omeprazole according to claim 5 further characterized by having less than 30 p.p.m. of residual methanol relative to omeprazole.

7. Omeprazole according to claim 1 further characterized by having less than 3 p.p.m. of residual toluene relative to omeprazole.

8. Omeprazole according to claim 7 further characterized by having less than 30 p.p.m. of residual methanol relative to omeprazole.

9. Omeprazole according to claim 6 containing less than 3 p.p.m. of residual chlorinated aliphatic hydrocarbon solvent relative to omeprazole.

10. Omeprazole according to claim 8 containing less than 3 p.p.m. of residual aromatic hydrocarbon solvent relative to omeprazole.

11. A composition comprising omeprazole according to claim 1.

12. The composition according to claim 11 wherein the omeprazole is further characterized by having less than 3 p.p.m. of residual toluene and less than 30 p.p.m. of residual methanol relative to omeprazole.

13. The composition according to claim 11 wherein the omeprazole is further characterized by having less than 3 p.p.m. of residual chloroform or methylene chloride or a mixture thereof and less than 30 p.p.m. of residual methanol relative to omeprazole.

14. A pharmaceutical composition comprising omeprazole according to claim 1 and a pharmaceutically acceptable excipient.

15. The pharmaceutical composition of claim 14 wherein the omeprazole is further characterized by having less than 3 p.p.m. of residual toluene and less than 30 p.p.m. of residual methanol relative to omeprazole.

16. The pharmaceutical composition of claim 14 wherein the omeprazole is further characterized by having less than 3 p.p.m. of residual chloroform or methylene chloride or a mixture thereof and less than 30 p.p.m. of residual methanol relative to omeprazole.

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