IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ASTRAZENECA AB, AKTIEBOLAGET HÄSSLE, KBI-E INC., KBI INC., and ASTRAZENECA LP,	)	
Plaintiffs,	)	
v.	)	C.A. No. 06-358-SLR
DEXCEL, LTD., DEXXON, LTD., DEXCEL PHARMA TECHNOLOGIES LTD., and CIPLA, LTD.,	)	
Defendants.	)	

AMENDED COMPLAINT

SUBJECT MATTER JURISDICTION AND VENUE

1. This is an action for patent infringement arising under the Patent and Food and Drug laws of the United States, Titles 35 and 21, United States Code. Jurisdiction and venue are based on 28 U.S.C. §§ 1331, 1338(a), 1391(b), 1391(c), 1400(b), 2201, 2202 and 35 U.S.C. § 271.

2. On information and belief, Dexcel, Ltd., Dexxon, Ltd., and Dexcel Pharma Technologies Ltd. (jointly and severally "DEXCEL") have infringed and are engaging in activities directed toward the further infringement of United States Patent Nos. 6,150,380 (the "'380 patent"); 4,786,505 (the "'505 patent"); and 4,853,230 (the "'230 patent"), by, *inter alia*, submitting a New Drug Application ("NDA") designated NDA No. 22-032 seeking approval from the United States Food and Drug Administration ("FDA") to commercially manufacture, use, and sell its proposed 20 mg omeprazole delayed-release tablets ("DEXCEL's Tablets").

3. In addition, on information and belief, Cipla, Ltd. ("CIPLA") has and will continue to aid, abet, induce, contribute to and otherwise participate in the infringement of said

patents by, inter alia, supplying the bulk omeprazole to be used as the active ingredient in DEXCEL's Tablets and has otherwise aided and abetted DEXCEL in the preparation and submission of the NDA and aided and abetted DEXCEL in its further preparations to commercialize DEXCEL's Tablets upon FDA approval of the NDA.

4. DEXCEL indicated in its notification letter dated April 17, 2006, entitled "Omeprazole Delayed Release Tablets, 20 mg" ("First Notice of Certification"), and in a supplemental letter of the same title dated May 4, 2006 ("Second Notice of Certification"), that it intends to market DEXCEL's Tablets before the expiration of the '380, '505, and '230 patents. The earliest such expiration occurs on April 20, 2007.

5. DEXCEL's submission of NDA No. 22-032, and its service of the First and Second Notices of Certification, indicates that DEXCEL intends to continue its current course of action. DEXCEL has alleged that approval by the FDA to market DEXCEL's Tablets is expected within the first quarter of 2007.

6. There has been and is now an actual, justiciable controversy between DEXCEL and CIPLA on the one hand, and Plaintiffs on the other hand, as to whether DEXCEL has infringed and will infringe the '380, '505, and '230 patents and as to whether CIPLA has and will continue to induce, contribute to, or otherwise aid and abet said infringement.

7. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§1331, 1338(a), 2201 and 2202.

8. Venue is proper in this Court pursuant to 28 U.S.C. §§1391(b), 1391(c), 1391(d) and 1400(b).

THE PARTIES AND PERSONAL JURISDICTION

9. Plaintiff AstraZeneca AB is a company organized and existing under the laws of Sweden, having its principal place of business at Södertälje, Sweden. AstraZeneca AB is the assignee of the '380 patent.

10. Plaintiff Aktiebolaget Hässle ("Hässle") is a company organized and existing under the laws of Sweden, having its principal place of business at Mölndal, Sweden. Hässle is the assignee of the '505 and '230 patents.

11. Plaintiff AstraZeneca LP is a limited partnership organized under the laws of Delaware, having its principal place of business at Wilmington, Delaware. AstraZeneca LP holds an approved NDA from the FDA for an omeprazole formulation which it sold under the name PRILOSEC®. AstraZeneca LP also holds an approved NDA from the FDA for an omeprazole formulation which is sold under the name PRILOSEC OTC®. AstraZeneca gives notice to the public that PRILOSEC® and PRILOSEC OTC® are protected by patents listed, inter alia, in the FDA Orange Book, by appropriately marking the patented products.

12. Plaintiff KBI Inc. ("KBI") is a Delaware corporation having its principal place of business at Whitehouse Station, New Jersey.

13. Plaintiff KBI-E Inc. ("KBI-E") is a Delaware corporation having its principal place of business at Wilmington, Delaware.

14. On information and belief, defendant Dexcel, Ltd. is an Israeli entity, having its headquarters and principal place of business at Southern Industrial Zone, Or Akiva, Israel 30600. On information and belief, Dexcel, Ltd. has developed, manufactures and distributes DEXCEL's Tablets through its affiliates.

15. On information and belief, defendant Dexxon, Ltd. is an Israeli entity, having its headquarters and principal place of business at Southern Industrial Zone, Or Akiva, Israel 30600. On information and belief, Dexxon, Ltd. has developed and manufactures DEXCEL's Tablets.

16. On information and belief, defendant Dexcel Pharma Technologies, Ltd. is an Israeli entity having a principal place of business at Southern Industrial Zone, Or Akiva, Israel, 30600. On information and belief, Dexcel Pharma Technologies, Inc. is the nominal owner and applicant of NDA No. 22-032.

17. On information and belief, defendant Cipla, Ltd. is an Indian entity having a place of business at Mumbai Central, Mumbai 400 008, India.

18. On information and belief, DEXCEL regularly does or solicits business in Delaware, has continuous and systematic contacts with Delaware, and through its various entities has engaged in activities related to the subject matter of this action and thus is subject to personal jurisdiction in this judicial district.

19. On information and belief, CIPLA is an alien corporation subject to service in any judicial district in the United States and is thus subject to personal jurisdiction in this judicial district. On information and belief, CIPLA has consented to personal jurisdiction in this district on at least one prior occasion.

FIRST CLAIM FOR RELIEF: '380 PATENT

20. AstraZeneca AB, Aktiebolaget Hässle, KBI, KBI-E and AstraZeneca LP (collectively, "Plaintiffs") reallege paragraphs 1-19, above, as if set forth specifically here.

21. The '380 patent (Exhibit A), entitled "Crystalline Form of Omeprazole", issued on November 21, 2000 to Astra Aktiebolag upon assignment from the inventors Karin Lövqvist, Gunnel Sundén, David Noreland, and Ingvar Ymén. The patent was subsequently assigned to AstraZeneca AB. The '380 patent claims, inter alia, a novel crystalline form of omeprazole, pharmaceutical compositions of this novel crystalline form of omeprazole, and methods of using omeprazole for the treatment of gastrointestinal disorders.

22. Plaintiff AstraZeneca AB has been and is still the owner of the '380 patent. The '380 patent will expire on November 10, 2018, and pediatric exclusivity relating to the '380 patent expires on May 10, 2019.

23. By the First Notice of Certification, DEXCEL notified Plaintiffs that it had submitted a NDA under 21 U.S.C. §355(b), seeking FDA approval to manufacture, use, and sell DEXCEL's Tablets and identifying 20 mg tablets of PRILOSEC OTC® and 10 mg, 20 mg, and 40 mg capsules of PRILOSEC® products in its NDA.

24. DEXCEL's First Notice of Certification fails to comply with the law, as specified in 21 U.S.C. § 355(b), and FDA rules and regulations, as specified in 21 C.F.R. § 314.52(c).

25. DEXCEL's First Notice of Certification does not allege and does not address non-infringement of claims 1-4 of the '380 patent. DEXCEL thus concedes that DEXCEL's Tablets meet all limitations of claims 1-4 of the '380 patent.

26. DEXCEL's First Notice of Certification does not address the validity or enforceability of claims 5 or 6 of the '380 patent. DEXCEL concedes that these claims are valid and enforceable.

27. DEXCEL has infringed the '380 patent under 35 U.S.C. § 271(e)(2) by filing its NDA, seeking approval from the FDA to engage in the commercial manufacture, use, or sale of a drug claimed in this patent, or the use of which is claimed in the this patent, prior to the expiration of the '380 patent.

28. On information and belief, DEXCEL's Tablets, if approved, will be administered to human patients in a therapeutically effective amount for the treatment of gastrointestinal disorders. On information and belief, this administration will occur at DEXCEL's active behest and with its intent, knowledge, and encouragement. On information and belief, DEXCEL will actively encourage, aid, and abet this administration with knowledge that it is in contravention of Plaintiffs' rights under the '380 patent.

29. On information and belief, DEXCEL's Tablets are especially made or especially adapted for use in the treatment of gastrointestinal disorders via the administration of a therapeutically effective amount of a pharmaceutical formulation containing the claimed omeprazole. On information and belief, DEXCEL is aware that DEXCEL's Tablets are so made or so adapted. On information and belief, DEXCEL is aware that DEXCEL's Tablets, if approved, will be used in contravention of Plaintiffs' rights under the '380 patent.

30. On information and belief, the manufacture, use and sale of DEXCEL's Tablets, if approved, will infringe one or more claims of the '380 patent.

31. CIPLA is jointly and severally liable for any infringement of the '380 patent. This is so because, upon information and belief, CIPLA participated in, contributed to,

aided, abetted, and/or induced the submission of NDA 22-032 by providing material information and physical product, including omeprazole product, to DEXCEL in connection with the preparation and submission of NDA 22-032, which information was relied upon and used by DEXCEL in the submission of NDA 22-032. If NDA 22-032 is approved by the United States Food & Frug Administration ("FDA"), the importation into the United States and commercial sale and offer for sale within the United States of DEXCEL's Tablets pursuant to NDA 22-032, and made using omperazole product supplied by CIPLA, will constitute infringement of the '380 patent.

32. In addition, on information and belief, CIPLA will, without authority, supply further material information and physical product, including omeprazole product, to DEXCEL for formulation into DEXCEL's Tablets for subsequent commercial importation into the United States, and commercial sale and offer for sale within the United States under NDA 22-032, in violation of the '380 patent.

33. By supplying further material information and physical product, including omeprazole product, to DEXCEL for formulation into DEXCEL's Tablets as stated above, CIPLA will knowingly and intentionally contribute to, aid, abet and/or induce the infringement of the '380 patent. Such acts constitute patent infringement under 35 U.S.C. §§271(a), 271(b), 271(c), 271(g) and/or 271(e)(2).

34. There therefore has been and is now an actual justiciable controversy between DEXCEL and CIPLA on the one hand, and Plaintiffs on the other hand, as to whether DEXCEL has infringed and will infringe, and as to whether CIPLA has infringed and will infringe, or has contributed to, induced, aided and/or abetted infringement of or will contribute to, induce, aid and/or abet infringement of, the '380 patent by the acts stated above. This is so

because DEXCEL has and will continue to, without altering course, engage in and make meaningful preparation to engage, in the infringing acts stated above and because CIPLA has and will continue to, without altering course, engage in and make meaningful preparation to engage in the infringing acts stated above.

SECOND CLAIM FOR RELIEF: '505 PATENT

35. Plaintiffs reallege paragraphs 1-19, above, as if set forth specifically here.

36. The '505 patent (Exhibit B), entitled "New Pharmaceutical Preparation For Oral Use," issued on November 22, 1988 to Hässle upon assignment from the inventors Kurt I. Lövgren, Åke G. Pilbrant, Mitsuru Yasumura, Satoshi Morigaki, Minoru Oda and Naohiro Ohishi. The '505 patent claims, inter alia, pharmaceutical preparations of omeprazole.

37. Plaintiff Hässle has been and is still the owner of the '505 patent. The '505 patent will expire on April 20, 2007, and pediatric exclusivity relating to the '505 patent expires on October 20, 2007.

38. By the Second Notice of Certification, DEXCEL notified Plaintiffs that it had submitted a NDA under 21 U.S.C. §355(b), seeking FDA approval to manufacture, use, and sell DEXCEL's Tablets and identifying 20 mg tablets of PRILOSEC OTC® and 10 mg, 20 mg, and 40 mg capsules of PRILOSEC® products in its NDA.

39. DEXCEL's Second Notice of Certification fails to comply with the law, as specified in 21 U.S.C. § 355(b), and FDA rules and regulations, as specified in 21 C.F.R. § 314.52(c).

40. DEXCEL alleged in the Second Notice of Certification that the '505 patent is not infringed by DEXCEL's Tablets.

41. DEXCEL's Second Notice of Certification does not address the validity or enforceability of any claim of the '505 patent. DEXCEL thus concedes that these claims are valid and enforceable.

42. DEXCEL has infringed the '505 patent under 35 U.S.C. § 271(e)(2) by filing its NDA, seeking approval from the FDA to engage in the commercial manufacture, use, or sale of a drug claimed in this patent or the use of which is claimed in this patent, prior to the expiration of the '505 patent.

43. On information and belief, DEXCEL's Tablets, if approved, will be administered to human patients in a therapeutically effective amount for the treatment of gastrointestinal disease. On information and belief, this administration will occur at DEXCEL's active behest and with its intent, knowledge and encouragement. On information and belief, DEXCEL will actively encourage, aid, and abet this administration with knowledge that it is in contravention of Plaintiffs' rights under the '505 patent.

44. On information and belief, DEXCEL's Tablets are especially made or especially adapted for use in the treatment of gastrointestinal disease via the administration of a therapeutically effective amount of a pharmaceutical formulation containing the claimed omeprazole. On information and belief, DEXCEL is aware that DEXCEL's Tablets are so made or so adapted. On information and belief, DEXCEL is aware that DEXCEL's Tablets, if approved, will be used in contravention of Plaintiffs' rights under the '505 patent.

45. On information and belief, the manufacture, use, or sale of DEXCEL's Tablets, if approved, will infringe one or more claims of the '505 patent.

46. CIPLA is jointly and severally liable for any infringement of the '505 patent. This is so because, upon information and belief, CIPLA participated in, contributed to,

aided, abetted and/or induced the submission of NDA 22-032 by providing material information and physical product, including omeprazole product, to DEXCEL in connection with the preparation and submission of NDA 22-032, which information was relied upon and used by DEXCEL in the submission of NDA 22-032. If NDA 22-032 is approved by the United States Food & Frug Administration ("FDA"), the importation into the United States and commercial sale and offer for sale within the United States of DEXCEL's Tablets pursuant to NDA 22-032, and made using omperazole product supplied by CIPLA, will constitute infringement of the '505 patent.

47. In addition, on information and belief, CIPLA will, without authority, supply further material information and physical product, including omeprazole product, to DEXCEL for formulation into DEXCEL's Tablets for subsequent commercial importation into the United States, and commercial sale and offer for sale within the United States under NDA 22-032, in violation of the '505 patent.

48. By supplying further material information and physical product, including omeprazole product, to DEXCEL for formulation into DEXCEL's Tablets as stated above, CIPLA will knowingly and intentionally contribute to, aid, abet and/or induce the infringement of the '505 patent. Such acts constitute patent infringement under 35 U.S.C. §§271(a), 271(b), 271(c), 271(g) and/or 271(e)(2).

49. There therefore has been and is now an actual justiciable controversy between DEXCEL and CIPLA on the one hand, and Plaintiffs on the other hand, as to whether DEXCEL has infringed and will infringe, and as to whether CIPLA has infringed and will infringe, or has contributed to, induced, aided and/or abetted infringement of or will contribute to, induce, aid and/or abet infringement of, the '505 patent by the acts stated above. This is so

because DEXCEL has and will continue to, without altering course, engage in and make meaningful preparation to engage, in the infringing acts stated above and because CIPLA has and will continue to, without altering course, engage in and make meaningful preparation to engage in the infringing acts stated above.

THIRD CLAIM FOR RELIEF: '230 PATENT

50. Plaintiffs reallege paragraphs 1-19, above, as if set forth specifically here.

51. The '230 patent (Exhibit C), entitled "Pharmaceutical Formulations of Acid Labile Substances For Oral Use," issued on August 1, 1989 to Hässle, upon assignment from the inventors Kurt I. Lövgren, Åke G. Pilbrant, Mitsuru Yasumura, Satoshi Morigaki, Minoru Oda and Naohiro Ohishi. The '230 patent claims, *inter alia*, pharmaceutical preparations of acid labile pharmaceutically active substances, including omeprazole.

52. Plaintiff Hässle has been and still is the owner of the '230 patent. The '230 patent will expire on April 20, 2007, and pediatric exclusivity relating to the '230 patent expires on October 20, 2007.

53. By the Second Notice of Certification, DEXCEL notified Plaintiffs that it had submitted a NDA under 21 U.S.C. §355(b), seeking FDA approval to manufacture, use, and sell DEXCEL's Tablets and identifying 20 mg tablets of PRILOSEC OTC® and 10 mg, 20 mg, and 40 mg capsules of PRILOSEC® products in its NDA.

54. DEXCEL's Second Notice of Certification fails to comply with the law, as specified in 21 U.S.C. § 355(b), and FDA rules and regulations, as specified in 21 C.F.R. § 314.52(c).

55. DEXCEL alleged in the Second Notice of Certification that the '230 patent is not infringed by DEXCEL's Tablets.

56. DEXCEL's Second Notice of Certification does not address the validity or unenforceability of any claim of the '230 patent. DEXCEL thus concedes that these claims are valid and enforceable.

57. DEXCEL has infringed the '230 patent under 35 U.S.C. § 271(e)(2) by filing its NDA, seeking approval from the FDA to engage in the commercial manufacture, use or sale of a drug claimed in this patent or the use of which is claimed in this patent, prior to the expiration of the '230 patent.

58. On information and belief, DEXCEL's Tablets, if approved, will be administered to human patients in a therapeutically effective amount for the treatment of gastrointestinal disorders. On information and belief, this administration will occur at DEXCEL's active behest and with its intent, knowledge, and encouragement. On information and belief, DEXCEL will actively encourage, aid, and abet this administration with knowledge that it is in contravention of Plaintiffs' rights under the '230 patent.

59. On information and belief, DEXCEL's Tablets are especially made or especially adapted for use in the treatment of gastrointestinal disorders via the administration of a therapeutically effective amount of a pharmaceutical formulation containing the claimed omeprazole. On information and belief, DEXCEL is aware that DEXCEL's Tablets are so made or so adapted. On information and belief, DEXCEL is aware that DEXCEL's Tablets, if approved, will be used in contravention of Plaintiffs' rights under the '230 patent.

60. On information and belief, the manufacture, use, or sale of DEXCEL's Tablets, if approved, will infringe one or more claims of the '230 patent.

61. CIPLA is jointly and severally liable for any infringement of the '230 patent. This is so because, upon information and belief, CIPLA participated in, contributed to,

aided, abetted and/or induced the submission of NDA 22-032 by providing material information and physical product, including omeprazole product, to DEXCEL in connection with the preparation and submission of NDA 22-032, which information was relied upon and used by DEXCEL in the submission of NDA 22-032. If NDA 22-032 is approved by the United States Food & Frug Administration ("FDA"), the importation into the United States and commercial sale and offer for sale within the United States of DEXCEL's Tablets pursuant to NDA 22-032, and made using omperazole product supplied by CIPLA, will constitute infringement of the '230 patent.

62. In addition, on information and belief, CIPLA will, without authority, supply further material information and physical product, including omeprazole product, to DEXCEL for formulation into DEXCEL's Tablets for subsequent commercial importation into the United States, and commercial sale and offer for sale within the United States under NDA 22-032, in violation of the '230 patent.

63. By supplying further material information and physical product, including omeprazole product, to DEXCEL for formulation into DEXCEL's Tablets as stated above, CIPLA will knowingly and intentionally contribute to, aid, abet and/or induce the infringement of the '230 patent. Such acts constitute patent infringement under 35 U.S.C. §§271(a), 271(b), 271(c), 271(g) and/or 271(e)(2).

64. There therefore has been and is now an actual justiciable controversy between DEXCEL and CIPLA on the one hand, and Plaintiffs on the other hand, as to whether DEXCEL has infringed and will infringe, and as to whether CIPLA has infringed and will infringe, or has contributed to, induced, aided and/or abetted infringement of or will contribute to, induce, aid and/or abet infringement of, the '230 patent by the acts stated above. This is so

because DEXCEL has and will continue to, without altering course, engage in and make meaningful preparation to engage, in the infringing acts stated above and because CIPLA has and will continue to, without altering course, engage in and make meaningful preparation to engage in the infringing acts stated above.

WHEREFORE, Plaintiffs respectfully request the following relief:

(a) A judgment declaring that the effective date of any approval of DEXCEL's NDA under Section 505(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(b)) for DEXCEL's Tablets must be no earlier than the latest expiration date of the infringed patents-in-suit, including pediatric exclusivity;

(b) A judgment declaring that the '380, '505, and '230 patents will be infringed by defendants DEXCEL and CIPLA if DEXCEL's Tablets are made, used, offered for sale or sold in the United States prior to the expiration of said patents;

(c) A judgment declaring that DEXCEL has not complied with the requirements of 35 U.S.C. § 271(e)(2), 21 U.S.C. § 355(b)(2)(A)(iv), 21 U.S.C. § 355(b)(3)(D)(ii), 21 C.F.R. § 314.50 and 21 U.S.C. § 314.52;

(d) A permanent injunction against any infringement by DEXCEL and/or CIPLA of the '380, '505, and '230 patents;

(e) A judgment that DEXCEL's and CIPLA's conduct is exceptional;

(f) Attorneys' fees in this action under 35 U.S.C. § 285;

(g) Costs and expenses in this action; and

(h) Such other relief as this Court may deem proper.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP

/s/ Jack B. Blumenfeld

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January 5, 2007

CERTIFICATE OF SERVICE

I hereby certify that on January 5, 2007, I electronically filed the foregoing with the Clerk of the Court using CM/ECF, which will send notification of such filing to Richard D. Kirk.

I further certify that I caused to be served copies of the foregoing document on January 5, 2007 upon the following in the manner indicated:

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EXHIBIT “A”

US006150380A

United States Patent [19]

Lövqvist et al.

[11] **Patent Number: 6,150,380**

[45] **Date of Patent: Nov. 21, 2000**

[54] **CRYSTALLINE FORM OF OMEPRAZOLE**

[75] Inventors: **Karin Lövqvist**, Mölndal; **Gunnel Sundén**, Göteborg; **David Noreland**, Södertälje; **Ingvar Ymén**, Saltsjö-Boo, all of Sweden

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

[21] Appl. No.: **09/202,251**

[22] PCT Filed: **Nov. 10, 1998**

[86] PCT No.: **PCT/SE98/02028**

§ 371 Date: **Dec. 10, 1998**

§ 102(e) Date: **Dec. 10, 1998**

[87] PCT Pub. No.: **WO99/08500**

PCT Pub. Date: **Feb. 25, 1999**

[51] **Int. Cl.**[7] **A61K 31/44**

[52] **U.S. Cl.** **514/338**; 546/273.7

[58] **Field of Search** 514/338; 546/273.7

[56] **References Cited**

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5,877,192	3/1999	Linberg et al.	514/338
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Erlandsson, Lournal of Chromatograph, 532 305–319, 1990.

Primary Examiner—Jane Fan

Attorney, Agent, or Firm—White & Case LLP

[57] **ABSTRACT**

The present invention relates to a novel crystalline form of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]sulfinyl]-1H-benzimidazole, known under the generic name omeprazole. Further, the present invention also relates to the use of the novel crystalline form of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]sulfinyl]-1H-benzimidazole for the treatment of gastrointestinal disorders, pharmaceutical compositions containing it as well as processes for the preparation of the novel crystalline form of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

6 Claims, 1 Drawing Sheet

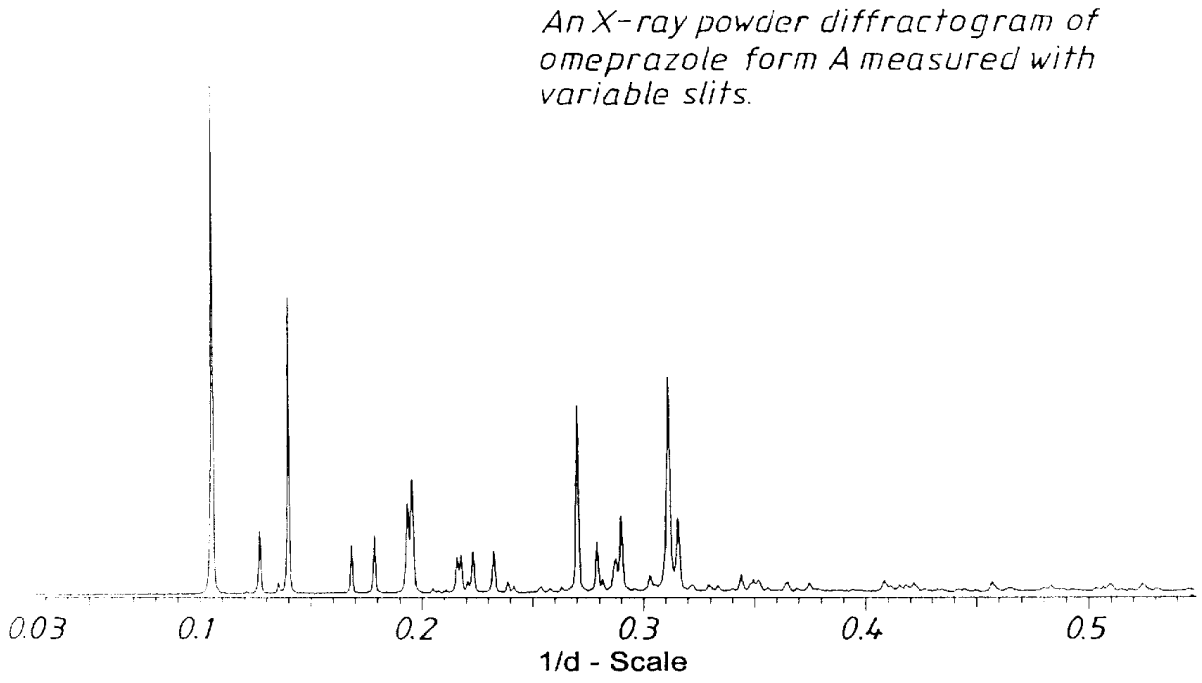


Fig. 1 An X-ray powder diffractogram of omeprazole form A measured with variable slits.

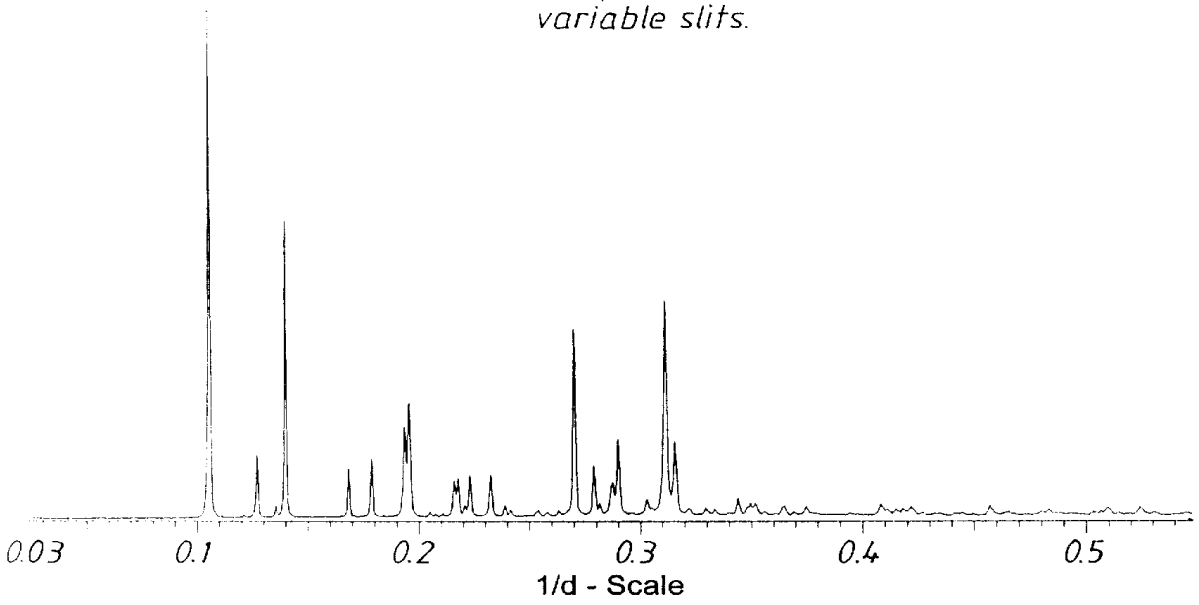
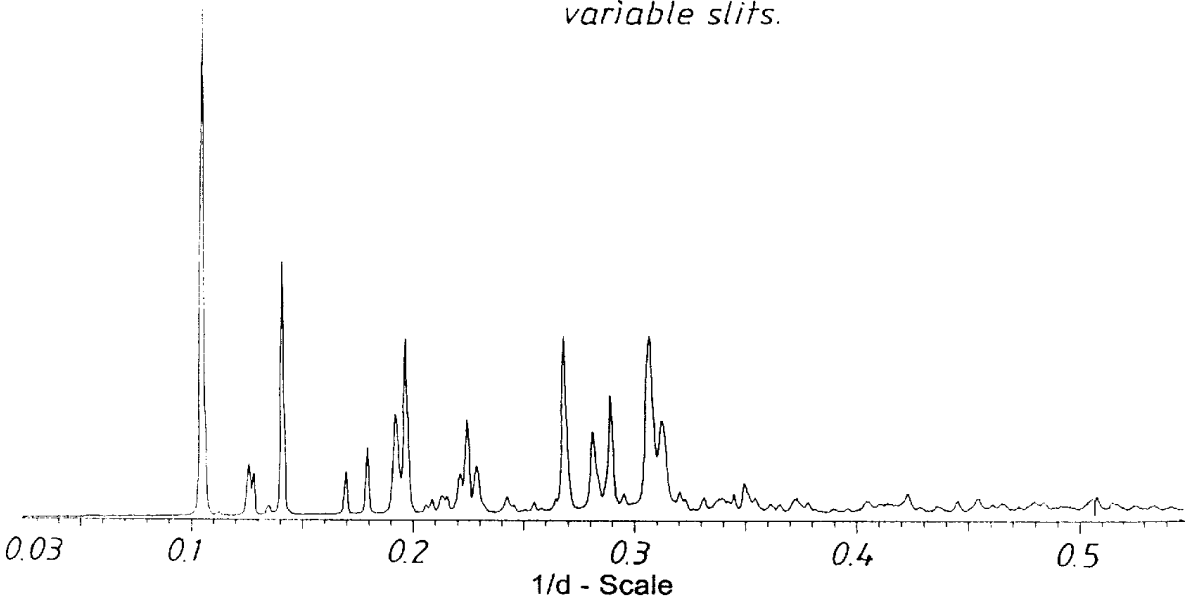


Fig. 2 An X-ray powder diffractogram of omeprazole form B measured with variable slits.



CRYSTALLINE FORM OF OMEPRAZOLE

FIELD OF THE INVENTION

The present invention relates to a novel crystalline form of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]sulfinyl]-1H-benzimidazole. 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole is known under the generic name omeprazole and its novel crystalline form is hereinafter referred to as omeprazole form A. Further, the present invention also relates to use of omeprazole form A for the treatment of gastrointestinal disorders, pharmaceutical compositions containing omeprazole form A and processes for the preparation of omeprazole form A.

BACKGROUND OF THE INVENTION AND PRIOR ART

The compound 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, having the generic name omeprazole, as well as therapeutically acceptable salts thereof, are described in EP 5129. The single crystal X-ray data and the derived molecular structure of the so far only known crystal form of omeprazole is described by Ohishi et al., Acta Cryst. (1989), C45, 1921–1923. This published crystal form of omeprazole is hereinafter referred to as omeprazole form B.

Omeprazole is a proton pump inhibitor, i.e. effective in inhibiting gastric acid secretion, and is useful as an antiulcer agent. In a more general sense, omeprazole may be used for treatment of gastric-acid related diseases in mammals and especially in man.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is an X-ray powder diffractogram of omeprazole form A.

FIG. **2** is an X-ray powder diffractogram of omeprazole form B.

DESCRIPTION OF THE INVENTION

It has surprisingly been found that the substance omeprazole can exist in more than one crystal form. It is an object of the present invention to provide omeprazole form A. Another object of the present invention is to provide a process for the preparation of omeprazole form A, substantially free from other forms of omeprazole. X-ray powder diffraction (XRPD) is used as a method of differentiating omeprazole form A from other crystalline and non-crystalline forms of omeprazole. Additionally it is an object of the present invention to provide pharmaceutical formulations comprising omeprazole form A.

Omeprazole form A is a crystalline form exhibiting advantageous properties, such as being well-defined, being thermodynamically more stable and less hygroscopic than omeprazole form B, especially at room temperature. Omeprazole form A does also show a better chemical stability, such as thermo stability and light stability, than omeprazole form B.

Omeprazole form B can under certain conditions, completely or partly, be converted into omeprazole form A. Omeprazole form A is thereby characterized in being thermodynamically more stable than omeprazole form B.

Omeprazole form A is further characterized as being essentially non-hygroscopic.

Omeprazole form A is characterized by the positions and intensities of the peaks in the X-ray powder diffractogram,

as well as by the unit cell parameters. The unit cell dimensions have been calculated from accurate Guinier data. The X-ray powder diffractogram data as well as the unit cell parameters for omeprazole form B are different compared to omeprazole form A. Omeprazole form A can thereby be distinguished from omeprazole form B, using X-ray powder diffraction.

Omeprazole form A, according to the present invention, is characterized in providing an X-ray powder diffraction pattern, as in FIG. **1**, exhibiting substantially the following d-values and intensities;

Form A		Form A	
d-value (Å)	Relative intensity	d-value (Å)	Relative intensity
9.5	vs	3.71	s
7.9	s	3.59	m
7.4	w	3.48	m
7.2	vs	3.45	s
6.0	m	3.31	w
5.6	s	3.22	s
5.2	s	3.17	m
5.1	s	3.11	w
4.89	w	3.04	w
4.64	m	3.00	w
4.60	m	2.91	w
4.53	w	2.86	w
4.49	m	2.85	w
4.31	m	2.75	w
4.19	w	2.67	w
4.15	w	2.45	w
3.95	w	2.41	w

The peaks, identified with d-values calculated from the Bragg formula and intensities, have been extracted from the Guinier diffractogram of omeprazole form A. The relative intensities are less reliable and instead of numerical values the following definitions are used;

% Relative Intensity*	Definition
25–100	vs (very strong)
10–25	s (strong)
3–10	m (medium)
1–3	w (weak)

*The relative intensities are derived from diffractograms measured with fixed slits.

Omeprazole form A according to the present invention is further characterized by a triclinic unit cell with parameters;

a=10.410(4)Å
b=10.468(3)Å
c=9.729(4)Å
α=111.51(3)°
β=116.78(3)°
γ=90.77(3)°

Omeprazole form A can also be characterized by Raman spectroscopy, where omeprazole form A is characterized by the absence of a band at 1364 cm^{-1}, which is observed for omeprazole form B, and by the ratio of the relative intensities of the 842 and 836 cm-1 bands. The ratio (intensity of 842 cm-1 band/intensity of 836 cm-I band) is <1 for omeprazole form A, while the ratio is >1 for omeprazole form B.

According to the invention there is further provided a process for the preparation of omeprazole form A.

Omeprazole form A is obtained upon slow crystallization and omeprazole form B is obtained from fast crystallization.

Omeprazole form A may be prepared by reaction crystallisation or recrystallizing omeprazole of any form, or mixtures of any forms, in an appropriate solvent, such as for instance methanol, at around room temperature and for a prolonged time period. Examples of prolonged time periods include, but are not limited to, a few hours, such as 2 hours, up to several weeks. Suitable solvents are alkyl alcohols and especially a lower alcohol comprising 1–4 carbon atoms.

Omeprazole form A may also be prepared by suspending omeprazole of any form, or mixtures of any forms, in an appropriate solvent at around room temperature and for a prolonged time period. Examples of appropriate solvents include, but are not limited to, methanol, ethanol, acetone, ethyl acetate, methyl tert. butyl ether, toluene, or any mixture thereof. Examples of prolonged time periods include, but are not limited to, a few hours, such as 2 hours, up to several weeks.

The omeprazole form A obtained according to the present invention is substantially free from other crystal and non-crystal forms of omeprazole, such as omeprazole form B. Substantially free from other forms of omeprazole shall be understood to mean that omeprazole form A contains less than 10%, preferably less than 5%, of any other forms of omeprazole, e.g. omeprazole form B.

Omeprazole form A in mixture with other solid form/forms of omeprazole, e.g. omeprazole form B, also exhibits advantageous properties, such as being chemically more stable than pure omeprazole form B. Mixtures comprising a certain amount of omeprazole form A, by weight, are also chemically more stable than other mixtures comprising a lesser amount of omeprazole form A, by weight. Such mixtures comprising omeprazole form A can be prepared, for example, by mixing omeprazole form A prepared according to the present invention with other solid forms of omeprazole, such as form B, prepared according to prior art.

The present invention also relates to mixtures comprising omeprazole form A in mixture with other solid forms of omeprazole. Such mixtures comprising omeprazole form A include for instance mixtures containing a detectable amount of omeprazole form A, 1%, 2%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 98% or 99% (by weight), of omeprazole form A.

Examples of other solid forms of omeprazole include, but are not limited to, omeprazole form B, amorphous forms, and other polymorphs.

A detectable amount of omeprazole form A is an amount that can be detected using conventional techniques, such as FT-IR, Raman spectroscopy, XRPD and the like.

The expression chemical stability includes, but is not limited to, thermo stability and light stability.

The compound of the invention, i.e. omeprazole form A, pre pared according to the present invention is analyzed, characterized and differentiated from omeprazole form B by X-ray powder diffraction, a technique which is known per se. Another suitable technique to analyze, characterize and differentiate omeprazole form A from omeprazole form B is by Raman spectroscopy.

Omeprazole form A is effective as a gastric acid secretion inhibitor, and is useful as an antiulcer agent. In a more general sense, it can be used for treatment of gastric-acid related conditions in mammals and especially in man, including e.g. reflux esophagitis, gastritis, duodenitis, gastric ulcer and duodenal ulcer. Furthermore, it may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable e.g. in patients on NSAID therapy, in patients with Non Ulcer Dyspepsia, in patients with symptomatic gastro-esophageal reflux disease, and in patients with gastrinomas. The compound of the invention may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre- and postoperatively to prevent aspiration of gastric acid and to treat stress ulceration. Further, the compound of the invention may be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections and diseases related to these. The compound of the invention may also be used for treatment of inflammatory conditions in mammals, including man.

Any suitable route of administration may be employed for providing the patient with an effective dosage of omeprazole form A according to the invention. For example, peroral or parenteral formulations and the like may be employed. Dosage forms include capsules, tablets, dispersions, suspensions and the like, e.g. enteric-coated capsules and/or tablets, capsules and/or tablets containing enteric-coated pellets of omeprazole. In all dosage forms omeprazole form A can be admixtured with other suitable constituents.

According to the invention there is further provided a pharmaceutical composition comprising omeprazole form A, as active ingredient, in association with a pharmaceutically acceptable carrier, diluent or excipient and optionally other therapeutic ingredients. Compositions comprising other therapeutic ingredients are especially of interest in the treatment of Helicobacter infections. The invention also provides the use of omeprazole form A in the manufacture of a medicament for use in the treatment of a gastric-acid related condition and a method of treating a gastric-acid related condition which method comprises administering to a subject suffering from said condition a therapeutically effective amount of omeprazole form A.

The compositions of the invention include compositions suitable for peroral or parenteral administration. The compositions may be conveniently presented in unit dosage forms, and prepared by any methods known in the art of pharmacy.

In the practice of the invention, the most suitable route of administration as well as the magnitude of a therapeutic dose of omeprazole form A in any given case will depend on the nature and severity of the disease to be treated. The dose, and dose frequency, may also vary according to the age, body weight, and response of the individual patient. Special requirements may be needed for patients having Zollinger-Ellison syndrome, such as a need for higher doses than the average patient. Children and patients with liver diseases as well as patients under long term treatment will generally benefit from doses that are somewhat lower than the average. Thus, in some conditions it may be necessary to use doses outside the ranges stated below. Such higher and lower doses are within the scope of the present invention.

In general, a suitable oral dosage form may cover a dose range from 5 mg to 250 mg total daily dose, administered in one single dose or equally divided doses. A preferred dosage range is from 10 mg to 80 mg.

The compound of the invention may be combined as the active component in intimate admixture with a pharmaceutical carrier according to conventional techniques, such as the oral formulations described in WO 96/01623 and EP 247 983, the disclosures of which are hereby incorporated as a whole by reference.

Combination therapies comprising omeprazole form A and other active ingredients in separate dosage forms, or in one fixed dosage form, may also be used. Examples of such active ingredients include anti-bacterial compounds, non-steroidal anti-inflammatory agents, antacid agents, alginates and prokinetic agents.

The examples which follow will further illustrate the preparation of the compound of the invention, i.e. omeprazole form A, but are not intended to limit the scope of the invention as defined hereinabove or as claimed below.

EXAMPLES

Example 1

Preparation of omeprazole form A

Omeprazole (55.8 g) is added a room temperature to methanol (348 ml) containing ammonia (1.3 ml; 25%). The suspension is thereafter stirred in darkness for approximately 45 hours and then filtered. The filtrate is dried 18 hours at 30° C. under reduced pressure (<5 mbar). Yield: 43.9 g.

Example 2

Preparation of omeprazole form B

Omeprazole (50 g)is added to methanol (750 ml) containing ammonia (0.7 ml; 25%) at 50° C. The solution is thereafter filtered and cooled in about 20 minutes to approximately 0° C. The formed crystals are filtered and washed with ice cooled methanol and then dried. is The filtrate was dried 24 hours at 40° C. under reduced pressure (<5 mbar). Yield: 39 g.

Example 3

Characterization of omeprazole form A and omeprazole form B using X-ray powder diffraction

X-ray diffraction analysis was performed according to standard methods which can be found in e.g. Bunn, C. W. (1948), Chemical Crystallography, Clarendon Press, London; or Klug, H. P. & Alexander, L. E. (1974), X-Ray Diffraction Procedures, John Wiley and Sons, New York. The unit cell parameters for omeprazole form A and B have been calculated from the Guinier X-ray powder diffractograms using the program "TREOR" by Werner, P. -E., Eriksson, L. and Westdahl, M., J. Appt. Crystallogr. 18 (1985) 367–370. The fact that the positions of all peaks in the diffractograms for omeprazole form A and form B may be calculated using the respective unit cell parameters, proves that the unit cells are correct and that the diffractograms are indicative of the pure forms. The diffractogram of omeprazole form A, prepared according to Example 1 in the present application, is shown in FIG. **1** and the diffractogram of omeprazole form B, prepared according to Example 2 in the present application is shown in FIG. **2**.

The peaks, identified with d-values calculated from the Bragg formula and intensities, have been extracted from the diffractograms for omeprazole forms A and form B, and are given in Table 1. In this table the unit cell parameters for omeprazole forms A and B are also given. The relative intensities are less reliable and instead of numerical values the following definitions are used;

% Relative Intensity	Definition
25–100	vs (very strong)
10–25	s (strong)
3–10	m (medium)
1–3	w (weak)

Some additional weak or very weak peaks found in the diffractograms have been omitted from table 1.

Table 1. X-ray powder diffraction data for omeprazole form A and form B shown in FIGS. **1** and **2**. All peaks noted for omeprazole form A and form B can be indexed with the unit cells given below.

Form A		Form B	
d-value (Å)	Relative intensity	d-value (Å)	Relative intensity
9.5	vs	9.6	vs
7.9	s	8.0	m
7.4	w	7.9	m
7.2	vs	7.5	w
6.0	m	7.1	vs
5.6	s	5.9	m
5.2	s	5.6	m
5.1	s	5.3	s
4.89	w	5.1	s
4.64	m	4.54	m
4.60	m	4.48	s
4.53	w	4.41	m
4.49	m	4.14	w
4.31	m	3.75	s
4.19	w	3.57	m
4.15	w	3.47	s
3.95	w	3.40	w
3.71	s	3.28	s
3.59	m	3.22	m
3.48	m	3.02	w
3.45	s	2.97	w
3.31	w	2.87	w
3.22	s	2.37	w
3.17	m		
3.11	w		
3.04	w		
3.00	w		
2.91	w		
2.86	w		
2.85	w		
2.75	w		
2.67	w		
2.45	w		
2.41	w		

The triclinic unit cells are:

Unit cell form A	Unit cell form B
a = 10.410(4) Å	a = 10.257(10) Å
b = 10.468(3) Å	b = 10.717(6) Å
c = 9.729(4) Å	c = 9.694(10) Å
α = 111.51(3)°	α = 112.14(7)°
β = 116.78(3)°	β = 115.56(5)°
γ = 90.77(3)°	γ = 91.76 (7)°

What is claimed is:

1. Omeprazole form A which is a non-salt racemate, wherein omeprazole form A provides an X-ray powder diffraction pattern exhibiting substantially the following d-values:

Form A		Form A	
d-value (Å)	Relative intensity	D-value (Å)	Relative intensity
9.5	vs	3.71	s
7.9	s	3.59	m
7.4	w	3.48	m
7.2	vs	3.45	s
6.0	m	3.31	w
5.6	s	3.22	s

-continued

Form A		Form A	
d-value (Å)	Relative intensity	D-value (Å)	Relative intensity
5.2	s	3.17	m
5.1	s	3.11	w
4.89	w	3.04	w
4.64	m	3.00	w
4.60	m	2.91	w
4.53	w	2.86	w
4.49	m	2.85	w
4.31	m	2.75	w
4.19	w	2.67	w
4.15	w	2.45	w
3.95	w	2.41	w.

2. Omeprazole form A, according to claim **1**, wherein omeprazole form A is defined by a triclinic unit cell with parameters a=10.410(4)Å, b=10.468(3)Å, c=9.729(4)Å, α=111.51(3)°, β=116.78(3)°, γ=90.77(3)°.

3. A pharmaceutical formulation comprising omeprazole form A according to claim **1** in admixture with a pharmaceutically acceptable excipient.

4. A method of treatment of gastrointestinal disorders which comprises administration of a therapeutically effective amount of omeprazole form A according to claim **1** to a patient suffering from gastrointestinal disorders.

5. A process for the preparation of omeprazole form A according to claim **1** comprising the steps of:

a) dissolving or suspending omeprazole of any form, or a mixture of omeprazole of any form, in a suitable solvent at 15–25° C.;

b) allowing the solution to crystallize for at least 2 hours, and

c) isolating the omeprazole form A thus obtained.

6. The process according to claim **5**, wherein the solvent used in step a) is selected from the group consisting of methanol, ethanol, acetone, ethyl acetate, methyl tert. butyl ether, toluene and any mixture thereof.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,150,380
DATED : November 21, 2000
INVENTOR(S) : Lövquist et al.

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

Title page,
Item [56], **References Cited,** OTHER PUBLICATIONS, insert
-- Ohishi et al., "Structure of 5-Methoxy-2-{[4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]- sulfinyl}-1H-benzimidazole(Omeprazole)", Acta Cryst. (1989), C45, 1921-1923. --

Signed and Sealed this

Sixth Day of August, 2002

Attest:

Attesting Officer

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

EXHIBIT “B”

United States Patent [19]

Lovgren et al.

[11] **Patent Number: 4,786,505**

[45] **Date of Patent: Nov. 22, 1988**

[54] **NEW PHARMACEUTICAL PREPARATION FOR ORAL USE**

[75] Inventors: **Kurt I. Lovgren**, Mölnlycke; **Ake G. Pilbrant**, Kungsbacka, both of Sweden; **Mitsuru Yasumura**; **Satoshi Morigaki**, both of Hyogo, Japan; **Minoru Oda**, Ohita, Japan; **Naohiro Ohishi**, Fukuoka, Japan

[73] Assignee: **Aktiebolaget Hassle**, Sweden

[21] Appl. No.: **40,491**

[22] Filed: **Apr. 20, 1987**

[30] **Foreign Application Priority Data**

Apr. 30, 1986 [GB] United Kingdom 8610572

[51] **Int. Cl.**[4] **A61K 9/22**; A61K 9/32

[52] **U.S. Cl.** **424/468**; 424/475; 424/479; 424/480; 424/482

[58] **Field of Search** 424/480, 482, 468, 475, 424/479; 427/2, 3

[56] **References Cited**

U.S. PATENT DOCUMENTS

2,540,979	2/1951	Clymer et al.	167/82
4,685,919	8/1987	Amidon et al.	427/2 X

FOREIGN PATENT DOCUMENTS

0005129	10/1979	European Pat. Off. .
1204363	8/1964	Fed. Rep. of Germany .
1617615	5/1966	Fed. Rep. of Germany .
2336218	5/1979	Fed. Rep. of Germany .
3046559	12/1980	Fed. Rep. of Germany .
WO85/03436	8/1985	PCT Int'l Appl. .
1485676	9/1977	United Kingdom .

Primary Examiner—Michael Lusignan

Attorney, Agent, or Firm—Brumbaugh, Graves, Donohue & Raymond

[57] **ABSTRACT**

Pharmaceutical preparation containing omeprazole together with an alkaline reacting compound or an alkaline salt of omeprazole optionally together with an alkaline compound as the core material, one or more subcoating layers comprising inert reacting compounds which are soluble or rapidly disintegrating in water, or polymeric, water soluble filmforming compounds, optionally containing pH-buffering alkaline compounds and an enteric coating as well as a process for the preparation thereof and the use in the treatment of gastrointestinal diseases.

14 Claims, No Drawings

NEW PHARMACEUTICAL PREPARATION FOR ORAL USE

FIELD OF THE INVENTION

The present invention is related to a new stable pharmaceutical preparation containing omeprazole for oral use, to a method for the manufacture of such a preparation and to a method of affecting gastric acid secretion and providing gastrointestinal cytoprotective effect when using them.

BACKGROUND OF THE INVENTION

From e.g. EP-A1-No. 0 005 129 omeprazole, 5-methoxy-2(((4-methoxy-3,5-dimethyl-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole, a potent inhibitor of gastric acid secretion is known. Omeprazole shows a powerful inhibitory action against secretion of gastric juice (Lancet, Nov. 27, 1982, p. 1223–1224) and can be used for the treatment of gastric and duodenal ulcers. Omeprazole is however susceptible to degradation/-transformation in acid reacting and neutral media. The half-life of omeprazole in water solutions at pH-values less than four is shorter than ten minutes. Also at neutral pH-values the degration reaction 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 (supp. 108) p. 113–120). The stability profile is similar in solid phase. The degradation of omeprazole is catalyzed by acidic reacting compounds and is stabilized in mixtures with alkaline reacting compounds. The stability of omeprazole is also affected by moisture and organic solvents.

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 in order to reach the small intestine without degradation.

In human pharmacological studies it was found that the rate of release omeprazole from a pharmaceutical dosage form can influence the total extent of absorption of omeprazole to the general circulation (Pilbrant and Cederberg, Scand. J. Gastroenterology 1985; 20 (suppl. 108) p. 113–120). A fully bioavailable dosage form of omeprazole must release the active drug rapidly in the proximal part of the gastrointestinal canal.

In order to obtain a pharmaceutical dosage form of omeprazole which prevents omeprazole from contact with acidic gastric juice, the cores must be enteric coated. Ordinary enteric coatings, however, are made of acidic compounds. If covered with such a conventional enteric coating, omeprazole rapidly decomposes by direct or indirect contact with it, with the result that the preparations become badly discolored and lose in omeprazole content with the passage of time.

In order to enhance the storage stability the cores which contain omeprazole must also contain alkaline reacting constituents. When such an alkaline core is enteric coated with an amount of a conventional enteric coating polymer such as, for example, cellulose acetate phthalate, that permits the dissolution of the coating and the active drug contained in the cores in the proximal part of the small intestine, it also will allow some diffusion of water of gastric juice through the enteric coating into the cores, during the time the dosage form resides in the stomach before it is emptied into the small intestine. The diffused water of gastric juice will dissolve parts of the core in the close proximity of the enteric coating layer and there form an alkaline solution inside the coated dosage form. The alkaline solution will interfere with the enteric coating and eventually dissolve it.

An enteric coated dosage form of omeprazole was reported by Pilbrant and Cederberg, in the above cited Scand. J. Gastroenterology 1985; 20 (suppl. 108) p. 113–120. The publication describes a conventional enteric coated dosage form and states that it has an acceptable storage stability—for clinical studies. It was later found that the stability of this dosage form was insufficient during long-term storage required for a marketed pharmaceutical dosage form.

If a conventional formulation of omeprazole is made, the stability is not satisfactory, particularly in resistance to humidity, and special moisture-proof packing has been adopted to minimize the troubles. However, this provides no satisfactory solution to the problems in today's drug distribution system, and also leads to increased costs. Under the circumstances, there has been a demand for the development of new enteric preparations of omeprazole with better stability.

In DE-A1-No. 3046 559 a way to coat a dosage form is described. First the dosage form is coated with a water insoluble layer containing microcrystalline cellulose and then with a second enteric coating with the aim to achieve a dosage form which releases the active drug in the colon. This method of preparation will not give the desired release of omeprazole in the small intestine.

U.S. Pat. No. 2,540,979 describes an enteric coated oral dosage form, where the enteric coating is combined with a second and/or first coating of a water insoluble "wax" layer. This method of preparation is not applicable on cores containing omeprazole since direct contact between substances such as cellulose acetate phthalate (CAP) and omeprazole causes degradation and discolouration of omeprazole.

DE-B2-No. 23 36 218 describes a method to produce a dialysis membrane consisting of a mixture of one or more conventional enteric coating polymers and one or more insoluble cellulose derivatives. Such a membrane will not give a proper protection of omeprazole in gastric juice.

DE-A1-No. 204 363 describes a three-layer coating procedure. The first layer is soluble in gastric but is insoluble in intestinal juice. The second is water soluble regardless of pH and the third layer is an enteric coating. This preparation as well as the preparation described in DE-A1-No. 1 617 615 result in a dosage form which is not dissolved in gastric juice and which only dissolves slowly in intestinal juice. Such preparations cannot be used for omeprazole, where a rapid release of the drug in the small intestine is needed.

DE-A1 No. 12 04 363 describes coating with three layers to achieve release of a drug in the ileum, an aim which is outside the scope of the present invention.

GB-A-No. 1 485 676 describes a way to obtain a preparation, which effervesces in the small intestine, by enteric coating a core containing the active drug and an effervescing system such as a combination of carbonate and/or bicarbonate salt and a pharmaceutically acceptable acid. The formulation cannot be adopted for a pharmaceutical dosage form containing omeprazole, as the presence of an acid in contact with omeprazole in the cores would give a result that omeprazole was degraded.

WO No. 85/03436 describes a pharmaceutical preparation, wherein cores containing active drugs mixted with for instance buffering components such as sodium dihydrogenphosphate with the aim of maintaining a constant pH and a constant rate of diffusion, are coated with a first coating which controls the diffusion. This formulation cannot be adopted for omeprazole where a rapid release in the small intestive is wanted. Direct application of an enteric coating onto the cores would also adversely influence the storage stability of such dosage forms containing omeprazole.

OUTLINE OF THE INVENTION

The object of the present invention is to provide 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 which has a good stability during long-term storage. The new dosage form is characterized in the following way. Cores containing omeprazole mixed with alkaline compounds or an alkaline salt of omeprazole optionally mixed with an alkaline compound are coated with two or more layers, whereby the first layer/layers is/are soluble in water o rapidly disintegrating in water and consist(s) of non-acidic, otherwise inert pharmaceutically acceptable substances. This/these first layer/layers separates/separate the alkaline core material from the outer layer, which is an enteric coating. The final, enteric coated dosage form is treated in a suitable way to reduce the water content to a very low level in order to obtain a good stability of the dosage form during long-term storage.

DETAILED DESCRIPTION OF THE INVENTION

Cores

Omeprazole is mixed with inert, preferably water soluble, conventional pharmaceutical constituents to obtain the preferred concentration of omeprazole in the final mixture and with an alkaline reacting, otherwise inert, pharmaceutically acceptable substance (or substances), which creates a "micro-pH" around each omeprazole particle of not less than pH=7, preferably not less than pH=8, when water is adsorbed to the particles of the mixture or when water is added in small amounts to the mixture. 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; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $Al_2O_3.6MgO.CO_2.12H_2O$, $(Mg_6Al_2(OH)_{16}CO_3.4H_2O)$, $MgO.Al_2O_3.2SiO_2.nH_2O$ or similar compounds; organic pH-buffering substances such as trihydroxymethylaminomethane or other similar, pharmaceutically acceptable pH-buffering substances. The stabilizing, high pH-value in the powder mixture can also be achieved by using an alkaline reacting salt of omeprazole such as the sodium, potassium, magnesium, calcium etc. salts of omeprazole, which are described in e.g. EP-A2-No. 124 495, either alone or in combination with a conventional buffering substance as previously described.

The powder mixture is then formulated into small beads i.e. pellets, tablets, hard gelatine or soft gelatine capsules by conventional pharmaceutical procedures. The pellets, tablets or gelatin capsules are used as cores for further processing.

Separating layer

The omeprazole containing alkaline reacting cores must be separated from the enteric coating polymer(s) containing free carboxyl groups, which otherwise causes degradation/discolouration of omeprazole during the coating process or during storage. The subcoating layer, in the following defined as the separating layer, also serves as a pH-buffering zone in which hydrogen ions diffusing from the outside in towards the alkaline core can react with hydroxyl ions diffusing from the alkaline core towards the surface of the coated articles. 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 $Al_2O_3.6MgO.CO_212H_2O$, $(Mg_6Al_2(OH)_{16}CO_3.4H_2O)$, $MgO.Al_2O_3.2SiO_2.nH_2O$ or similar compounds; or other pharmaceutically acceptable pH-buffering compounds such as, for instance the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, citric or other suitable, weak, inorganic or organic acids.

The separating layer consists of one or more water soluble inert layer, optionally containing pH-buffering compounds.

The separating layer(s) can be applied to the cores—pellets or tablets—by conventional coating procedures in a suitable coating pan 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 the pharmaceutically acceptable, water soluble, inert compounds or polymers used for film-coating applications such as, for instance sugar, polyethylene glycol, polyvinylpyrroline, polyvinyl alcohol, hydroxypropyl cellulose, methylcellulose, hydroxymethyl cellulose, hydroxypropyl methylcellulose, polyvinyl acetal diethylaminoacetate or the like. The thickness of the separating layer is not less than 2 μm, for small spherical pellets preferably not less than 4 μm, for tablets preferably not less than 10 μm.

In the case of tablets another method to apply the coating can be performed by the drycoating technique. First a tablet containing omeprazole is compressed as described above. Around this tablet a layer is compressed using a suitable tableting machine. The outer, separating layer, consists of pharmaceutically acceptable, in water soluble or in water rapidly disintegrating tablet excipients. The separating layer has a thickness of not less than 1 mm. Ordinary plasticizers colorants, pigments, titanium dioxide, talc and other additives may also be included into the separating layer.

In case of gelatin capsules the gelatin capsule itself serves as separating layer.

Enteric coating layer

The eneric coating layer is applied on to the subcoated cores by conventional coating techniques such as, for instance, pan coating or fluidized bed coating using solutions of polymers in water and/or suitable organic solvents or by using latex suspensions of said polymers. As enteric coating polymers can be used, for example, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, carboxymethylethylcellulose, co-polymerized meth-

acrylic acid/methacrylic acid methyl esters such as, for instance, compounds known under the trade name Eudragit ®L 12,5 or Eudragit ®L 100 (Röhm Pharma), or similar compounds used to obtain enteric coatings. The enteric coating can also be applied using water-based polymer dispersions, e.g. Aquateric ® (FMC Corporation), Eudragit ®L100-55 (Röhm Pharma), Coating CE 5142 (BASF). The enteric coating layer can optionally contain a pharmaceutically acceptable plasticizer such as, for instance, cetanol, triacetin, citric acid esters such as, for instance, those known under the trade name Citroflex ® (Pfizer), phthalic acid esters, dibutyl succinate or similar plasticizers. The amount of plasticizer is usually optimized for each enteric coating polymer(s) and is usually in the range of 1–20% of the enteric coating polymer(s). Dispersants such as talc, colorants and pigments may also be included into the enteric coating layer.

Thus, the special preparation according to the invention consists of cores containing omeprazole mixed with an alkaline reacting compound or cores containing an alkaline salt of omeprazole optionally mixed with an alkaline reacting compound. The alkaline reacting core material and/or alkaline salt of the active ingredient, omeprazole, enhance the stability of omeprazole. The cores suspended in water forms a solution or a suspension which has a pH, which is higher than that of a solution in which the polymer used for enteric coating is just soluble. The cores are coated with an inert reacting water soluble or in water rapidly disintegrating coating, optionally containing a pH-buffering substance, which separates the alkaline cores from the enteric coating. Without this separating layer the resistance towards gastric juice would be too short and/or the storage stability of the dosage form would be unacceptably short. The sub-coated dosage form is finally coated with an enteric coating rendering the dosage form insoluble in acid media, but rapidly disintegrating-/dissolving in neutral to alkaline media such as, for instance the liquids present in the proximal part of the small intestine, the site where dissolution is wanted.

Final dosage form

The final dosage form is either an enteric coated tablet or capsule or in the case of enteric coated pellets, pellets dispensed in hard gelatin capsules or sachets or pellets formulated into tablets. It is essential for the long term stability during storage that the water content of the final dosage form containing omeprazole (enteric coated tablets, capsules or pellets) is kept low, preferably not more than 1.5% by weight. As a consequence the final package containing hard gelatin capsules filled with enteric coated pellets preferably also contain a desiccant, which reduces the water content of the gelatin shell to a level where the water content of the enteric coated pellets filled in the capsules does not exceed 1.5% by weight.

Process

A process for the manufacturer of the oral dosage form represents a further aspect of the invention. After the forming of the cores the cores are first coated with the separating layer and then with the enteric coating layer. The coating is carried out as described above.

The preparation according to the invention is especially advantageous in reducing gastric acid secretion and/or providing a gastrointestinal cytoprotective effect. 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 disease. In general the daily dose will be in the range of 1–100 mg of omeprazole. A method for the treatment of such conditions using the novel oral dosage form respresents a further aspect of the invention.

The invention is described in detail in the following examples:

EXAMPLES

Example 1

The effect of different magnesium compounds was evaluated in the form of enteric coated tablets. Tablet cores were first made by known techniques according to the formulations listed in Table 1, followed by application of separating layers and enteric coating layers as shown in Table 2.

TABLE 1

	Formulations for the tablet cores (mg)						
Formulations No.	1	2	3	4	5	6	7
Omeprazol	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Lactose	134.0	119.0	119.0	119.0	118.8	118.5	119.0
Hydroxypropyl cellulose (low substitution	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Hydroxypropyl cellulose	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Talc	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Na_2HPO_4	—	15.0	—	—	0.2	—	—
Na lauryl sulfate	—	—	—	—	—	0.5	—
MgO	—	—	15.0	—	—	—	—
$Mg(OH)_2$	—	—	—	15.0	15.0	15.0	—
Synthetic hydrotalcite $[Al_2O_3.6MgO.CO_2.12H_2O]$	—	—	—	—	—	—	15.0
Total	160.0	160.0	160.0	160.0	160.0	160.0	160.0

TABLE 2

	Formulations for coatings (mg)			
Formulation No.	I	II	III	IV
Separating layer (inner):				
Hydroxypropyl cellulose	—	2.0	2.0	2.0
Magnesium hydroxide	—	—	0.3	—
Synthetic hydrotalcite	—	—	—	0.3
Separating layer (outer):				
Hydroxypropyl cellulose	—	2.0	2.0	2.0
Enteric coating layer:				
Hydroxypropyl methylcellulose phthalate	7.0	7.0	7.0	7.0
Cetyl alcohol	0.5	0.5	0.5	0.5

The tablets thus obtained were stored in open form under so called accelerated conditions, that is 40° C.,

and 75% relative humidity, and the changes in appearance with the passage of time were observed. Storage for six months under these conditions corresponds to storage at normal temperature for three years. This means that high stability sufficient for paractical use may be assured if a drug remains intact for about one week under the mentioned conditions. The result is summerized in Table 3. As may be seen from the table, a remarkable stabilizing effect is achieved when a magnesium compound is contained in the inner separating layer.

TABLE 3

Stabilizing Effect (Appearance of Preparations)

Coating Layer	Core material 1	2	3	4	5	6	7
I At the start	C	A	A	A	A	A	A
60° C.; after 7 days	E	D	C	C	C	C	D
40° C.; 75% RH; after 7 days	F	E	B	B	B	B	E
II At the start	A	A	A	A	A	A	A
60° C.; after 7 days	E	B	A	A	A	A	C
40° C.; 75% RH; after 7 days	E	D	A	A	A	A	D
III At the start	A	A	A	A	A	A	A
60° C.; after 15 days	B	A	A	A	A	A	A
40° C.; after 30 days	A	A	A	A	A	A	A
40° C.; 75% RH; after 15 days	B	A	A	A	A	A	A
IV At the start	A	A	A	A	A	A	A
60° C.; after 15 days	B	A	A	A	A	A	A
40° C.; after 30 days	A	A	A	A	A	A	A
40° C.; 75% RH; after 15 days	B	A	A	A	A	A	A

A: white,
B: brownish white,
C: faint brown,
D: light brown,
E: brown,
F: deep brown.

All the samples evaluated as A (white) in the above table showed no descoloration even on split surfaces. The samples evaluated as B (brownish white) showed little change in appearance, but some discoloration was observed on split surfaces.

Table 4 shows the result of a stability test on the omeprazole preparation according to Example 1 (Formulation No 4-IV). The formulation was stored in a closed glass bottle at room temperature for the indicated period of time. This clearly demonstrates that preparations with unusually high stability were obtained.

TABLE 4

Stability of enteric coated omeprazole preparations (Tablets of Formulation No. 4-IV)

Storage Period	Appearance	Omeprazole Content (%)
At the start of test	White	100.0
1 year at room temperature	White	99.9
2 years at room temperature	White	100.0

Example 2

	Uncoated pellets	
I	Mannitol powder	16 150 g
	Lactose anhydrous	800 g
	Hydroxypropyl cellulose	600 g
	Microcrystalline cellulose	400 g
II	Omeprazole	2 000 g
	Sodium lauryl sulphate	50 g
	Disodium hydrogen phosphate	80 g
	Distilled water	4 400 g

The dry ingredients (I) were premixed in a mixer. Addition of a granulation liquid (II) containing suspended omeprazole was made and the mass was wet-mixed to a proper consistency. The wet mass was pressed through an extruder and spheronized to pellets. The pellets were dried and classified into suitable particle size ranges.

	Subcoated pellets	
II	Uncoated omeprazole pellets	6 000 g
	Hydroxypropyl methylcellulose	240 g
	Distilled water	4 800 g

The polymer solution (III) was sprayed on the uncoated pellets in a fluidized bed apparatus, The spray guns were placed above the fluidized bed.

	Enteric-coated pellets	
IV	Subcoated pellets	500 g
	Hydrozypropyl methylcellulose phthalate	57 g
	Cetyl alcohol	3 g
	Acetone	540 g
	Ethanol	231 g

The polymer solution (IV) was sprayed on the subcoated pellets in a fluidized bed apparatus with spray guns placed above the bed. After drying to a water content of 0.5% the enteric coated pellets were classified and filled into hard gelatin capsules in an amount of 225 mg, corresponding to 20 mg of omeprazole. 30 capsules were packed in tight containers together with a desiccant.

Example 3

This example illustrates that a variety of polymers can be used for subcoating, e.g. hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, polyethylene glycol, polyvinyl alcohols.

	Uncoated pellets	
I	Mannitol powder	1 620 g
	Lactose anhydrous	80 g
	Hydroxypropyl cellulose	60 g
	Microcrystalline cellulose	40 g
II	Omeprazole	200 g
	Sodium lauryl sulphate	1.0 g
	Disodium hydrogen phosphate	9.3 g
	Distilled water	515 g

The uncoated pellets were prepared as described in Example 2.

	Subcoated pellets	
III	Uncoated omeprazole pellets	500 g
	Polyvinylpyrrolidone	20 g
	Ethanol	400 g

The subcoated pellets were prepared as described in Example 2.

	Enteric-coated pellets	
IV	Subcoated pellets	500 g
	Hydroxypropyl methylcellulose phthalate	45 g
	Cetyl alcohol	5 g
	Acetone	219 g

-continued

Enteric-coated pellets	
Ethanol	680 g

The enteric-coated pellets were prepared as described in Example 2.

Example 4

	Uncoated pellets	
I	Mannitol powder	1 610 g
	Lactose anhydrous	80 g
	Hydroxypropyl cellulose	60 g
	Microcrystalline cellulose	40 g
II	Omeprazole	200 g
	Pluronic F68	10 g
	Disodium hydrogen phosphate	24 g
	Distilled water	450 g

The uncoated pellets were prepared as described in Example 2.

	Subcoated pellets	
III	Uncoated pellets	500 g
	Polyvinylpyrrolidone	30 g
	Ethanol	400 g

The subcoated pellets were prepared as described in Example 2.

	Enteric coated pellets	
IV	Subcoated pellets	500 g
	Hydroxypropyl methylcellulose phthalate	45 g
	Cetyl alcohol	5 g
	Methylene chloride	371 g
	Ethanol	680 g

The enteric coated pellets were prepared as described in Example 2.

Example 5

This example illustrates that a variety of polymers can be used as enteric coating material e.g. cellulose acetate phthalate, poly-(vinyl acetate/vinyl alcohol phthalate), hydroxypropyl methylcellulose phthalate, poly-(methacrylic acid/methacrylic acid methyl esters), poly-(acrylic acid/methacrylic acid methyl esters). The polymers can be applied with/without plasticizer, e.g. polyethylene glycols, triacetin, dimethyl polysiloxan, Citroflex ®, cetyl alcohol, stearyl alcohol, diethyl phthalate.

Enteric-coated pellets can also be manufactured from water-based polymer dispersions, e.g. Aquateric (FMC Corporation), Eudragit ®L 100-55, Coating CE 5142 (BASF).

	Uncoated pellets	
I	Lactose powder	277 g
	Lactose anhydrous	118 g
	Hydroxypropyl cellulose	25 g
	Colloidal silica	25 g
II	Omeprazole	50 g
	Sodium lauryl sulphate	5 g
	Disodium hydrogen phosphate	2 g
	Sodium dihydrogen phosphate	0.1 g

-continued

Uncoated pellets	
Distilled water	170 g

The uncoated pellets were prepared as described above.

Subcoated pellets

The uncoated pellets were subcoated as described in Example 2.

	Enteric coated pellets	
III	Subcoated pellets	500 g
	Eudragit L 100	45 g
	Stearyl alcohol	4.5 g
	Ethanol	1 320 g

The enteric coated pellets were prepared as described above.

Example 6

Formulations with the sodium salt of omeprazole.

	Uncoated pellets	
I	Omeprazole sodium salt	339 g
	Mannitol powder	2 422 g
	Lactose anhydrous	120 g
	Hydroxypropyl cellulose	90 g
	Microcrystalline cellulose	60 g
II	Sodium lauryl sulphate	7 g
	Distilled water	650 g

The preparation was made as described in Example 2 with the exception that the omeprazole sodium salt was added together with the other ingredients in mixture I.

	Subcoated pellets	
III	Uncoated pellets	500 g
	Hydroxypropyl methylcellulose	20 g
	Aluminium hydroxide/magnesium carbonate	4 g
	Distilled water	400 g
IV	Pellets subcoated with III	500 g
	Hydroxypropyl methylcellulose	20 g
	Distilled water	400 g

The two subcoat layers, III and IV, were applied to the uncoated pellets in a fluidized bed apparatus in consecutive order as previously described.

	Enteric coated pellets	
V	Subcoated pellets	500 g
	Hydroxypropyl methylcellulose phthalate	57 g
	Cetyl alcohol	3 g
	Acetone	540 g
	Ethanol	231 g

The preparation of enteric coated pellets was performed as described in Example 2.

Example 7 and 8

Formulations with the magnesium salt of omeprazole.

Uncoated pellets		Example No 7	Example No 8
I	Omeprazole magnesium salt	222 g	222 g
	Mannitol powder	1 673 g	1 473 g
	Microcrystalline cellulose	100 g	100 g
	Magnesium hydroxide	—	200 g
II	Sodium lauryl sulphate	5 g	5 g
	Distilled water	500 g	375 g

The preparation was made as described in Example 2 with the exception that the omeprazole magnesium salt was added together with the other ingredients in mixture I.

Subcoated pellets		Example 7 and 8
III	Uncoated pellets	500 g
	Hydroxypropyl methylcellulose	20 g
	Distilled water	400 g

The pellets were prepared as described in Example 2.

Enteric coated pellets		Examples 7 and 8
IV	Subcoated pellets	500 g
	Hydroxypropyl methylcellulose phthalate	57 g
	Cetyl alcohol	3 g
	Acetone	540 g
	Ethanol	231 g

The enteric coated pellets were prepared as described in Example 2.

Example 9 and 10

Manufacture of tablets.

Tablet cores		Examples No 9	Examples No 10
I	Omeprazole	400 g	—
	Omeprazole sodium salt, corresponding to omeprazole 400 g	—	426 g
	Lactose, anhydrous	1 420 g	1 409 g
	Polyvinylpyrrollidone, crosslinked	100 g	100 g
	Sodium carbonate, anhydrous	15 g	—
II	Methyl cellulose	12 g	12 g
	Distilled water	200 g	200 g
	Magnesium stearate	30 g	30 g

The powder mixture I was carefully homogenized and granulated by the solution II. The wet mass was dried in a fluidized bed dryer using an inlet air temperature of +50° C. for 30 minutes. The dried mixture was then forced through a sieve with an apperture of 0.5 mm. After mixing with magnesium stearate the granulate was tableted on a tableting machine using 6 mm punches. The tablet weight was 100 mg.

Subcoating

The tablets containing omeprazole were subcoated with approximately 10% by weight of hydroxypropyl methylcellulose from a water solution using a perforated coating pan apparatus.

The tablets containing omeprazole sodium salt were subcoated using the dry coating technique. A tablet granulate containing

Lactose anhydrous	4 000 g
Polyvinylpyrrolidone, (PVP)	180 g
Ethanol 95%	420 g
Magnesium stearate	42 g

was prepared in the following way. The lactose was granulated with a solution of PVP in ethanol and dried. After drying magnesium stearate was admixed.

The granulate mass was dry coated around the tablet cores of example 9 using a Manesty Dry Cota ® tableting machine. The tablet weight of the dry coated tablets was 475 mg. Each tablet contained 20 mg of omeprazole.

Enteric coating

The subcoated tablets obtained above were enteric coated using the same coating solution:

Hydroxypropyl methylcellulose phthalate	1 500 g
Cetyl alcohol	105 g
Methylene chloride	15 000 g
Isopropanol	15 000 g
Distilled water	3 150 g

The coating was applied in a perforated coating pan apparatus. An approximate amount of one kg of coating solution was applied for each kg of tablets.

COMPARATIVE EXAMPLES

Examples I, II and III

These examples illustrative that the buffer salt used effects the enteric-coated omeprazole pellets properties when the sub-coating layer is absent. A high amount of buffer salt is needed in order to obtain a long shelf life for the product. At the same time this type of pellets shows inferior acid resistance properties. C.f. also the Example 4 above.

Uncoated pellets		Examples No I	Examples No II	Examples No III
I	Mannitol powder	1 610 g	1 610 g	1 610 g
	Lactose anhydrous	80 g	80 g	80 g
	Hydroxypropyl cellulose	60 g	60 g	60 g
	Microcrystalline cellulose	40 g	40 g	40 g
II	Omeprazole	200 g	200 g	200 g
	Pluronic F68	10 g	10 g	10 g
	Disodium hydrogen phosphate	2 g	8 g	24 g
	Distilled water	450 g	450 g	450 g

The uncoated pellets were prepared as described in Example 2 above.

Enteric coated pellets	
Uncoated pellets	500 g
Hydroxypropyl methylcellulose	45 g

-continued

	Enteric coated pellets	
III	phthalate	
	Cetyl alcohol	5 g
	Methylene chloride	371 g
	Ethanol	680 g

The coated pellets were prepared as described in Example 2 above.

Example IV

This formulation is the same as in Example 6 above, but no subcoating layer was used.

	Uncoated pellets	
I	Omeprazole sodium salt	339 g
	Mannitol powder	2 422 g
	Lactose anhydrous	120 g
	Hydroxypropyl cellulose	90 g
	Microcrystalline cellulose	60 g
II	Sodium lauryl sulphate	7 g
	Distilled water	650 g

The preparation was made as described in Example 6.

	Enteric-coated pellets	
	Uncoated pellets	500 g
III	Hydroxypropyl methylcellulose phthalate	57 g
	Cetyl alcohol	3 g
	Acetone	540 g
	Ethanol	231 g

The enteric coated pellets were prepared as described in Example 2.

Example V

This formulation is the same as in Example 8 above, but no subcoating layer was used.

	Uncoated pellets	
I	Omeprazole magnesium salt	222 g
	Mannitol powder	1 473 g
	Microcrystalline cellulose	100 g
	Magnesium hydroxide	200 g
II	Sodium lauryl sulphate	5 g
	Distilled water	375 g

The preparation was made as described in Example 8.

	Enteric coated pellets	
	Uncoated pellets	500 g
III	Hydroxypropyl methylcellulose phthalate	57 g
	Cetyl alcohol	3 g
	Acetone	540 g
	Ethanol	231 g

The pellets were prepared as described in Example 2 above.

Properties of the enteric coated pellets

For the preparations according to Examples 2–8 and comparative Examples I–V above one or both of the following studies have been performed.

Acid resistance

The following resistance of the formulations was studied in the following way: The formulations were added to gastric fluid USP (without enzyme), 37° C. (paddle) 100 r/min. After 2 hours the actual amount of omeprazole remaining intact in the formulations was determined.

Rate of dissolution in buffer solution

In order to establish the rate of dissolution in the small intestine, the formulations were added to a buffer solution. Buffer solution 37° C., USP dissolution apparatus No 2 (paddle), 100 r/min. After 10 or 30 minutes the amount of omeprazole dissolved was determined. The results are presented in the following Table 5.

Example No	Omeprazole content mg/g	Acid resistance, amount intact omeprazole (%) after 2 hours	% dissolved omeprazole at different pH:s and after 10 or 30 min		
			%	pH	min
2	89.2	95	100	6.8	10
3	90	96	91	6.0	10
4	88	89	(*)		
5	82	93	70	7.5	30
6	81.3	87	93	6.8	10
7	91	95	(**)		
8	89	98	(**)		
I	93	97	(*)		
II	92	94	(*)		
III	94	58	(*)		
IV	86.5	4			
V	91	93	(**)		

(*) The stability of the formulation was studied during storage in glass bottles also containing a desiccant device. After one month storage at +50° C. the formulation according to Example 4 was virtually intact with no change in appearance or physicochemical characteristics. Pellets according to Example I and II turned brown due to degradation, while the pellets according to Example III retained to original white colour.

(**) The formulations according to Examples 7 and 8 were white and not affected by the coating process. The enteric coated pellets according to Example V, where the enteric coating was applied directly on the cores according to Example 8, was discoloured already during the enteric coating process.

Further comparative test

This example demonstrates the effect of the moisture content of the preparations according to the invention on storage stability.

The stability of omeprazole pellets according to the invention was compared with that of omeprazole pellets with higher water content. Omeprazole pellets were prepared according to the invention with a water content of 1%. Two other portions of the same formulation were conditioned to a water content of 2% and 5% respectively. The three formulations, packed in tight containers not contining a desiccant, were stored for one month at +50° C. After this time the packages were opened and the pellets were assayed for the amount of omeprazole by HPLC. The formulation according to the invention had an omeprazole content of 98.5% of the initial value. The other two formulations with a water content of 2 and 5% respectively were virtually totally degraded and had only trace amounts of intact omeprazole.

DISCUSSION

From the results given in Table 5 it can be seen that formulations containing omeprazole with acceptable acid resistance can be prepared by using a conventional enteric coating technique (see for instance Examples I, II and V). However, it is also obvious that the storage

stability of the formulations according to Examples I, II and V is not acceptable, since a discolouration, showing a degradation of omeprazole, occours during short storage at an elevated storage temperature (Examples I and II) or already during the enteric coating process (Example V).

If the amount of alkaline substances in the cores is increased to a level where omeprazole has an acceptable storage stability (Example III) or if an alkaline reacting salt of omeprazole is used in the preparation of the cores (Example IV), then, without the separating layer of the invention, the resistance to dissolution in acid media becomes unacceptably low and much or all of the active substance will degrade already in the stomach and thus, it has no effect on the gastric acid secretion.

When the preparation is carried out according to the inventon as for instance in Example 4, a good resistance towards gastric juice as well as a good stability during long-term storage is obtained. This is in contrast with the formulations in Examples I, II and III where either an acceptable acid resistance or an acceptable storage stability can be achieved—but not both. The same comparison can be made between the formulations according to Examples 7 and 8 according to the invention and the formulation according to Example V, where the separating layer was omitted. Examples 7 and 8 differ in that a buffering substance, magnesium hydroxide, has been included in the cores of Example 8. This further improves the acid resistance as well as the storage stability of Example 8 in comparison with Example 7.

The further comparative test shows the great importance of a low water content in the preparations.

Thus in order to prepare pharmaceutical formulations of omeprazole for oral use, which exert good stability during long-term storage as well as good stability during the residence in the stomach after administration, the preparation is made in the following way:

(a) Omeprazole together with an alkaline reacting compound or compounds or an alkaline reacting salt of omeprazole optionally mixed with alkaline reacting compound are included in the core material.

(b) The core material is subcoated with one or more inert, in water soluble or in water rapidly disintegrating layers, which separate the alkaline reacting core from the enteric coating. The subcoating layer may optionally contain pH-buffering compounds.

(c) The subcoated cores are coated with an acid insoluble enteric coating, optionally containing plasticizers.

Biopharmaceutical studies

The hard gelatin capsules according to Example 2 were administered to 12 healthy, young male volunteers in the following way:

The volunteers came to the laboratory in the morning after having abstained from food since 10 p.m. the night preceeding the experimental day. A zero time blood sample was taken. One omeprazole capsule according to Example 2 was administered together with 150 ml of tap water. Further blood samples were taken during the day.

In another experiment the same volunteers were administered 20 mg of omeprazole in the form of a suspension of micronized omeprazole in a sodium bicarbonate water solution. In order to reduce the degradation of omeprazole in the stomach to a minimum, sodium bicarbonate solution was given to the subjects just before the administration of the omeprazole suspension and at further four times with a 10-minutes interval after the drug intake. The concentration of omeprazole in blood plasma was assayed by high pressure liquid chromatography (Persson, Lagerström and Grundevik. Scand J Gastroenterol 1985, 20, (suppl 108), 71–77. The mean plasma concentrations are given in Table 6.

TABLE 6

The plasma concentrations (μmol/l) after 20 mg single oral doses of omeprazole given as hard gelatin capsules according to Example 2 and as a suspension of micronized omeprazole in sodium bicarbonate solution.

Time (min)	Capsules	Suspension
10		0.84
20		0.90
30	0.03	0.84
45		0.64
60	0.22	0.44
90	0.36	0.24
120	0.39	0.13
150	0.29	
180	0.20	0.04
210	0.10	
240	0.05	0.01
300	0.02	0
360	0.01	
420	0	

Although the plasma concentration peak at different times, the two formulations are bioequivalent. The mean relative bioavailability of the capsules in comparision with the suspension was 85%+23% (S.D.). The comparison was based on the total area under individual plasma concentration versus time curves.

Thus, by preparing capsules according to the invention it is possible to obtain a preparation with the same bioavailability as a suspension containing the same amount of micronized active compound. It is, however, to be noticed that when the suspension is administered, the patients must also be given sodium bicarbonate solution frequently in order to minimize pre-absorption degradation of omeprazole in the stomach.

We claim:

1. An oral pharmaceutical preparation comprising

(a) a core region comprising an effective amount of a material selected from the group consisting of omeprazole plus an alkaline reacting compound, an alkaline omeprazole salt plus an alkaline reacting compound and an alkaline omeprazole salt alone;

(b) an inert subcoating which is soluble or rapidly disintegrating in water disposed on said core region, said subcoating comprising one or more layers of materials selected from among tablet excipients and polymeric film-forming compounds; and

(c) an outer layer disposed on said subcoating comprising an enteric coating.

2. A preparation according to claim **1** wherein the subcoating layer comprises one or more of magnesium oxide, magnesium hydroxide or composite substance [$Al_2O_3.6MgO.CO_2.12H_2O$ or $MgO.Al_2O_3.2SiO_2.n$-H_2O], wherein n is not an integer and less than 2.

3. A preparation according to claim **1** wherein the subcoating comprises two or more sub-layers.

4. A preparation according to claim **3** wherein the subcoating comprises hydroxypropyl methylcellulose, hydroxypropyl cellulose or polyvinylpyrrolidone.

5. A preparation according to claim **1** wherein the alkaline core comprises omeprazole and pH-buffering alkaline compound rendering to the micro-environment of omeprazole a pH of 7–12.

6. A preparation according to claim 5 wherein the alkaline compound comprises one or more of magnesium oxide, hydroxide or carbonate, aluminium hydroxide, aluminium, calcium, sodium or potassium carbonate, phosphate or citrate, the composite aluminium/-magnesium compounds $Al_2O_3.6MgO.CO_2.12H_2O$ or $MgO.Al_2O_3.2SiO_2.nH_2O$, where n is not an integer and less than 2.

7. A preparation according to claim 1, wherein the core region comprises a salt of omeprazole selected from along the sodium, potassium, magnesium, calcium and ammonium salts.

8. A preparation according to claim 1 wherein the enteric coating comprises hydroxypropyl methylcellulose pthalate, cellulose acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl ester or polyvinyl acetate phthalate, optionally containing a plasticizer.

9. A preparation according to claim 1 wherein the water content of the final dosage form containing omeprazole does not exceed 1.5% by weight.

10. A method for the treatment of gastrointestinal disease comprising administering to a host in need of such treatment a therapeutically effective amount of a preparation according to claim 1.

11. A preparation according to claim 1, wherein the subcoating further comprises an alkaline buffering compound.

12. A preparation according to claim 1, wherein the core comprises omeprazole and disodium hydrogen phosphate, and the subcoating comprises hydroxy propyl methyl cellulose.

13. A preparation according to claim 1, wherein the alkaline core comprises omeprazole and magnesium hydroxide, the subcoating comprises a layer comprising hydroxypropyl cellulose and synthetic hydrotalcite, and the outer layer comprises hydroxypropyl cellulose.

14. A process for the preparation of an oral pharmaceutical preparation containing omeprazole, comprising

(a) preparing a core comprising an effective amount of a material selected from the group consisting of omeprazole plus an alkaline reacting compound, an alkaline omeprazole salt plus an alkaline reacting compound and an alkaline omeprazole salt alone;

(b) coating the core with one or more layers of an inert subcoating material selected from among tablet excipients and polymeric film-forming compounds to form a subcoated core; and

(c) coating the subcoated core with an enteric coating.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 4,786,505

DATED : November 22, 1988

INVENTOR(S) : Kurt I. Lovgren et al.

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

First page, first column, last line, "4,685,919" should read --4,685,918--;

First page, second column, after "1485676 9/1977 United Kingdom" insert

--0077956 5/1983 European
862376 3/1961 Great Britain

Other Documents

Developement of an oral formulation of omeprazole
Pilbrant A. and Cederberg C., Department of Pharmaceutics and Medicine, pgs-113-120.--.

Column 1, line 41, after "release" insert --of--;

Column 2, line 45, "204 363" should read --1 204 363--;

Column 4, line 39, "polyvinylpyrroline" should read --polyvinylpyrrolidone--;

Column 6, line 20, "1-100 mg" should read --1-400 mg--;

Column 14, between lines 17 and 19, insert --TABLE 5--;

Column 17, line 11, "along" should read --among--;

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 4,786,505
DATED : November 22, 1988
INVENTOR(S) : Kurt I. Lovgren et al.

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

Column 17, line 15, "pthalate" should read -- phthalate --.

Signed and Sealed this
Eighteenth Day of July, 1989

Attest:

Attesting Officer

DONALD J. QUIGG

Commissioner of Patents and Trademarks

EXHIBIT “C”

United States Patent [19]

Lovgren et al.

[11] **Patent Number: 4,853,230**

[45] **Date of Patent: * Aug. 1, 1989**

[54] **PHARMACEUTICAL FORMULATIONS OF ACID LABILE SUBSTANCES FOR ORAL USE**

[75] Inventors: **Kurt I. Lovgren**, Mölnlycke; **Ake G. Pilbrant**, Kungsbacka, both of Sweden; **Mitsuru Yasumura**; **Satoshi Morigaki**, both of Hyogo; **Minoru Oda**, Ohita; **Naohiro Ohishi**, Fukuoka, all of Japan

[73] Assignee: **Aktiebolaget Hassle**, Molndal, Sweden

[*] Notice: The portion of the term of this patent subsequent to Nov. 22, 2005 has been disclaimed.

[21] Appl. No.: **40,490**

[22] Filed: **Apr. 20, 1987**

[30] **Foreign Application Priority Data**

Apr. 30, 1986 [GB] United Kingdom 8610573

[51] **Int. Cl.**[4] **A61K 9/46**

[52] **U.S. Cl.** **424/466**; 424/468; 424/475; 424/479; 424/480; 424/482; 424/456

[58] **Field of Search** 424/470, 495, 468, 480, 424/482, 466, 471, 472

[56] **References Cited**

U.S. PATENT DOCUMENTS

2,540,979	2/1951	Clymer et al.	167/82
3,131,123	4/1964	Masquelier	424/466
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FOREIGN PATENT DOCUMENTS

0005129	6/1981	European Pat. Off. .	
0077956	5/1983	European Pat. Off.	424/495
WO85/03436	8/1985	PCT Int'l Appl. .	
0862376	3/1961	United Kingdom	424/470
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OTHER PUBLICATIONS

Pilbrant, A and Cederberg, C, "Development of an Oral Formulation of Omeprazole," Scand. J. Gastroenterology, 1985, pp. 113–120.

Blanchi, A. et al., "Control of Acute Zollinger–Ellison Syndrome with Intravenous Omeprazole", The Lancet, Nov. 27, 1982, pp. 1223–1224.

Primary Examiner—Thurman K. Page

Attorney, Agent, or Firm—Brumbaugh, Graves, Donohue & Raymond

[57] **ABSTRACT**

Pharmaceutical preparation containing an acid labile compound together with an alkaline reacting compound or an alkaline salt of an acid labile compound optionally together with an alkaline compound as the core material, one or more subcoating layers comprising inert reacting compounds which are soluble or rapidly disintegrating in water, or polymeric, water soluble filmforming compounds, optionally containing pH-buffering alkaline compounds and an enteric coating as well as a process for the preparation thereof and the use in the treatment of gastrointestinal diseases.

15 Claims, No Drawings

PHARMACEUTICAL FORMULATIONS OF ACID LABILE SUBSTANCES FOR ORAL USE

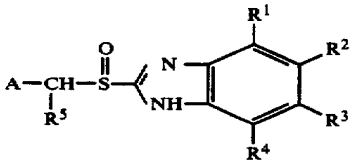
FIELD OF THE INVENTION

The present invention is related to new pharmaceutical preparations containing acid labile substances for oral use, to a method for the manufacture of such preparations and to a method of affecting gastric acid secretion and providing gastrointestinal cytoprotective effect when using them.

BACKGROUND OF THE INVENTION

Acid labile substances present a problem to the formulator when formulating a pharmaceutical dosage form for oral use. In order to prevent the substances from contact with the acid reacting gastric juice after oral intake, the conventional way to solve this problem is to coat the dosage form with an enteric coating. The coating is a group of substances/polymers with the common feature of being practically insoluble in acid media, while they are soluble in neutral to alkaline media. For substances that are labile in acid media, but have better stability in neutralto alkaline media, it is often advantageous to add alkaline reacting inactive constituents in order to increase the stability of the active compound during manufacture and storage.

A group of comounds exerting these stability properties are substituted benzimidazoles with the geneal formula I



wherein A is an optionally substituted heterocyclic group and R^1, R^2, R^3, and R^4 are the same or different as defined below and R^5 is H or a lower alkyl, or the compound 2-[(2-dimethylaminobenzyl)sulfinyl]-benzimidazole.

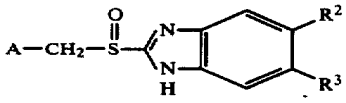
The compounds with the general formula I are virtually biologically inactive as such, but degrade/transform to active inhibitors of certain enzyme systems in acid media.

As examples of compounds with the mentioned properties the compounds described in the patents U.S. Pat. No. 4045 563, EP-1-0 005 129 and BE-898 880 and the patent applications EP-85850258,6, EP-A1-0 080 602, EP-0127 736, EP-0 134 400, EP-0 130 729, EP-0 150 586, DE-3415971 GB-2 082 580 and SE-A-8504048-3 may be mentioned. The last application describes 2-(2-disubstituted-aminobenzyl)sulfinyl benzimidazoles, e.g. 2-(2-dimethylaminobenzyl)sulfinyl benzimidazole, also called, NC-1300 and presented by Prof. S. Okabe at the Symposium on Drug Activity held on Oct. 17, 1985 in Nagoya, Japan, and which interacts with the H^+K^+-ATPase after acid degradation within the parietal cells. (See for instance B. Wallmark, A. Brändstroöm and H. Larson "Evidence for acid-induced transformation of omeprazole into an active inhibitor of H^+K^+-ATPase within the partial cell", Biochemica et Biophysica Acta 778, 549–558, 1984). Other compounds with similar properties are further mentioned in the patent U.S. Pat. No. 4 182 766 and the patent applications GB-2 141 429, EP-O 146 370 and GB-2 082 580. A common feature of these compounds are that they are transformed into the biologically active compounds via rapid degradation/-transformation in acid media.

The stability profile of some compounds with the general formula I above is exemplifide in the Table 1 below, where the half-life of the degradation/transformation reaction in solution at pH 2 and 7 are given.

TABLE 1

Rate of degradation/transformation of compounds with the general structure



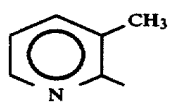
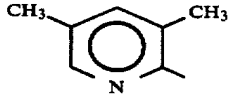
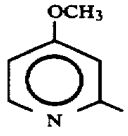
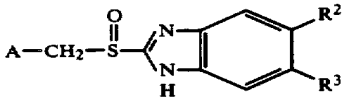
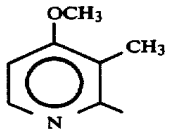
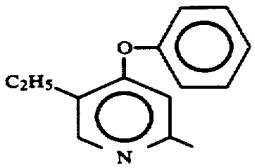
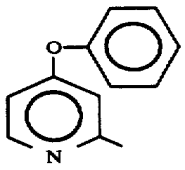
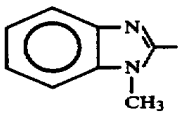
Compound No	A	R^2 R^3	Half-life (mintues) for the transformation to the active moiety at pH = 2	at pH = 7
1.		5-$COOCH_3$;6-CH_3	11	150
2.		5-CH_3;H	5.4	1700
3.		5-CF_3;H	1.9	122

TABLE 1-continued

Rate of degradation/transformation of compounds with the general structure



Compound No	A	R^2 R^3	Half-life (mintues) for the transformation to the active moiety at pH = 2	at pH = 7
4.		5-CF_3;H	2.0	8.8
5.		5-OCH_3;H	3.7	1620
6.		5-OCH_3;H	4.0	3900
7.		5-C_2H_5;H	33	not determined

Substituted sulfoxides, such as for instance the substituted benzimidazoles described in EP-1-0005129 are potent inhibitors of gastric acid secretion. The substituted benzimidazoles are susceptible to degradation/-transformation in acid reacting and neutral media.

It is an inherent property of these compounds to be activated to the active moiety in the acid environment within the parietal cells. The activated compound interacts with the enzyme in the parietal cells, which mediates the production of hydrochloric acid in the gastric mucosa. All compounds of the class of substituted benzimidazoles, containing a sulfoxide grouping, which interferes with the H^+K^+-ATPase in the parietal cells hitherto known are all also degraded in acid media.

A pharmaceutical dosage form of acid labile substances, which prevents the substances from contact with acidic gastric juice, must be enteric coated. Ordinary enteric coatings, however, are made of acidic compounds. If covered with such a conventional enteric coating, the acid labile substance rapidily decomposes by direct or indirect contact with it, with the result that the preparations become badly discoloured and lose in content of the active compound with the passage of time.

In order to enhance the storage stability, the cores which contain the acid labile substance must also contain alkaline reacting constituents. When such an alkaline core is enteric coated with an amount of a conventional enteric coating polymer such as, for example, cellulose acetate phthalate, that permits the dissolution of the coating and the active drug contained in the cores in the proximal part of the small intestine, it also will allow some diffusion of water or gastric juice through the enteric coating into the cores, during the time the dosage form resides in the stomach before it is emptied into the small intestine. The diffused water or gastric juice will dissolve parts of the core in the close proximity of the enteric coating layer and there form an alkaline solution inside the coateddosage form. The alkaline solution will interfere with the enteric coating and eventually dissolve it.

In DE-A1-3 046 559 a way to coat a dosage form is described. First the dosage form is coated with a water insoluble layer containing microcrystalline cellulose and then with a second enteric coating with the aim to achieve a dosage form which releases the active drug in the colon. This method of preparation will not give the desired release of the compounds with the general formula I above in the small intestine.

U.S. Pat. No. 2 540 979 describes an enteric coated oral dosage form, where the enteric coating is combined with a second and/or first coating of a water insoluble "wax" layer. This method of preparation is not applica-

ble on cores containing a compound with the general formula I since direct contact between substances such as cellulose acetate phthalate (CAP) and a compound of formula I causes degradation and discolouration of the compounds of the formula I.

DE-B2-23 36 218 describes a method to produce a dialysis membrane consisting of a mixture of one or more conventional enteric coating polymers and one or more insoluble cellulose derivatives. Such a membrane will not give a proper protection of the acid labile compounds of the formula I in gastric juice.

DE-A1-1 204 363 describes a three-layer coating procedure. The first layer is soluble in gastric but is insoluble in intestinal juice. The second is water soluble regardless of pH and the third layer is an enteric coating. This preparation as well as the preparation described in DE-A1-1 617 615 result in a dosage form which is not dissolved in gastric juice and which only dissolves slowly in intestinal juice. Such preparations cannot be used for the compounds of the formula I, where a rapid release of the drug in the small intestine is needed. DE-A1 12 04 363 describes coating with three layers to achieve release of a drug in the ileum, an aim which is outside the scope of the present invention. GB-A-1 485 676 describes a way to obtain a preparation which effervesces in the small intestine. This is obtained by the enteric coating of a core containing the active drug and an effervescing system such as a combination of carbonate and/or bicarbonate salt and a pharmaceutically acceptable acid. This formulation cannot be adopted for a pharmaceutical dosage form containing a compound of formula I as the presence of an acid in contact with a compound of formula I in the cores would give as a result that the compound of formula I was degraded.

WO No. 85/03436 describes a pharmaceutical preparation, wherein cores containing active drugs mixed with for instance buffering components such as sodium dihydrogenphosphate with the aim of maintaining a constant pH and a constant rate of diffusion, are coated with a first coating which controls as the diffusion. This formulation cannot be adopted for acid labile compounds where a rapid release in the small intestive is wanted. Direct application of an enteric coating onto the cores would also adversely influence the storage stability of such dosage forms containing acid labile compounds.

Outline of the invention

According to the present invention it has been found that the known acid labile compounds with the general formula I above in which R^1, R^2, R^3 and R^4 are the same or different and are

(a) hydrogen
(b) halogen, e.g. F, Cl, Br, I
(c) —CN
(d) —CHO
(e) $-CF_3$
(f) $-C(=O)-R^{11}$
(g) $-O-C(=O)-R^{12}$
(h) $-CH(OR^{13})_2$
(i) $-(Z)_n-B-D$
(j) aryl containing up to 10 carbon atoms
(k) aryloxy containing up to 10 carbon atoms, optionally substituted by alkyl containing 1–6 carbon atoms

-continued

(l) -alkylthio containing 1–6 carbon atoms
(m) $-NO_2$
(n) -alkylsulfinyl containing 1–6 carbon atoms
(o) or wherein adjacent groups R^1, R^2, R^3 and R^4 together with the adjacent carbon atoms in the benzimidazole ring form a 5-, 6-, 7-membered monocyclic ring or a 9-, 10- or 11-membered bicyclic ring, which rings may be saturated or unsaturated and may contain 0–3 hetero atoms selected from —N— and —O—, and which rings may be optionally substituted with 1–4 substituents selected from alkyl groups with 1–3 carbon atoms, alkylene radicals containing 4–5 carbon atoms giving spiro compounds, or two or four of these substituents together form one or two oxo groups ($-C(=O)-$), whereby if R^1 and R^2, R^2 and R^3 or R^3 and R^4 together with the adjacent carbon atoms in the benzimidazole ring form two rings they may be condensed with each other, in which formulas R^{11} and R^{12}, which are the same or different, are
(a) aryl containing up to 10 carbon atoms
(b) alkoxy containing 1–4 carbon atoms
(c) alkoxyalkoxy containing 1–3 carbon atoms in each alkoxy part
(d) arylalkoxy containing 1–2 carbon atoms in the alkoxy part and up to 10 carbon atoms in the aryl part
(e) aryloxy containing up to 10 carbon atoms
(f) dialkylamino containing 1–3 carbon atoms in the alkyl parts, or
(g) pyrrolidino or piperidino, optionally substituted with alkyl containing 1–3 carbon atoms;

R^{13} is (a) alkyl containing 1–4 carbon atoms, or (b) alkylene containing 2–3 carbon atoms;

Z is —O— or $-C(=O)-$;

n is 0 or 1;

B is (a) alkylene containing 1–6 carbon atoms (b) cycloalkylene containing 3–6 carbon atoms (c) alkenylene containing 2–6 carbon atoms (d) cycloalkylene containing 3–6 carbon atoms, or (e) alkynylene containing 2–6 carbon atoms;

D is (a) H (b) —CN (c) $-C(=O)-R^9$ (d) $-(Y)_m-(C(=O))_r-R^{10}$

wherein

R^9 is (a) alkoxy containing 1–5 carbon atoms, or (b) dialkylamino containing 1–3 carbon atoms in the alkyl parts;

m is 0 or 1;

r is 0 or 1;

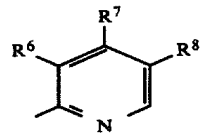
Y is (a) —O— (b) —NH— (c) $-NR^{10}-$;

R^{10} is (a) H (b) alkyl containing 1–3 carbon atoms (c) arylalkyl containing 1–2 carbon atoms in the alkyl part and up to 10 carbon atoms in the aryl part (d) aryl containing up to 10 carbon atoms;

R^5 is H, CH_3 or C_2H_5;

-continued

A is expecially a pyridyl group in which R^6 and R^8 are the same or different, are



R^7 is
- (a) H or
- (b) alkyl containing 1–6 carbon atoms;
- (a) H
- (b) alkyl containing 1–8 carbon atoms
- (c) alkoxy containing 1–8 carbon atoms
- (d) alkenyloxy containing 2–5 carbon atoms
- (e) alkynyloxy containing 2–5 carbon atoms
- (f) alkoxyalkoxy containing 1–2 carbon atoms in each alkoxy group
- (g) aryl containing up to 10 carbon atoms
- (h) arylalkyl containing 1–6 carbon atoms in the alkyl part and up to 10 carbon atoms in the aryl part
- (i) aryloxy containing up to 10 carbon atoms, optionally substituted by alkyl containing 1–6 carbon atoms
- (j) arylalkoxy contiaining 1–6 carbon atoms in the alkoxy part and up to 10 carbon atoms in the aryl part
- (k) dialkylaminoalkoxy containing 1–2 carbon atoms in the alkyl substituents on the amino nitrogen and 1–4 carbon atoms in the alkoxy group
- (l) oxacycloalkyl containing one oxygen atom and 3–7 carbon atoms
- (m) oxacycloalkoxy containing two oxygen atoms and 4–7 carbon atoms
- (n) oxacycloalkylalkyl containing one oxygen atom and 4–7 carbon atoms
- (o) oxacycloalkylalkoxy containing two oxygen atoms and 4-6 carbon atoms, or
- (p) R^6 R^7, or R^7 and R^8 together with the adjacent carbon atoms in the pyridine ring form a ring wherein the part constituted by R^6 and R^7, or R^7 and R^8, is

$-CH=CH-CH=CH-$

$-O-(CH_2)_p-$

$-S-(CH_2)_v-$

$-CH_2(CH_2)_p-$

$-O-CH=CH-$

$-NH-CH=CH-$

$-N(CH_3)-CH=CH-$

wherein p is 2, 3 or 4, v is 2 or 3 and the O and N atoms always are attached to position 4 in the pyridine ring; provided that not more than one of R^6, R^7 and R^8 is hydrogen can be formulated into an enteric coated dosage form.

The object of the present invention is thus an enteric coated dosage form of acid labile compounds with the general formula I defined above except the compound omeprazole, 5-methoxy-2-(4-methoxy-3,5dimethyl-2-pyridinyl methyl sulfinyl-1H-benzimidazole. Another compound, which may be enteric coated according to the invention is 2-(2-dimethylaminobenzyl)sulfinyl-benzimidazole. The new preparations are resistant to dissolution in acid media, dissolve rapidly in neutral to alkaline media and have a good stability during long-term storage. The new dosage form is characterized in the following way. Cores containing the acid labile compound mixed with alkaline compounds or an alkaline salt of the acid labile compound optionally mixed with an alkaline compound are coated with two or more layers, whereby the first layer/layers is/are soluble in water or rapidly disintegrating in water and consist(s) of non-acidic, otherwise inert pharmaceutically acceptable substances. This/these first layer/layers separates/separate the alkaline core material from the outer layer, which is an enteric coating. The final, enteric coated dosage form is treated in a suitable way to reduce the water content to a very low level in order to obtain a good stability of the dosage form during long-term storage.

As examples of compounds especially suitable for the pharmaceutical dosage form according to the invention the compounds listed in Table 1 can be mentioned.

The half-life of degradation of the compounds 1–6 in Table 1 in water solution at pH-values less than four is in most cases shorter than ten minutes. Also at neutral pH-values the degradation reaction proceeds rapidly, e.g. at pH=7 the half-life of degradation is between 10 minutes and 65 hours while at higher pH-values the stability in solution for most compounds is much better. The stability profile is similar in solid phase. The degradation is catalyzed by acid reacting substances. The acid labile compounds are stabilized in mixtures with alkaline reacting substances.

From what is said about the stability properties of the acid labile compounds listed above it is obvious that an oral dosage form of the said compounds must be protected from contact with the acid reacting gastric juice in order to reach the small intestine without degradation.

DETAILED DESCRIPTION OF THE INVENTION

Cores

The acid labile active compound is mixed with inert, preferably water soluble, conventional pharmaceutical constituents to obtain the preferred concentration of the active compound in the final mixture and with an alkaline reacting, otherwise inert, pharmaceutically acceptable substance (or substances), which creates a "micro-pH" around each particle of active compound of not less than pH=7, preferably not less than pH=8, when water is adsorbed to the particles of the mixture or when water is added in small amounts to the mixture. 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; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances such as $Al_2O_3.6MgO\ CO_2.12H_2O$, $(Mg_6Al_2(OH)_{16}CO_3 4H_2O)$, $MgO.Al_2O_3.2SiO_2.nH_2O$, wherein n not is an integer and less than 2 or similar compounds; organic pH-buffering substances such as trishydroxymethylaminomethane or other similar, pharmaceutically acceptable pH-buffering substances. The stabilizing, high pH-value in the powder mixture can also be achieved by using an alkaline reacting, salt of the active compound such as the sodium, potassium, magnesium, calcium etc. salts of acid labile compounds, either alone or in combination with a conventional buffering substance as previously described.

The powder mixture is then formulated into small beads i.e. pellets or tablets, by conventional pharmaceutical procedures. The pellets, tablets or gelatin capsules are used as cores for further processing.

Separating layer

The alkaline reacting cores containing an acid labile compound must be separated from the enteric coating

polymer(s) containing free carboxyl groups, which otherwise causes degradation/discolouration of the acid labile compound during the coating process of during storage. The subcoating layer, (the separating layer), also serves as a pH-buffering zone in which hydrogen ions diffusing from the outside in towards the alkaline core can react with hydroxyl ions diffusing from the alkaline core towards the surface of the coated articles. 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 $Al_2O_3.6MgO\ CO_2.12H_2O$, $(Mg_6Al_2(OH)_{16}CO_3, 4H_2O)$, $MgO.Al_2O_3.2SiO_2.nH_2O$, wherein n not is an integer and less than 2 or similar compounds; or other pharmaceutically acceptable pH-buffering substances such as, for instance the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, citric or other suitable, weak, inorganic or organic acids.

The separating layer consists of one or more water soluble inert layers, optionally containing pH-buffering substances.

The separating layer(s) can be applied to the cores—pellets or tablets—by conventional coating procedures in a suitable coating pan 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 the pharmaceutically acceptable, water soluble, inert compounds or polymers used for film-coating applications such as, for instance sugar, polyethylene glycol, polyvinylpyrrollidone, polyvinyl alcohol, hydroxypropyl cellulose, hydroxymethyl cellulose, hydroxypropyl methylcellulose or the like. The thickness of the separating layer is not less than 2 μm, for small spherical pellets preferably not less than 4 μm, for tablets preferably not less than 10 μm.

In the case of tablets another method to apply the coating can be performed by the drycoating technique. First a tablet containing the acid labile compound is compressed as described above. Around this tablet another layer is compressed using a suitable tableting machine. The outer, separating layer, consists of pharmaceutically acceptable, in water soluble or in water rapidly disintegrating tablet excipients. The separating layer has a thickness of not less than 1 mm. Ordinary plasticizers, pigments, titanium dioxide talc and other additives may also be included into the separating layer.

In the case of gelatin capsules the gelatin capsule itself serves as separating layer.

Enteric coating layer

The enteric coating layer is applied on to the subcoated cores by conventional coating techniques such as, for instance, pan coating or fluidized bed coating using solutions of polymers in water and/or suitable organic solvents or by using latex suspensions of said polymers. As enteric coating polymers can be used, for example, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl esters such as, for instance, compounds known under the trade name Eudragit ® L 12,5 or Eudragit ® L 100, (Röhm Pharma) or similar compounds used to obtain enteric coatings.

The enteric coating can also be applied using water-based polymer dispersions, e.g. Aquateric (FMC Corporation), Eudragit ® L 100-55 (Röhm Pharma), Coating CE 5142 (BASF). The enteric coating layer can optionally contain a pharmaceutically acceptable plasticizer such as, for instance, cetanol, triacetin, citric acid esters such as, for instance, those known under the trade name Citroflex ® (Pfizer) phthalic acid esters, dibutyl succinate or similar plasticizers.

The amount of plasticizer is usually optimized for each enteric coating polymer(s) and is usually in the range of 1–20% of the enteric coating polymer(s). Dispersants such as talc, colourants and pigments may also be included into the enteric coating layer.

Thus the special preparation according to the invention consists of cores containing the acid labile compound mixed with an alkaline reacting compound or cores containing an alkaline salt of the acid labile compound optionally mixed with an alkaline reacting compound. The cores suspended in water forms a solution or a suspension which has a pH, which is higher than that of a solution in which the polymer used for enteric coating is just soluble. The cores are coated with a water soluble or in water rapidly disintegrating coating, optionally containing a pH-buffering substance, which separates the alkaline cores from the enteric coating. Without this separating layer the resistance towards gastric juice would be too short and the storage stability of the dosage form would be unacceptably short. The sub-coated dosage form is finally coated with an enteric coating rendering the dosage form insoluble in acid media, but rapidly disintegrating/dissolving in netural to alkaline media such as, for instance the liquids present in the proximal part of the small intestine, the site where dissolution is wanted.

Final dosage form

The final dosage form is either an enteric coated tablet or capsule or in the case of enteric coated pellets, pellets dispensed in hard gelatin capsules or sachets or pellets formulated into tablets. It is essential for the long term stability during storage that the water content of the final dosage form containing acid labile compound (enteric coated tablets, capsules or pellets) is kept low, preferably not exceeding 1.5% by weight.

Process

A process for the manufacture of the oral dosage form represents a further aspect of the invention. After the forming of the cores the cores are first coated with the separating layer and then with the enteric coating layer. The coating is carried out as described above.

The preparation according to the invention is especially advantageous in reducing gastric acid secretion and/or providing a gastrointestinal cytoprotective effect. It is usually administered one to several times a day. The typical daily dose of the active substance varies and will depend on various factors such as for example the individual requirement of the patients, the mode of administration and the disease. In general the dosage will be in the range of 1 to 400 mg per day of active substance. A method for the treatment of such conditions using the vovel oral dosage form represents a further aspect of the invention.

The invention is described in detail in the following examples:

EXAMPLES

Examples 1–3 exemplify the invention.

EXAMPLE 1

	Uncoated pellets	
I	Lactose powder	253 g
	Lactose anhydrous	167 g
	Hydroxypropyl cellulose	25 g
II	Compound 1, Table I	50 g
	Sodium lauryl sulphate	5 g
	Disodium hydrogen phosphate	1.5 g
	Sodium dihydrogen phosphate	0.1 g
	Distilled water	125 g

The dry ingredients (I) were premixed in a mixer. Addition of a granulation liquid (II) containing the suspended active compound was made and the mass was wet-mixed to a proper consistency. The wet mass was pressed through an extruder and spheronized to pellets. The pellets were dried and classified into suitable particle size ranges.

	Subcoated pellets	
III	Uncoated pellets	500 g
	Hydroxypropyl methylcellulose	20 g
	Distilled water	400 g

The polymer solution (III) was sprayed onto the uncoated pellets in a fluidized bed apparatus. The spray guns were placed above the fluidized bed.

	Enteric coated pellets	
IV	Subcoated pellets	500 g
	Hydroxypropyl methylcellulose phthalate	57 g
	Cetyl alcohol	3 g
	Acetone	540 g
	Ethanol	231 g

The polymer solution (IV) was sprayed on the subcoated pellets in a fluidized bed apparatus with spray guns placed above the bed. After drying to a water content of 0.5% the enteric coated pellets were classified and filled into hard gelatin capsules in an amount of 284 mg, corresponding to 25 mg of active compound 1. 30 capsules were packed in tight containers together with a desiccant.

EXAMPLE 2

Formulation with the sodium salt of compound 2 according to Table I.

	Uncoated pellets	
I	Compound 2, Table I sodium salt	339 g
	Mannitol powder	2 422 g
	Lactose anhydrous	120 g
	Hydroxypropyl cellulose	90 g
	Microcrystalline cellulose	60 g
II	Sodium lauryl sulphate	7 g
	Distilled water	650 g

The preparation was made as described in Example 1 with the exception that the sodium salt of compound 2 was added together with the other ingredients in mixture I.

	Subcoated pellets	
III	Uncoated pellets	500 g
	Hydroxypropyl methylcellulose	20 g
	Aluminium hydroxide/magnesium carbonate	4 g
	Distilled water	400 g
	Pellets subcoated with III	500 g
IV	Hydroxypropyl methylcellulose	20 g
	Distilled water	400 g

The two subcoat layers, III and IV, were applied to the uncoated pellets in a fluidized bed apparatus in consecutive order as previously described.

	Enteric coated pellets	
V	Subcoated pellets	500 g
	Hydroxypropyl methylcellulose phthalate	57 g
	Cetyl alcohol	3 g
	Acetone	540 g
	Ethanol	231 g

The preparation of enteric coated pellets was performed as described in Example 1.

EXAMPLE 3

Formulation with compound 6, according to Table 1. This example gives the composition of one unit dose according to the invention.

Tablet core	
Compound 6, Table 1	15 mg
Lactose	119 mg
Hydroxypropyl cellulose (low substitution)	5 mg
Hydroxypropyl cellulose (low substitution)	1 mg
Talc	5 mg
$Mg(OH)_2$	15 mg
Total	160 mg

Tablet cores having the composition above and each weighing 160 mg were first made by known techniques.

Separating layer (inner)	
Hydroxypropyl cellulose	2 mg
Synthetic hydrotalcite $[Al_2O_3.6MgO.CO_2.12H_2O]$	0.3 mg
Separating layer (outer)	
Hydroxypropyl cellulose	2 mg

The two separating layers were applied to the cores by known coating techniques.

Enteric coating layer	
Hydroxypropyl methylcellulose phthalate	7 mg
Cetyl alcohol	0.5 mg

The enteric coating solution was sprayed on the cores coated by the two separating layers by known enteric coating techniques.

We claim:

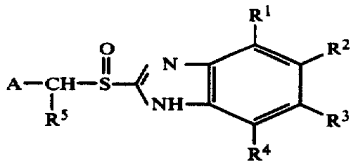
1. A pharmaceutical preparation comprising:

(a) an alkaline reacting core comprising an acid-labile pharmaceutically active substance and an alkaline reacting compound different from said active substance, an alkaline salt of an acid labile pharmaceutically active substance, or an alkaline salt of an acid labile pharmaceutically active substance and an alkaline reacting compound different from said active substance;

(b) an inert subcoating which rapidly dissolves or disintegrates in water disposed on said core region, said subcoating comprising one or more layers comprising materials selected from the group consisting of tablet excipients, film-forming compounds and alkaline compounds; and

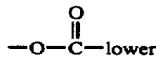
(c) an enteric coating layer surrounding said subcoating layer, wherein the subcoating layer isolates the alkaline reacting core from the enteric coating layer such that the stability of the preparation is enhanced.

2. A preparation according to claim 1, wherein the acid labile compound has the general formula I,



I

wherein A is an optionally substituted heterocyclic group, R^1, R^2, R^3 and R^4 are the same or different and select from among hydrogen, lower alkyl, lower alkoxy, $-CF_3$,



alkyl or halogen and R^5 is H or a lower alkyl group wherein "lower" denotes 1–6 carbon atoms except the compound omerprazole, 5-methoxy-2[[(4-methoxy-3,5 dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole; or the acid labile compound is 2-[(2-dimethylaminobenzyl)sulfinyl]-benzimidazole.

3. A preparation according to dlaim 1 wherein the subcoating layer comprises one or more of magnesium oxide, magnesium hydroxide or composite substance [$Al_2O_3.6MgO.CO_2.12H_2O$ or $MgO.Al_2O_3.2SiO_2.nH_2O$], wherein n is not an integer and less than two.

4. A preparation according to claim 2 wherein the subcoating comprises two or more sub-layers.

5. A preparation according to claim 4 wherein the subcoafting comprises hyroxypropyl methylcellulose, hyroxypropyl cellulose or polyvinyl-pyrrolidone.

6. A preparation according to claim 1, wherein an alkaline core comprises the acid labile compound and a pH-buffering alkaline reacting compound which renders to the micro-environment of the acid labile compound a pH of 7–12.

7. A preparation according to claim 6 wherein the alkaline reacting compound comprises one or more of magnesium oxide, hydroxide or carbonate, aluminium hydroxide, aluminium, calcium, sodium or potassium carbonate, phosphate or citrate, the composite aluminium/magnesium compounds $Al_2O_3.6MgO.CO_2.12H_2O$ or $MgO.Al_2O_3.2SiO_2.nH_2O$, wherein n is not an integer and less than two.

8. A preparation according to claim 1, wherein the alkaline core comprises an alkaline salt of the acid labile compound such as the sodium, potassium, magnesium calcium or ammonium salt.

9. A preparation according to claim 7 wherein the alkaline core comprises an alkaline salt of the acid labile compound mixed with an inert, alkaline compound.

10. A preparation according to claim 1, wherein the enteric coating comprises hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl ester or polyvinyl acetate phthalate, optionally containing a plasticizer.

11. A preparation according to claim 1, wherein the water content of the final dosage form containing the acid labile compound does not exceed 1.5% by weight.

12. Process for the preparation of an oral pharmaceutical formulation containing an acid labile compound in which cores containing the acid labile compound mixed with an alkaline reacting compound or compounds or an alkaline salt of the acid labile compound optionally mixed with an alkaline reacting compound or compounds are coated with one or more inert reacting subcoating layers whereafter the subcoated cores are further coated with an enteric coating layer.

13. A method for the treatment of gastrointestinal disease characterized in that a preparation according to claim 1 is administered to a host in the need of such treatment in a therapeutically effective amount.

14. A preparation according to claim 8, wherein the salt of the acid labile compound is selected from among the sodium, potassium, magnesium, calcium and ammonium salts.

15. A preparation according to claim 1, wherein the subcoating further comprises an alkaline buffering compound.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,853,230

DATED : August 1, 1989

INVENTOR(S) : Kurt I. Lovgren, et al.

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

Cover page, first column, under "Notice", change "Nov. 22, 2005" to --April 20, 2007--.

Signed and Sealed this

Fifteenth Day of July, 1997

Attest:

Attesting Officer

BRUCE LEHMAN

Commissioner of Patents and Trademarks