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EMC

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

TAKEDA PHARMACEUTICAL CO., LTD., TAKEDA PHARMACEUTICALS NORTH AMERICA, INC., TAKEDA PHARMACEUTICALS LLC, AND TAKEDA PHARMACEUTICALS AMERICA, INC., Plaintiffs, v. IMPAX LABORATORIES, INC., Defendant.	CV 11 1610 CASE NO. **COMPLAINT FOR PATENT INFRINGEMENT**

Plaintiffs Takeda Pharmaceutical Company Limited, Takeda Pharmaceuticals North America, Inc., Takeda Pharmaceuticals LLC, and Takeda Pharmaceuticals America, Inc. (collectively, "Plaintiffs"), state the following as their Complaint against Defendant Impax Laboratories, Inc.:

I.

THE PARTIES

1. Plaintiff Takeda Pharmaceutical Company Limited ("TPC") is a Japanese corporation with its principal place of business at 1-1, Doshomachi 4-chome, Chuo-ku, Osaka, Japan. TPC's business includes the research, development, and marketing of pharmaceutical products.

2. TPC is the owner of record and assignee of U.S. Patent No. 6,462,058 (the "'058 Patent"), U.S. Patent No. 6,664,276 (the "'276 Patent"), U.S. Patent No. 6,939,971 (the "'971 Patent"), U.S. Patent No. 7,285,668 (the "'668 Patent"), and U.S. Patent No. 7,790,755 (the "'755 Patent") (collectively, the "Asserted Patents").

3. Plaintiff Takeda Pharmaceuticals North America, Inc. ("TPNA"), is a Delaware corporation with its principal place of business at One Takeda Parkway, Deerfield, IL 60015. TPNA's business includes the research, development, and marketing of pharmaceutical products. TPNA is the registered holder of approved New Drug Application No. 22-287. In addition, TPNA has the exclusive right to import dexlansoprazole delayed release capsules into the United States and sell those capsules to Takeda Pharmaceuticals LLC.

4. Plaintiff Takeda Pharmaceuticals LLC ("Takeda LLC") is a Delaware limited liability company, having a principal place of business at One Takeda Parkway, Deerfield, IL 60015. Takeda LLC's business includes the purchase and sale of pharmaceutical products. Takeda LLC is an exclusive licensee of the Asserted Patents.

5. Plaintiff Takeda Pharmaceuticals America, Inc. ("TPA"), is a Delaware corporation, having a principal place of business at One Takeda Parkway, Deerfield, IL 60015. TPA's business includes the purchase, sale, and marketing of pharmaceutical products. TPA has the exclusive right

to purchase dexlansoprazole delayed release capsules from Takeda LLC and sell those capsules to the public in the United States.

6. Plaintiffs are informed and believe, and thereupon allege, that Defendant Impax Laboratories, Inc. ("Impax") is a Delaware corporation with its principal place of business at 30831 Huntwood Ave., Hayward, CA 94544.

7. Unless specifically stated otherwise, the acts complained of herein were committed by, on behalf of, and/or for the benefit of Impax.

II.

NATURE OF THE ACTION

8. This is an action for patent infringement. This action relates to an Abbreviated New Drug Application ("ANDA") filed by Impax with the United States Food and Drug Administration ("FDA") for approval to market generic versions of Plaintiffs' DEXILANT products.

9. Plaintiffs are informed and believe, and thereupon allege, that Impax has been infringing, is infringing, or will infringe one or more claims of each of the Asserted Patents.

III.

JURISDICTION AND VENUE

10. This action arises under the patent laws of the United States, 35 U.S.C. § 1 *et seq.*, including 35 U.S.C. § 271, and the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202. This Court has subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338(a).

11. This Court has personal jurisdiction over Impax because it conducts business in this district, has its principal place of business within this district, owns or leases space in this district, purposefully avails itself of the rights and benefits of California law, and has been infringing, contributing to the infringement of and/or actively inducing others to infringe claims of the Asserted Patents in California and elsewhere.

12. Plaintiffs are informed and believe, and thereupon allege, that a substantial part of the events giving rise to Plaintiffs' claims occurred in the Northern District of California. Venue is proper in this Court pursuant to 28 U.S.C. §§ 1391(b), 1391(c), 1391(d) and/or 1400(b).

IV.

FACTUAL BACKGROUND

A. Asserted Patents

1. The ’058 Patent

13. On October 8, 2002, U.S. Patent No. 6,462,058, titled “Benzimidazole Compound Crystal,” was duly and legally issued to Takeda Chemical Industries, Ltd., as assignee of named inventors Akira Fujishima, Isao Aoki, and Keiji Kamiyama. On June 29, 2004, Takeda Chemical Industries, Ltd., changed its name to Takeda Pharmaceutical Company Limited (i.e., TPC). The change of the name of the assignee of the ’058 Patent to TPC was recorded in the United States Patent and Trademark Office (“PTO”) on January 19, 2005. A true and correct copy of the ‘058 Patent is attached as Exhibit A to this Complaint.

14. The expiration date of the ’058 Patent listed in the *Approved Drug Products with Therapeutic Equivalence Evaluations* (published by the FDA and commonly known as the Orange Book) is June 15, 2020.

2. The ’276 Patent

15. On December 16, 2003, U.S. Patent No. 6,664,276, titled “Benzimidazole Compound Crystal,” was duly and legally issued to Takeda Chemical Industries, Ltd., as assignee of named inventors Akira Fujishima, Isao Aoki, and Keiji Kamiyama. On June 29, 2004, Takeda Chemical Industries, Ltd., changed its name to Takeda Pharmaceutical Company Limited (i.e., TPC). The change of the name of the assignee of the ’276 Patent to TPC was recorded in the PTO on January 19, 2005. A true and correct copy of the ‘276 Patent is attached as Exhibit B to this Complaint.

16. The expiration date of the ’276 Patent listed in the Orange Book is June 15, 2020.

3. The ’971 Patent

17. On September 6, 2005, U.S. Patent No. 6,939,971, titled “Benzimidazole Compound Crystal,” was duly and legally issued to TPC, as assignee of named inventors Akira Fujishima, Isao

Aoki, and Keiji Kamiyama. A true and correct copy of the ‘971 Patent is attached as Exhibit C to this Complaint.

18. The expiration date of the ’971 Patent listed in the Orange Book is June 15, 2020.

4. The ’668 Patent

19. On October 23, 2007, U.S. Patent No. 7,285,668, titled “Process for the Crystallization of (R)- or (S)-Lansoprazole,” was duly and legally issued to TPC, as assignee of named inventors Hideo Hashimoto and Tadashi Urai. A true and correct copy of the ‘668 Patent is attached as Exhibit E to this Complaint.

20. The expiration date of the ’668 Patent listed in the Orange Book is June 15, 2020.

5. The ’755 Patent

21. On September 7, 2010, U.S. Patent No. 7,790,755, titled “Controlled Release Preparation,” was duly and legally issued to TPC, as assignee of named inventors Yohko Akiyama, Takashi Kurasawa, Hiroto Bando, and Naoki Nagahara. A true and correct copy of the ‘755 Patent is attached as Exhibit F to this Complaint.

22. The expiration date of the ’755 Patent listed in the Orange Book is August 2, 2026.

B. DEXILANT

23. Plaintiff TPNA is the registered holder of approved New Drug Application No. 22-287 for the manufacture and sale of the drug dexlansoprazole, a proton pump inhibitor, for the treatment of all grades of erosive esophagitis, maintaining healing of esophagitis, and treating heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (“GERD”). Plaintiff TPA sells dexlansoprazole in the United States under the trade name DEXILANT, in 30 mg and 60 mg dosage forms. The 30 mg and 60 mg dosage forms of DEXILANT were approved by the FDA on January 30, 2009.[1]

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[1] Plaintiffs originally marketed the drug dexlansoprazole under the proprietary name KAPIDEX. On March 4, 2010, the FDA announced that TPNA would start marketing KAPIDEX under the new name DEXILANT to avoid potential confusion with two other medications, CASODEX and KADIAN.

24. Plaintiffs are informed and believe, and thereupon allege, that DEXILANT is the first and only acid reflux disease treatment specifically designed for the release of medicine in two stages over time. The key to this two-stage release is DEXILANT's Dual Delayed Release™ formulation ("DDR"). DDR combines two different types of granules in one pill. DEXILANT releases one dose of medicine within an hour of taking a pill. Then, around four to five hours later, DEXILANT releases a second dose of medicine.

25. The Asserted Patents are listed in the Orange Book in support of Plaintiffs' DEXILANT (dexlansoprazole) delayed release capsules, in 30 mg and 60 mg dosage forms.

C. <u>Infringement by Impax</u>

26. Plaintiffs are informed and believe, and thereupon allege, that Impax has submitted ANDA No. 202-576 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). The ANDA seeks approval to market dexlansoprazole delayed release capsules in 30 mg and 60 mg dosage forms (the "Proposed Capsules") as a generic version of DEXILANT, prior to the expiration dates of the Asserted Patents.

27. On March 8, 2011, TPNA received a letter dated March 7, 2011 (the "Notice Letter") via overnight delivery from Impax addressed to TPC, TPNA, and TPA. This was the first Notice Letter that any of the Plaintiffs received related to ANDA No. 202-576.

28. The Notice Letter stated that the ANDA included a Paragraph IV Certification that, in Impax's opinion, the Asserted patents are invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, or sale of the Proposed Capsules.

29. Plaintiffs are informed and believe, and thereupon allege, that the ANDA does not provide any valid basis for concluding that the Asserted Patents are invalid, unenforceable, or will not be infringed by the commercial manufacture, use, or sale of the Proposed Capsules.

30. Plaintiffs are informed and believe, and thereupon allege, that the submission of the ANDA to the FDA constitutes infringement of the Asserted Patents under 35 U.S.C. § 271(e)(2). Moreover, any commercial manufacture, use, offer to sell, sale, or import of the Proposed Capsules would infringe the Asserted Patents under 35 U.S.C. § 271(a)–(c).

31. Plaintiffs commenced this action within 45 days of receiving the Notice Letter, as required by 21 U.S.C. § 355(j)(5)(B)(iii).

V.

CLAIMS FOR RELIEF

COUNT I

(Patent Infringement of U.S. Patent No. 6,462,058)

32. Plaintiffs incorporate by reference and reallege paragraphs 1 through 31 above as though fully restated herein.

33. Pursuant to 35 U.S.C. § 271(e)(2), Impax's submission of ANDA No. 202-576 to the FDA seeking approval to engage in the commercial manufacture, use, or sale of the Proposed Capsules was an act of infringement of the '058 Patent.

34. Unless Impax is enjoined by the Court, Plaintiffs will be substantially and irreparably harmed by Impax's infringement of the '058 Patent. Plaintiffs do not have an adequate remedy at law.

COUNT II

(Patent Infringement of U.S. Patent No. 6,664,276)

35. Plaintiffs incorporate by reference and reallege paragraphs 1 through 34 above as though fully restated herein.

36. Pursuant to 35 U.S.C. § 271(e)(2), Impax's submission of ANDA No. 202-576 to the FDA seeking approval to engage in the commercial manufacture, use, or sale of the Proposed Capsules was an act of infringement of the '276 Patent.

37. Unless Impax is enjoined by the Court, Plaintiffs will be substantially and irreparably harmed by Impax's infringement of the '276 Patent. Plaintiffs do not have an adequate remedy at law.

COUNT III

(Patent Infringement of U.S. Patent No. 6,939,971)

38. Plaintiffs incorporate by reference and reallege paragraphs 1 through 37 above as though fully restated herein.

39. Pursuant to 35 U.S.C. § 271(e)(2), Impax's submission of ANDA No. 202-576 to the FDA seeking approval to engage in the commercial manufacture, use, or sale of the Proposed Capsules was an act of infringement of the '971 Patent.

40. Unless Impax is enjoined by the Court, Plaintiffs will be substantially and irreparably harmed by Impax's infringement of the '971 Patent. Plaintiffs do not have an adequate remedy at law.

COUNT V

(Patent Infringement of U.S. Patent No. 7,285,668)

41. Plaintiffs incorporate by reference and reallege paragraphs 1 through 40 above as though fully restated herein.

42. Pursuant to 35 U.S.C. § 271(e)(2), Impax's submission of ANDA No. 202-576 to the FDA seeking approval to engage in the commercial manufacture, use, or sale of the Proposed Capsules was an act of infringement of the '668 Patent.

43. Unless Impax is enjoined by the Court, Plaintiffs will be substantially and irreparably harmed by Impax's infringement of the '668 Patent. Plaintiffs do not have an adequate remedy at law.

COUNT VI

(Patent Infringement of U.S. Patent No. 7,790,755)

44. Plaintiffs incorporate by reference and reallege paragraphs 1 through 43 above as though fully restated herein.

45. Pursuant to 35 U.S.C. § 271(e)(2), Impax's submission of ANDA No. 202-576 to the FDA seeking approval to engage in the commercial manufacture, use, or sale of the Proposed Capsules was an act of infringement of the '755 Patent.

46. Unless Impax is enjoined by the Court, Plaintiffs will be substantially and irreparably harmed by Impax's infringement of the '755 Patent. Plaintiffs do not have an adequate remedy at law.

COUNT VII

(Declaratory Judgment as to U.S. Patent Nos. 6,462,058, 6,664,276, 6,939,971, 7,285,668, and 7,790,755)

47. Plaintiffs incorporate by reference and reallege paragraphs 1 through 46 above as though fully restated herein.

48. These claims arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

49. Plaintiffs are informed and believe, and thereupon allege, that Impax has made, and will continue to make, substantial preparation in the United States to manufacture, use, sell, offer to sell, and/or import the Proposed Capsules prior to patent expiry.

50. Plaintiffs are informed and believe, and thereupon allege, that Impax intends to engage in the commercial manufacture, use, sale, or offer for sale within the United States or importation into the United States of the Proposed Capsules upon receipt of final FDA approval of ANDA No. 202-576.

51. Pursuant to 35 U.S.C. § 271(a), (b), and/or (c), Impax's commercial manufacture, use, sale, or offer for sale within the United States or importation into the United States of the Proposed Capsules will constitute infringement of the '058, '276, '971,'668, and '755 Patents.

52. Impax's infringing commercial manufacture, use, sale, or offer for sale within the United States or importation into the United States of the Proposed Capsules complained of herein will begin following FDA approval of ANDA No. 202-576.

53. Impax maintains, and Plaintiffs deny, that the Asserted Patents are invalid, unenforceable, or will not be infringed by the commercial manufacture, use, sale, offer for sale, or importation into the United States of the Proposed Capsules. Accordingly, there is a real, substantial, and continuing justiciable case or controversy between Plaintiffs and Impax regarding whether Impax's commercial manufacture, use, sale, offer for sale, or importation into the United States of the Proposed Capsules according to ANDA No. 202-576 will infringe one or more claims of the Asserted Patents. Plaintiffs thus are entitled to a declaration that the making, using, sale,

offer for sale, and importation into the United States of the Proposed Capsules according to ANDA No. 202-576 infringe one or more claims of the Asserted Patents.

VI.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs pray for judgment as follows:

A. For a declaration that Impax has infringed each of the Asserted Patents;

B. For a declaration that the commercial use, sale, offer for sale, manufacture, and/or importation by Impax of the Proposed Capsules would infringe each of the Asserted Patents;

C. For a determination, pursuant to 35 U.S.C. § 271(e)(4)(A), that the effective date for approval of the ANDA, under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)), be no earlier than the expiration date of the last of the Asserted Patents, including any extensions or adjustments;

D. For an order preliminarily and permanently enjoining Impax and its affiliates, subsidiaries, officers, directors, employees, agents, representatives, licensees, successors, assigns, and all those acting for them and on their behalf, or acting in concert with them directly or indirectly, from infringing the Asserted Patents; and

E. For such other and further relief as this Court deems just and proper.

Respectfully Submitted,

DATED: April 1, 2010

MUNGER, TOLLES & OLSON LLP

By: ______________________
HEATHER E. TAKAHASHI

Attorneys for Plaintiffs
TAKEDA PHARMACEUTICAL CO., LTD., TAKEDA PHARMACEUTICALS NORTH AMERICA, INC., TAKEDA PHARMACEUTICALS LLC, AND TAKEDA PHARMACEUTICALS AMERICA, INC.

Exhibit A

US006462058B1

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

(10) **Patent No.:** **US 6,462,058 B1**
(45) **Date of Patent:** **Oct. 8, 2002**

(54) **BENZIMIDAZOLE COMPOUND CRYSTAL**

(75) Inventors: **Akira Fujishima**, Sanda; **Isao Aoki**, Kawanishi; **Keiji Kamiyama**, Ibaraki, all of (JP)

(73) Assignee: **Takeda Chemical Industries, Ltd.**, Osaka (JP)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/674,624**

(22) PCT Filed: **Jun. 15, 2000**

(86) PCT No.: **PCT/JP00/03881**

§ 371 (c)(1), (2), (4) Date: **Nov. 3, 2000**

(30) **Foreign Application Priority Data**

Jun. 17, 1999 (JP) 11-171509

(51) **Int. Cl.**[7] **C07D 401/12**; A61K 31/4439
(52) **U.S. Cl.** **514/338**; 546/273.7
(58) **Field of Search** 546/273.7; 514/338

(56) **References Cited**

FOREIGN PATENT DOCUMENTS

EP	0174726 A1	3/1986
EP	0302720 A1	2/1989
WO	WO 92/08716	5/1992
WO	WO 96/02535	2/1996
WO	WO 96/17077	6/1996
WO	WO 97/02261	1/1997
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CA 127:336721, Curin et al. 1997.*

CA 127:362535, Vrecer et al. 1997.*

CA 124:331460, Katsuki et al. 1996.*

H. Katsuki et al. "Determination of R(+)– and S(–)–lansoprazole using chiral stationary–phase liquid chromatography and their enantioselective pharmacokinetics in humans", Chemical Abstracts, vol. 124, No. 25, p. 19 (1996) (Abstract).

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Primary Examiner—Jane Fan
(74) *Attorney, Agent, or Firm*—Mark Chao; Elaine M. Ramesh

(57) **ABSTRACT**

A novel crystal of (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof of the present invention is useful for an excellent antiulcer agent.

8 Claims, No Drawings

BENZIMIDAZOLE COMPOUND CRYSTAL

This application is the National Stage of International Application No. PCT/JP00/03881, filed on Jun. 15, 2000.

TECHNICAL FIELD

The present invention relates to a crystal of a benzimidazole compound showing antiulcer action.

BACKGROUND ART

2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof having an antiulcer action is reported in JP-A-61-50978, etc.

There is a demand for a more stable and excellently absorbable antiulcer agent.

DISCLOSURE OF INVENTION

Having chiral sulfurin themolecular structure thereof, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole occurs in two kinds of optical isomers. After extensive exploration, the present inventors succeeded in optically resolving and crystallizing the (R)-isomer of 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole, for the first time found that this crystal serves satisfactorily as a pharmaceutical, made further investigation based on this finding, and developed the present invention.

Accordingly, the present invention relates to:

[1] a crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof;

[2] a crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H- benzimidazole;

[3] a crystal according to the above [2] wherein the X-ray powder diffraction analysis pattern has characteristic peaks at interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom;

[4] a pharmaceutical composition which comprises the crystal according to the above [1];

[5] a pharmaceutical composition according to the above [4], which is for treating or preventing digestive ulcer;

[6] a method for treating or preventing digestive ulcer in a mammal in need thereof which comprises administering to said mammal an effective amount of the crystal according to the above [1] with a pharmaceutically acceptable excipient, carrier or diluent;

[7] use of the crystal according to the above [1] for manufacturing a pharmaceutical composition for treating or preventing digestive ulcer, and so forth.

The "salt" of "(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof" includes, for example, metal salts, salts with organic bases, salts with basic amino acids, and so forth. Preferred are physiologically acceptable salts.

Metal salts include, for example, alkali metal salts such as sodium salt and potassium salt; and alkaline earth metal salts such as calcium salt, magnesium salt and barium salt. Salts with organic bases include, for example, salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N-dibenzylethylenediamine, etc. Salts with basic amino acids include, for example, salts with arginine, lysine, etc.

The crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof may be a hydrate or not.

Said "hydrate" includes 0.5 hydrate to 5.0 hydrate. Among others, 0.5 hydrate, 1.0 hydrate, 1.5 hydrate, 2.0 hydrate and 2.5 hydrate are preferred. More preferred is 1.5 hydrate.

The crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluorbethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof can be produced by subjecting 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof to an optical resolution or subjecting 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]thio]-1H-benzimidazole to an asymmetrical oxidization to obtain the (R)-isomer, followed by crystallizing the resultant isomer.

Methods of optical resolution include per se known methods, for example, a fractional recrystallization method, a chiral column method, a diastereomer method, and so forth. Asymmetric oxidation includes per se known methods.

The "fractional recrystallization method" includes a method in which a salt is formed between a racemate and an optically active compound [e.g., (+)-mandelic acid, (−)-mandelic acid, (+)-tartaric acid, (−)-tartaric acid, (+)-1-phenethylamine, (−)-1-phenethylamine, cinchonine, (−)-cinchonidine, brucine, etc.], which salt is separated by fractional recrystallization etc., and, if desired, subjected to a neutralization process, to give a free optical isomer.

The "chiral column method" includes a method in which a racemate or a salt thereof is applied to a column for optical isomer separation (chiral column). In the case of liquid chromatography, for example, optical isomers are separated by adding a racemate to a chiral column such as ENANTIO-OVM (produced by Tosoh Corporation) or the DAICEL CHIRAL series (produced by Daicel Corporation), and developing the racemate in water, a buffer (e.g., phosphate buffer), an organic solvent (e.g., hexane, ethanol, methanol, isopropanol, acetonitrile, trifluoroacetic acid, diethylamine, triethylamine, etc.), or a solvent mixture thereof. In the case of gas chromatography, for example, a chiral column such as CP-Chirasil-DeX CB (produced by GL Science) is used to separate optical isomers.

The "diastereomer method" includes a method in which a racemate and an optically active reagent are reacted (preferably, an optically active reagent is reacted to the 1-position of the benzimidazole group) to give a diastereomer mixture, which is then subjected to ordinary separation means (e.g., fractional recrystallization, chromatography, etc.) to obtain either diastereomer, which is subjected to a chemical reaction (e.g., acid hydrolysis, base hydrolysis, hydrogenolysis, etc.) to cut off the optically active reagent moiety, whereby the desired optical isomer is obtained. Said "optically active reagent" includes, for example,a optically active organic acids such as MTPA [a-methoxy-a-(trifluoromethyl)phenylacetic acid] and (−)-menthoxyacetic acid; and optically active alkoxymethyl halides such as (1R-endo)-2-(chloromethoxy)-1,3,3-trimethylbicyclo[2.2.1]heptane, etc.

2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof is produced by the methods described in JP-A-61-50978, U.S. Pat. No. 4,628,098 etc. or analogous methods thereto.

Methods of crystallization includes per se known methods, for example, a crystallization from solution, a crystallization from vapor, and a crystallization from molten form.

Methods of the "crystallization from solution" include, for example, a concentration method, a slow cooling method, a reaction method (diffusion method, electrolysis method), a hydrothermal growth method, a fusing agent method, and so forth. Solvents to be used include, for example, aromatic hydrocarbons (e.g., benzenejjtolue, xylene, etc.), pharmaceutical composition with good reproducibility. In addition, when orally administered, the crystal of the present invention is more absorbable and more rapidly shows its action than the racemate. In addition, when administered, the crystal of the present invention shows a higher Cmax (maximum blood concentration) and a greater AUC (area under the concentration-time curve) than the racemate, and becomes less likely to be metabolized partly because of the increased protein-binding rate, thus showing an extended duration of action. The crystal of the present invention is therefore useful as a pharmaceutical of low doses and with a low prevalence of adverse reactions.

The crystal of the present invention is useful in mammals (e.g., humans, monkeys, sheep, bovines, horses, dogs, cats, rabbits, rats, mice, etc.) for the treatment and prevention of digestive ulcer (e.g., gastric ulcer, duodenal ulcer, stomal ulcer, Zollinger-Ellison syndrome, etc.), gastritis, reflux esophagitis, NUD (non-ulcer dyspepsia), gastric cancer and gastric MALT lymphoma; *Helicobacter pylori* eradication; suppression of upper gastrointestinal hemorrhage due to digestive ulcer, acute stress ulcer and hemorrhagic gastritis; suppression of upper gastrointestinal hemorrhage due to invasive stress (stress from major surgery necessitating intensive management after surgery, and from cerebral vascular disorder, head trauma, multiple organ failure and extensive burns necessitating intensive treatment); treatment and prevention of ulcer caused by a nonsteroidal anti-inflammatory agent; treatment and prevention of hyperacidity and ulcer due to postoperative stress; pre-anesthetic administration etc.

The crystal of the present invention is of low toxicity, and can be safely administered orally or non-orally (e.g., topical, rectal and intravenous administration, etc.), as such or in the form of pharmaceutical compositions formulated with a pharmacologically acceptable carrier, e.g., tablets halogenated hydrocarbons (e.g., dichloromethane, chloroform, etc.), saturated hydrocarbons (e.g., hexane, heptane, cyclohexane, etc.), ethers (e.g., diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, etc.), nitriles (e.g., acetonitrile, etc.), ketones (e.g., acetone, etc.), sulfoxides (e.g., dimethylsulfoxide, etc.), acid amides (e.g., N,N-dimethylformamide, etc.), esters (e.g., ethyl acetate, etc.), alcohols (e.g., methanol, ethanol, isopropyl alcohol, etc.), water, and so forth. These solvents may be used singly or in mixtures of two or more kinds in appropriate ratios (e.g., 1:1 to 1:100).

Methods of the "crystallization from vapor" include, for example, a gasification method (sealed tube method, gas stream method), a gas phase reaction method, a chemical transportation method, and so forth.

Methods of the "crystallization from molten form" include, for example, a normal freezing method (pulling-up method, temperature gradient method, Bridgman method), a zone melting method (zone leveling method, float zone method), a special growth method (VLS method, liquid phase epitaxis method), and so forth.

For analyzing the crystal obtained, X-ray diffraction crystallographic analysis is commonly used. In addition, crystal orientation can also be determined by a mechanical method, an optical method, etc.

A thus obtained crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof (hereinafter also referred to as "crystal of the present invention") is useful as a pharmaceutical because it shows excellent antiulcer action, gastric acid secretion-inhibiting action, mucosa-protecting action, anti-*Helicobacter pylori* action, etc., and because it is of low toxicity. Furthermore, by crystallizing the (R)-isomer, not only its stability is improved but also its handling is facilitated so that it can be prepared as a solid (including sugar-coated tablets and film-coated tablets), powders, granules, capsules (including soft capsules), orally disintegrating tablets, liquids, injectable preparations, suppositories, sustained-release preparations and patches, in accordance with a commonly known method.

The content of the crystal of the present invention in the pharmaceutical composition of the present invention is about 0.01 to 100% by weight relative to the entire composition. Varying depending on subject of administration, route of administration, target disease etc., its dose is normally about 0.5 to 1,500 mg/day, preferably about 5 to 150 mg/day, based on the active ingredient, for example, when it is orally administered as an antiulcer agent to an adult human (60 kg). The crystal of the present invention may be administered once daily or in 2 to 3 divided portions per day.

Pharmacologically acceptable carriers that may be used to produce the pharmaceutical composition of the present invention include various organic or inorganic carrier substances in common use as pharmaceutical materials, including excipients, lubricants, binders, disintegrants; water-soluble polymers and basic inorganic salts for solid preparations; and solvents, dissolution aids, suspending agents, isotonizing agents, buffers and soothing agents for liquid preparations. Other ordinary pharmaceutical additives such as preservatives, antioxidants, coloring agents, sweetening agents, souring agents, bubbling agents and flavorings may also be used as necessary.

Such "excipients" include, for example, lactose, sucrose, D-mannitol, starch, cornstarch, crystalline cellulose, light silicic anhydride and titanium oxide.

Such "lubricants" include, for example, magnesium stearate, sucrose fatty acid esters, polyethylene glycol, talc and stearic acid.

Such "binders" include, for example, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, crystalline cellulose, α-starch, polyvinylpyrrolidone, gum arabic powder, gelatin, pullulan, and low-substitutional hydroxypropyl cellulose.

Such "disintegrants" include (1) crosslinked povidone, (2) what is called super-disintegrants such as crosslinked carmellose sodium (FMC-Asahi Chemical) and carmellose calcium (Gotoku Yakuhin), (3) carboxymethyl starch sodium (e.g., product of Matsutani Chemical), (4) low-substituted hydroxypropyl cellulose (e.g., product of Shin-Etsu Chemical), (5) cornstarch, and so forth. Said "crosslinked povidone" may be any crosslinked polymer having the chemical name 1-ethenyl-2-pyrrolidinone homopolymer, including polyvixnylpyrrolidone (PVPP) and 1-vinyl-2-pyrrolidinone homopolymer, and is exemplified by Colidon CL (produced by BASF), Polyplasdon XL (produced by ISP), Polyplasdon XL-10 (produced by ISP) and Polyplasdon INF-10 (produced by ISP).

Such "water-soluble polymers" include, for example, ethanol-soluble water-soluble polymers [e.g., cellulose derivatives such as hydroxypropyl cellulose (hereinafter also referred to as HPC), polyvinylpyrrolidone] and ethanol-insoluble water-soluble polymers [e.g., cellulose derivatives such as hydroxypropylmethyl cellulose (hereinafter also referred to as HPMC), methyl cellulose and carboxymethyl cellulose sodium, sodium polyacrylate, polyvinyl alcohol, sodium alginate, guar gum].

Such "basic inorganic salts" include, for example, basic inorganic salts of sodium, potassium, magnesium and/or calcium. Preferred are basic inorganic salts of magnesium and/or calcium. More preferred are basic inorganic salts of magnesium. Such basic inorganic salts of sodium include, for example, sodium carbonate, sodium hydrogen carbonate, disodium hydrogenphosphate, etc. Such basic inorganic salts of potassium include, for example, potassium carbonate, potassium hydrogen carbonate, etc. Such basic inorganic salts of magnesium include, for example, heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metasilicate aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite [$Mg_6Al_2(OH)_{16}.CO_3.4H_2O$], alumina hydroxide magnesium, and so forth. Among others, preferred is heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, etc. Such basic inorganic salts of calcium include, for example, precipitated calcium carbonate, calcium hydroxide, etc.

Such "solvents" include, for example, water for injection, alcohol, propylene glycol, macrogol, sesame oil, corn oil and olive oil.

Such "dissolution aids" include, for example, polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate and sodium citrate.

Such "suspending agents" include, for example, surfactants such as stearyltriethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride and monostearic glycerol; and hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethyl cellulose sodium, methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose and hydroxypropyl cellulose.

Such "isotonizing agents" include, for example, glucose, D-sorbitol, sodium chloride, glycerol and D-mannitol.

Such "buffers" include, for example, buffer solutions of phosphates, acetates, carbonates, citrates etc.

Such "soothing agents" include, for example, benzyl alcohol.

Such "preservatives" include, for example, p-oxybenzoic acid esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid and sorbic acid.

Such "antioxidants" include, for example, sulfites, ascorbic acid and α-tocopherol.

Such "coloring agents" include, for example, food colors such as Food Color Yellow No. 5, Food Color Red No. 2 and Food Color Blue No. 2; and food lake colors and red oxide.

Such "sweetening agents" include, for example, saccharin sodium, dipotassium glycyrrhetinate, aspartame, stevia and thaumatin.

Such "souring agents" include, for example, citric acid (citric anhydride), tartaric acid and malic acid.

Such "bubbling agents" include, for example, sodium bicarbonate.

Such "flavorings" may be synthetic substances or naturally occurring substances, and include, for example, lemon, lime, orange, menthol and strawberry.

The crystal of the present invention may be prepared as a preparation for oral administration in accordance with a commonly known method, by, for example, compression-shaping it in the presence of an excipient, a disintegrant, a binder, a lubricant, or the like, and subsequently coating it as necessary by a commonly known method for the purpose of taste masking, enteric dissolution or sustained release. For an enteric preparation, an intermediate layer may be provided by a commonly known method between the enteric layer and the drug-containing layer for the purpose of separation of the two layers.

For preparing the crystal of the present invention as an orally disintegrating tablet, available methods include, for example, a method in which a core containing crystalline cellulose and lactose is coated with the crystal of the present invention and a basic inorganic salt, and is further coated with a coating layer containing a water-soluble polymer, to give a composition, which is coated with an enteric coating layer containing polyethylene glycol, further coated with an enteric coating layer containing triethyl citrate, still further coated with an enteric coating layer containing polyethylene glycol, and still yet further coated with mannitol, to give fine granules, which are mixed with additives and shaped. The above-mentioned "enteric coating layer" includes, for example, aqueous enteric polymer substrates such as cellulose acetate phthalate (CAP), hydroxypropylmethyl cellulose phthalate, hydroxymethyl cellulose acetate succinate, methacrylic acid copolymers (e.g., Eudragit L30D-55 (trade name; produced by Rohm), Colicoat MAE30DP (trade name; produced by BASF), Polyquid PA30 (trade name; produced by San-yo Chemical)), carboxymethylethyl cellulose and shellac; sustained-release substrates such as methacrylic acid polymers (e.g., Eudragit NE30D (trade name), Eudragit RL30D (trade name), Eudragit RS30D (trade name), etc.); water-soluble polymers; plasticizers such as triethyl citrate, polyethylene glycol, acetylated monoglycerides, triacetin and castor oil; and mixtures thereof. The above-mentioned "additive" includes, for example, water-soluble sugar alcohols (e.g., sorbitol, mannitol, maltitol, reduced starch saccharides, xylitol, reduced palatinose, erythritol, etc.), crystalline cellulose (e.g., Ceolas KG 801, Avicel PH 101, Avicel PH 102, Avicel PH 301, Avicel PH 302, Avicel RC-591 (crystalline cellulose carmellose sodium)), low-substituted hydroxypropyl cellulose (e.g., LH-22, LH-32, LH-23, LH-33 (Shin-Etsu Chemical) and mixtures thereof); binders, souring agents, bubbling agents, sweetening agents, flavorings, lubricants, coloring agents, stabilizers, excipients, disintegrants etc. are also used.

The crystal of the present invention may be used in combination with 1 to 3 other active ingredients.

Such "other active ingredients" include, for example, anti-*Helicobacter pylori* activity substances, imidazole compounds, bismuth salts, quinolone compounds, and so forth. Of these substances, preferred are anti-*Helicobacter pylori* action substances, imidazole compounds etc. Such "anti-*Helicobacter pylori* action substances" include, for example, antibiotic penicillins (e.g., amoxicillin, benzylpenicillin, piperacillin, mecillinam, etc.), antibiotic cefems (e.g., cefixime, cefaclor, etc.), antibiotic macrolides (e.g., erythromycin, clarithromycin. etc.), antibiotic tetracyclines (e.g., tetracycline, minocycline, streptomycin, etc.), antibiotic aminoglycosides (e.g., gentamicin, amikacin, etc.), imipenem. and so forth. Of these substances, preferred are antibiotic penicillins, antibiotic macrolides etc. Such "imidazole compounds" include, for example, metronidazole, miconazole, etc. Such "bismuth salts" include, for example, bismuth acetate, bismuth citrate, etc. Such "quinolone compounds" include, for example, ofloxacin, ciploxacin, etc.

Such "other active ingredients" and the crystal of the present invention may also be used in combination as a mixture prepared as a single pharmaceutical composition [e.g., tablets, powders, granules, capsules (including soft capsules), liquids, injectable preparations, suppositories, sustained-release preparations, etc.], in accordance with a commonly known method, and may also be prepared as separate preparations and administered to the same subject simultaneously or at a time interval.

BEST MODE FOR CARRYING OUT THE INVENTION

The present invention is hereinafter described in more detail by means of, but is not limited to, the following reference examples, examples and experimental examples.

In the following reference examples and examples, the term "room temperature" indicates about 15 to 30° C.

Melting points were measured using the Micro Melting Point Apparatus (produced by Yanagimoto Seisakusho), and uncorrected values are shown.

^{1}H-NMR spectra were determined with $CDCl_3$ as the solvent using Varian Gemini-200; data are shown in chemical shift δ (ppm) from the internal standard tetramethylsilane.

IR was determined using SHIMADZU FTIR-8200.

UV was determined using the HITACHI U-3200 spectrophotometer.

Optical rotation $[\alpha]_D$ was determined at 20° C. using the DIP-370 digital polarimeter (produced by JASCO).

Optical purity was determined by HPLC (column: CHIRALCEL OD 4.6 mm dia.×250 mm, temperature: about 20° C., mobilephase: hexane/2-propanol=80/20 or hexane/2-propanol=85/15, flow rate: 1.0 ml/min, detection wavelength: 285 nm) using a chiral column.

Crystal X-ray diffraction data for determining the absolute structure of sulfoxide were obtained by means of a 4-circle diffractometer (RIGAKU AFC5R) using the Cu-$K\alpha$ ray. After the initial phase was determined by the direct method, the fine structure was analyzed using SHELXL-93. X-ray powder diffraction was determined using the X-ray Powder Diffraction meter Rigaku RINT2500 (ultraX18) No. PX-3.

The other symbols used herein have the following definitions:

s: singlet

d: doublet

t: triplet

q: quartet

m: multiplet

bs: broad singlet

J: binding constant

EXAMPLES

Reference Example 1

Isolation of (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-Lansoprazole)

2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (lansoprazole) (racemate) (3.98 g) was dissolved in the following mobile phase (330 ml) and acetonitrile (37 ml) and fractionated by HPLC (column: CHIRALCEL OD 20 mm dia.×250 mm, temperature: 30° C., mobile phase: hexane/2-propanol/ethanol=255/35/10, flowrate: 16 ml/min, detection wavelength: 285 nm, 1 shot: 20–25 mg). Fractions of optical isomers of shorter retention time were combined and concentrated; the individual lots were combined and dissolved in ethanol and filtered through a 0.45 pm filter; after hexane was added, the filtrate was again evaporated to dryness to yield R(+)-lansoprazole (1.6 g, optical purity>97.6%ee) as an amorphous substance.

The amorphous substance obtained was subjected to fractionation and isolation in the same manner as above to yield R(+)-lansoprazole.(1.37 g, optical purity>99.9%ee) as an amorphous substance.

$[\alpha]_D$=+174.3°(c=0.994%, $CHCl_3$)

Reference Example 2

Isolation of (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-Lansoprazole)

Lansoprazole (racemate) (34.2 g) was dissolved in 2-propanol (1,710 ml) and hexane (1,140 ml) containing triethylamine (0.2%) and fractionated by HPLC (column: CHIRALCEL OD 50 mm dia. ×500 mm, temperature: room temperature, mobile phase: hexane/2-propanol=85/15, flow rate: 60 ml/min, detection wavelength: 285 mn, single injection: about 300 mg) to isolate the individual optical isomers. Fractions of an optical isomer of shorter retention time were combined and concentrated; the individual lots were combined and dissolved in ethanol (250 ml); after triethylamine (3 ml) was added, the solution was filtered through a 0.45 μm filter. After the filtrate was concentrated, hexane was added, and the filtrate was again evaporated to dryness to yield R(+)-lansoprazole (9.31 g, optical purity 98.3%ee) as an amorphous substance.

Reference Example 3

Production of (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-Lansoprazole)

In a nitrogen atmosphere, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]thio]benzimidazole (20.0 g, 0.057 mol), toluene (100 ml), water (55 mg, 0.0031 mol as based on total water content) and diethyl (+)-tartrate (2.12 ml, 0.012 mol) were mixed and stirred at 50 to 55° C. for 30 minutes. After titanium (IV) isopropoxide (1.66 ml, 0.0057 mol) was added to the mixture in a nitrogen atmosphere, the mixture was stirred at 50 to 55° C. for 1 hour. After diisopropylethylamine (3.25 ml, 0.019 mol) was added to the resulting mixed liquor under cooling in a nitrogen atmosphere, cumene hydroperoxide (30.6 ml, content 82%, 0.17 mol) was added at 0 to 5° C., followed by 3.5 hours of stirring at 0 to 5° C., to cause the reaction.

Analysis of the reaction liquor by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected a sulfide at 1.32% and a sulfone at 1.81% as related substances in the reaction liquor, with no other related substances detected. The enantiomer excess rate of the title compound in said reaction liquor was 96.4%ee.

Reference Example 4

Crystal of (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-Lansoprazole)

(1) In a nitrogen stream, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]thio]benzimidazole (4.5 kg, 12.7 mol, containing 1.89 g of water), toluene (22 l), water (25 g, 1.39 mol, or 1.49 mol if based on total water content) and diethyl (+)-tartrate (0.958 l, 5.60 mol) were mixed. In a nitrogen stream, titanium (IV) isopropoxide (0.747 l, 2.53 mol) was added to this mixture at 50 to 60° C., and the mixture was stirred at the above temperature for 30 minutes. After diisopropylethylamine (0.733 l, 4.44 mol) was added to the resulting mixed liquor at room temperature in a nitrogen stream, cumene hydroperoxide (6.88 l, content 82%, 37.5 mol) was added at −5 to 5° C., followed by 1.5 hours of stirring at −5 to 5° C., to yield a reaction liquor.

Analysis of the reaction liquor by HPLC (column: Capcell Pak (Shiseido, Co. Ltd.), mobile phase: solvent mixture (acetonitrile/water/triethylamine=50/50/1); adjusted to. pH 7.0 with phosphoric acid, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected a sulfide at 1.87% and a sulfone at 1.59% as related substances in the reaction liquor, with no other related substances detected.

(2) To the reaction liquor obtained in (1) above, a 30% aqueous solution of sodium thiosulfate (17 l) was added, in a nitrogen stream, to decompose the residual cumene hydroperoxide. To the organic layer obtained by liquid separation, water (4.5 l), heptane (13.5 l), t-butyl methyl ether (18 l) and heptane (27 l) were added sequentially in this order, and this mixture was stirred to cause crystallization. The resulting crystal was separated and washed with t-butyl methyl ether-toluene (t-butyl methyl ether:toluene=4:1) (4 l) to yield a wet crystal of (R)-lansoprazole having the following powder X-ray diffraction interplanar spacings (d).

The results of powder X-ray diffraction analysis of this wet crystal are shown below.

The wet crystal yielded a powder X-ray diffraction pattern with characteristic peaks appearing at powder X-ray diffraction interplanar spacings (d) of 5.85, 4.70, 4.35, 3.66 and 3.48 Angstrom.

Analysis of this crystal by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected a sulfone at 0.90% as a related substance in the crystal, with no sulfide or any other related substance detected. The (R)-lansoprazole enantiomer excess rate in this crystal was 100%ee.

(3) With stirring, a suspension in acetone (20 l) of 10 the wet crystal obtained in (2) above was added drop by drop into a mixed liquor of acetone (7 l) and water (34 l), then water (47 l) was added. The precipitated crystal was separated and washed with acetone-water (acetone:water=1:3) (4 l) and water (12 l) to yield a wet crystal of (R)-lansoprazole having the following powder X-ray diffraction interplanar spacings (d).

The results of powder X-ray diffraction analysis of this wet crystal are shown below.

The wet crystal yielded a powder X-ray diffraction pattern with characteristic peaks appearing at powder X-ray diffraction interplanar spacings (d) of 8.33, 6.63, 5.86 and 4.82 Angstrom.

Analysis of this crystal by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.)i mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected no sulfone, sulfide or any other related substance in the crystal. The (R)-lansoprazole enantiomer excess rate in this crystal was 100%ee.

(4) After the wet crystal obtained in (3) above was dissolved in ethyl acetate (45 l) and water (3 l), this solution was divided into liquid layers. The trace amount of insoluble matter in the organic layer was filtered off, then triethylamine (0.2 l) was added, after which the filtrate was concentrated under reduced pressure to a liquid volume of about 7 l. To this concentrate, methanol (2.3 l), about 12.5% aqueous ammonia at about 50° C. (23 l) and t-butyl methyl ether at about 50° C. (22 l) were added, and this liquid was divided into layers. To the organic layer, about 12.5% aqueous ammonia (11 l) was added, and this liquid was divided into layers (this operation was repeated once again). The water layers were combined, and ethyl acetate (22 l) was added, and then acetic acid was added drop by drop to reach a pH of about 8 under cooling. The liquid was divided into layers, and the water layer was extracted with ethyl acetate (11 l). The organic layers were combined and washed with about 20% saline (11 l). After triethylamine (0.2 l) was added, the organic layer was concentrated under reduced pressure. Acetone (5 l) was added to the concentrate, and this mixture was concentrated under reduced pressure. The concentrate was dissolved in acetone (9 l), and this solution was added drop by drop into a mixed liquor of acetone (4.5 l) and water (22.5 l), and then water (18 l) was added drop by drop to the mixed liquor obtained. The precipitated crystal was separated and washed sequentially with cold acetone-water (acetone:water=1:3) (3 l) and water (12 l) to yield a wet crystal of (R)-lansoprazole having the following powder X-ray diffraction interplanar spacings (d).

The results of powder X-ray diffraction analysis of this wet crystal are shown below.

The wet crystal yielded a powder X-ray diffraction pattern with characteristic peaks appearing at powder X-ray diffraction interplanar spacings (d) of 8.33, 6.63, 5.86 and 4.82 Angstrom.

Analysis of this crystal by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected no sulfone, sulfide or any other related substance in the crystal. The (R)-lansoprazole enantiomer excess rate in this crystal was 100%ee.

(5) The wet crystal obtained in (4) above was dissolved in ethyl acetate (32 l). The water layer was separated by a

liquid separation procedure, and the organic layer obtained was concentrated under reduced pressure to a liquid volume of about 14 l. To the residual liquid, ethyl acetate (36 l) and activated charcoal (270 g) were added, after stirring, the activated charcoal was removed by filtration. The filtrate was concentrated under reduced pressure to a liquid volume of about 14 l. At about 40° C., heptane (90 l) was added drop by drop to the residual liquid. After stirring at the above temperature for about 30 minutes, the resulting crystal was separated, washed with about 40° C. ethyl acetate-heptane (ethyl acetate:heptane=1:8) (6 l), and dried to yield 3.4 kg of the title compound.

The results of powder X-ray diffraction analysis of this crystal are shown below.

The crystal yielded a powder X-ray diffraction pattern with characteristic peaks appearing at powder X-ray diffraction interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

Analysis of this crystal by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected no sulfone, sulfide or any other related substance in the crystal. The (R)-lansoprazole enantiomer excess rate in this crystal was 100%ee.

Example 1

Crystal of (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-Lansoprazole)

Amorphous R(+)-lansoprazole as obtained in Reference Example 1 (100 mg) was dissolved in acetonitrile (1 ml), which was gradually evaporated at room temperature in a nitrogen stream. After a crystal began to form, diethyl ether (1.5 ml) was added and the container was stoppered and kept standing at room temperature.

The crystal thus formed was subjected to X-ray structural analysis, and the absolute configuration of sulfoxide was found to be the R-configuration by a method using a Flack parameter. The remaining portion of the crystal was collected by filtration, twice washed with diethyl ether (1 ml), and dried under reduced pressure, to yield crystals of R(+)-lansoprazole (38 mg).

m.p.: 144.0–144.5° C. (dec.); Elemental analysis; Calculated: C: 52.03, H: 3.82, N: 11.38, S: 8.–68, F: 15.43, O: 8.66; Found: C: 52.08, H: 3.76, N: 11.58, S: 8.75, F: 15.42; ^{1}H-NMR: 2.25 (3H, s), 4.40 (2H, q, J=7.8 Hz), 4.68 (1H, d, J=13.8 Hz), 4.85 (1H, d, J=13.8 Hz), 6.69 (1H, d, J=6.0 Hz), 7.29–7.39 (2H, m), 7.52 (1H, m), 7.81 (1H, m), 8.37 (1H, d, J=6.0 Hz), 11.00 (1H, bs). IR(νcm^{-1}): 3081, 3042, 2984, 1586, 1478, 1441, 1306, 1267, 1163. UVmax($CHCl_3$): 283.7 nm; $[\alpha]_D$=+199.2° (c=0.202%, $CHCl_3$).

TABLE 1

Crystal Data and Structure Refinement Parameters	
Molecular formula:	$C_{16}H_{14}N_3O_2F_3S$
Molecular weight:	369.36
Crystal color, habit:	Colorless, tabular
Crystal Dimension:	0.40 × 0.30 × 0.04 (mm)
Crystal system:	Monoclinic
Lattice constants:	a = 8.549(1) (Å)
	b = 23.350(1) (Å)
	c = 8.720(2) (Å)
	β 32 103.90(1) (°)
	v = 1,689.8(4) (Å)
Space group:	$P2_1$
Z:	4
Density (calculated):	1.452 (g/cm^3)

TABLE 1-continued

Crystal Data and Structure Refinement Parameters	
Effective reflection: number/parameter number:	9.12
R (I ≧ 2σ(I)):	0.036
Flack parameter:	−0.02(2)

Example 2

Crystal of (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-Lansoprazole)

Amorphous (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole as obtained in Reference Example 2 (9.17 g) was dissolved in acetone (20 ml) and water (15 ml) was added with gentle heating. After the solution was kept standing at room temperature overnight, water (20 ml) was added, followed by ultrasonication. After being collected by filtration, the solid was washed with water (30 ml, 20 ml), then washed with diisopropyl ether (20 ml), and dried under reduced pressure, to yield a solid (9.10 g). The solid obtained (9.00 g) was dissolved in acetone (30 ml), and after the solution was filtered, diisopropylether (50 ml) was added to the filtrate. A crystal seed was placed, and the mixture was kept standing at room temperature overnight. Precipitated crystals were collected by filtration, washed 3 times with diisopropyl ether (10 ml), and dried under reduced pressure, to yield crystals (7.85 g). The crystals obtained (7.80 g) were dissolved under heating in acetone (22.5 ml) and water (30 ml), and this solution was kept standing at room temperature for 1 hour. A precipitated solid was collected by filtration, washed with acetone-water (1:4) (15 ml), and dried under reduced pressure, to yield a solid (3.88 g). The solid obtained (3.88 g) was dissolved under heating in acetone (4 ml) and diisopropyl ether (14 ml) was added. This solution was kept standing at room temperature for 30 minutes. Precipitated crystals were collected by filtration, twice washed with diisopropyl ether (6 ml), and dried under reduced pressure, to yield crystals of R(+)-lansoprazole (3.40 g, optical purity 99.8%ee).

m.p.: 147.0–148.0° C. (dec.); Elemental analysis; Calculated: C: 52.03, H: 3.82, N: 11.38, S: 8.68, F: 15.43, O: 8.66; Found: C: 51.85, H: 3.92, N: 11.26, S: 8.82, F: 15.22; ^{1}H-NMR: 2.24 (3H, s), 4.38 (2H, q, J=7.8 Hz), 4.74 (1H, d, J=13.6 Hz), 4.87 (1H, d, J=13.6 Hz), 6.68 (1H, d, J=5.8 Hz), 7.26–7.36 (2H, m), 7.45(1H,m), 7.78 (1H, m), 8.35 (1H, d, J=5.8 Hz). IR(νcm^{-1}): 3083, 3034, 2975, 1586, 1478, 1441, 1306, 1267, 1163; UVmax($CHCl_3$): 283.6 nm; $[\alpha]_D$=+180.3° (c=1.004%, $CHCl_3$).

TABLE 2

X-ray Powder Diffraction Data

2θ (°)	Half-value width	d-value (Å)	Relative intensity (%)
7.560	0.141	11.6841	100
13.060	0.165	6.7733	44
15.160	0.141	5.8394	55
15.440	0.141	5.7342	84
20.040	0.165	4.4271	23
21.720	0.165	4.0883	89
22.560	0.141	3.9380	24
22.820	0.141	3.8937	24
24.080	0.165	3.6927	37

TABLE 2-continued

X-ray Powder Diffraction Data

2θ (°)	Half-value width	d-value (Å)	Relative intensity (%)
26.120	0.118	3.4088	32
28.680	0.165	3.1100	20

Example 3

Crystal of (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-Lansoprazole) 1.5 Hydrate

Amorphous (R)-2-[[[3-methyl,-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole as obtained in Reference Example 1 (100 mg) was dissolved in ethanol (0.15 ml), and water. (0.15 ml) was added. After a seed was placed, the solution was kept standing at room temperature for 1 hour. Precipitated crystals were collected by filtration, twice washed with water (2 ml), and dried under reduced pressure, to yield crystals of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole) 1.5 hydrate (96 mg).

m.p. : 76.0–80.0° C.; Elemental analysis; Calculated: C: 48.48, H: 4.32, N: 10.60, S: 8.09, F: 14.38, O: 14.13; Found: C: 48.52, H: 4.44, N: 10.49.

TABLE 3

X-ray Powder Diffraction Data

2θ (°)	Half-value width	d-value (Å)	Relative intensity (%)
6.680	0.165	13.2212	9
9.200	0.165	9.6046	21
9.960	0.141	8.8734	25
10.980	0.165	8.0513	42
13.380	0.141	6.6120	22
14.960	0.141	5.9170	63
15.680	0.165	5.6469	100
17.640	0.212	5.0237	34
19.760	0.212	4.4892	33
25.420	0.188	3.5010	23
29.800	0.188	2.9957	20

Experimental Example 1

Suppressive action on gastric mucosal injury due to stress of water immersion restraint in rat.

Male SD rats (7 weeks of age, weighing 230 to 250 g) were fasted for 24 hours, after which they were stressed by being housed in restraint cages and immersed to below the xiphoid process in a standing position in a 23° C. constant-temperature water chamber. After 5 hours, the rats were removed from the cages and sacrificed using gaseous carbon dioxide, and their stomachs excised. After the lower portion of the esophagus was clipped, a 1% formalin solution (10 ml) was injected into the stomach via the duodenum, which was then occluded, and the stomach was immersed in the same solution. After 10 minutes, an incision was made along the greater curvature, and the length (mm) of each mucosal injury was measured under a stereomicroscope. The overall sum of the injury lengths in each stomach was taken as the gastric mucosal injury index.

The crystals of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole) as obtained in Example 2 were suspended in 0.5% methyl cellulose (pH 9.5) containing 0.05 M $NaHCO_3$ and orally administered at 30 minutes before stressing (dosing volume 2 ml/kg). Each treatment group comprised 9 animals. The control group (solvent administration group) and the drug administration group were compared by Steel's test.

The results are shown in Table 4.

TABLE 4

Sample	Dose (mg/kg)	Gastric mucosal injury index (mm)	Suppression rate (%)
Control	—	10.9 ± 1.9	—
(R)-lansoprazole crystal	3	0.2 ± 0.2*	98.0

Each figure of gastric mucosal injury index is the mean ± standard error for the 9 animals in each group.
*$p < 0.01$ (versus control group, Steel's test)

Experimental Example 2

The crystals of R (+)-lansoprazole as obtained in Example 2 (about 5 mg) and amorphous R(+)-lansoprazole as obtained in Reference Example 1 (about 5 mg) were each taken in a colorless glass bottle, and their stability during storage at 60° C. (stopper removed) was examined. A 25 ml solution (concentration: about 0.2 mg/ml) of the sample after completion of storage in the mobile phase, along with a standard solution prepared using the initial lot, was analyzed under the HPLC conditions shown below, and the R(+)-lansoprazole content (residual percentage) was calculated from the peak area obtained. The results are shown in Table 5.

HPLC analytical conditions Detection wavelength:	UV 275 nm
Column:	YMC Pro C18, 4.6 × 150 mm
Mobile phase:	Fluid prepared by adding phosphoric acid to water/acetonitrile/triethyl amine (63:37:1) to reach pH 7.
Flow rate:	1.0 ml/min
Column temperature:	40° C.
Sample injection volume:	10 μl

TABLE 5

Stability of R(+)-Lansoprazole Crystal and Amorphous

Sample	Duration of storage	Description	Content (Residual percentage)
Crystal	1 week	Light-brown	97.0
	2 weeks	Brown	93.8
	4 weeks	Brown	91.7
Amorphous	1 week	Brown	70.8
	2 weeks	Blackish brown	57.5

When the sample was stored at 60° C. (exposed), the crystal of Example 2 retained a content exceeding 90% for up to 4 weeks, whereas the amorphous form of Reference Example 1 showed reduction in content to 70.8% after 1 week and 57.5% after 2 weeks. This finding demonstrates that the crystal of R(+)-lansoprazole is more stable and more preferable for use as a pharmaceutical etc. than the amorphous form.

INDUSTRIAL APPLICABILITY

The crystal of the present invention is useful as a pharmaceutical because it shows excellent antiulcer action, gastric acid secretion inhibiting action, mucosa-protecting action, anti-*Helicobacter pylori* action etc., and because it is of low toxicity. Furthermore, by crystallizing the (R)-isomer, not only its stability is improved but also its handling is facilitated so that it can be prepared as a solid pharmaceutical composition with good reproducibility. In addition, when orally administered, the crystal of the present invention is more absorbable and more rapidly shows its action than the racemate. In addition, when administered, the crystal of the present invention shows a higher Cmax and a greater AUC. than the racemate, and becomes less likely to be metabolized partly because of the increased protein-binding rate, thus showing an extended duration of action. The crystal of the present invention is therefore useful as a pharmaceutical of low dosage and with a low prevalence of adverse reactions.

What is claimed is:

1. A crystal of (R)-2-(((3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole wherein the X-ray powder diffraction analysis pattern has characteristic peaks at interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

2. A crystal of (R)-2-(((3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole 1.5 hydrate wherein the X-ray powder diffraction analysis pattern has characteristic peaks at interplanar spacings (d) of 13.22, 9.60, 8.87, 8.05, 6.61, 5.92, 5.65, 5.02, 4.49, 3.50 and 3.00 Angstrom.

3. A pharmaceutical composition which comprises the crystal according to claim **1** and a pharmaceutically acceptable excipient, carrier or diluent.

4. A pharmaceutical composition which comprises the crystal according to claim **2** and a pharmaceutically acceptable excipient, carrier or diluent.

5. A method for manufacturing a pharmaceutical composition for treating or preventing digestive ulcer comprising formulating the composition with the crystal of claim **1**.

6. A method for treating or preventing digestive ulcer in a mammal in need thereof which comprises administering to said mammal an effective amount of the crystal according to claim **1** with a pharmaceutically acceptable excipient, carrier or diluent.

7. A method for manufacturing a pharmaceutical composition for treating or preventing digestive ulcer comprising formulating the composition with the crystal of claim **2**.

8. A method for treating or preventing digestive ulcer in a mammal in need thereof which comprises administering to said mammal an effective amount of the crystal according to claim **2** with a pharmaceutically acceptable excipient, carrier or diluent.

* * * * *

Exhibit B

US006664276B2

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

(10) **Patent No.: US 6,664,276 B2**
(45) **Date of Patent: *Dec. 16, 2003**

(54) **BENZIMIDAZOLE COMPOUND CRYSTAL**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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(65) **Prior Publication Data**

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Related U.S. Application Data

(63) Continuation of application No. 09/674,624, filed as application No. PCT/JP00/03881 on Jun. 15, 2000, now Pat. No. 6,462,058.

(30) **Foreign Application Priority Data**

Jun. 17, 1999 (JP) 11-171509

(51) **Int. Cl.**[7] **C07D 401/12**; A61K 31/4439
(52) **U.S. Cl.** **514/338**; 546/273.7
(58) **Field of Search** 514/338; 546/273.7

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(57) **ABSTRACT**

A novel crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof of the present invention is useful for an excellent antiulcer agent.

6 Claims, No Drawings

BENZIMIDAZOLE COMPOUND CRYSTAL

This application is a continuation of U.S. patent application Ser. No. 09/674,624 filed on Nov. 3, 2000, now issued U.S. Pat. No. 6,462,058, which application was the National Stage of International Application No. PCT/JP00/03881, filed on Jun. 15, 2000.

DESCRIPTION

1. Technical Field

The present invention relates to a crystal of a benzimidazole compound showing antiulcer action.

2. Background Art

2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof having an antiulcer action is reported in JP-A-61-50978, etc.

There is a demand for a more stable and excellently absorbable antiulcer agent.

DISCLOSURE OF INVENTION

Having chiral sulfur in the molecular structure thereof, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole occurs in two kinds of optical isomers. After extensive exploration, the present inventors succeeded in optically resolving and crystallizing the (R)-isomer of 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole, for the first time found that this crystal serves satisfactorily as a pharmaceutical, made further investigation based on this finding, and developed the present invention.

Accordingly, the present invention relates to:

[1] a crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof;

[2] a crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole;

[3] a crystal according to the above [2] wherein the X-ray powder diffraction analysis pattern has characteristic peaks at interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom;

[4] a pharmaceutical composition which comprises the crystal according to the above [1];

[5] a pharmaceutical composition according to the above [4], which is for treating or preventing digestive ulcer;

[6] a method for treating or preventing digestive ulcer in a mammal in need thereof which comprises administering to said mammal an effective amount of the crystal according to the above [1] with a pharmaceutically acceptable excipient, carrier or diluent;

[7] use of the crystal according to the above [1] for manufacturing a pharmaceutical composition for treating or preventing digestive ulcer, and so forth.

The "salt" of "(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof" includes, for example, metal salts, salts with organic bases, salts with basic amino acids, and so forth. Preferred are physiologically acceptable salts.

Metal salts include, for example, alkali metal salts such as sodium salt and potassium salt; and alkaline earth metal salts such as calcium salt, magnesium salt and barium salt. Salts with organic bases include, for example, salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N-dibenzylethylenediamine, etc. Salts with basic amino acids include, for example, salts with arginine, lysine, etc.

The crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof may be a hydrate or not.

Said "hydrate" includes 0.5 hydrate to 5.0 hydrate. Among others, 0.5 hydrate, 1.0 hydrate, 1.5 hydrate, 2.0 hydrate and 2.5 hydrate are preferred. More preferred is 1.5 hydrate.

The crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof can be produced by subjecting 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof to an optical resolution or subjecting 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]thio]-1H-benzimidazole to an asymmetrical oxidization to obtain the (R)-isomer, followed by crystallizing the resultant isomer.

Methods of optical resolution includes per se known methods, for example, a fractional recrystallization method, a chiral column method, a diastereomer method, and so forth. Asymmetric oxidation includes per se known methods.

The "fractional recrystallization method" includes a method in which a salt is formed between a racemate and an optically active compound [e.g., (+)-mandelic acid, (−)-mandelic acid, (+)-tartaric acid, (−)-tartaric acid, (+)-1-phenethylamine, (−)-1-phenethylamine, cinchonine, (−)-cinchonidine, brucine, etc.], which salt is separated by fractional recrystallization etc., and, if desired, subjected to a neutralization process, to give a free optical isomer.

The "chiral column method" includes a method in which a racemate or a salt thereof is applied to a column for optical isomer separation (chiral column). In the case of liquid chromatography, for example, optical isomers are separated by adding a racemate to a chiral column such as ENANTIO-OVM (produced by Tosoh Corporation) or the DAICEL CHIRAL series (produced by Daicel Corporation), and developing the racemate in water, a buffer (e.g., phosphate buffer), an organic solvent (e.g., hexane, ethanol, methanol, isopropanol, acetonitrile, trifluoroacetic acid, diethylamine, triethylamine, etc.), or a solvent mixture thereof. In the case of gas chromatography, for example, a chiral column such as CP-Chirasil-DeX CB (produced by GL Science) is used to separate optical isomers.

The "diastereomer method" includes a method in which a racemate and an optically active reagent are reacted (preferably, an optically active reagent is reacted to the 1-position of the benzimidazole group) to give a diastereomer mixture, which is then subjected to ordinary separation means (e.g., fractional recrystallization, chromatography, etc.) to obtain either diastereomer, which is subjected to a chemical reaction (e.g., acid hydrolysis, base hydrolysis, hydrogenolysis, etc.) to cut off the optically active reagent moiety, whereby the desired optical isomer is obtained. Said "optically active reagent" includes, for example, optically active organic acids such as MTPA [α-methoxy-α-(trifluoromethyl)phenylacetic acid] and (−)-menthoxyacetic acid; and optically active alkoxymethyl halides such as (1R-endo)-2-(chloromethoxy)-1,3,3-trimethylbicyclo[2.2.1]heptane, etc.

2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof is produced by the methods described in JP-A-61-50978, U.S. Pat. No. 4,628,098 etc. or analogous methods thereto.

Methods of crystallization includes per se known methods, for example, a crystallization from solution, a crystallization from vapor, and a crystallization from molten form.

Methods of the "crystallization from solution" include, for example, a concentration method, a slow cooling method, a reaction method (diffusion method, electrolysis method), a hydrothermal growth method, a fusing agent method, and so forth. Solvents to be used include, for example, aromatic hydrocarbons (e.g., benzene, toluene, xylene, etc.), halogenated hydrocarbons (e.g., dichloromethane, chloroform, etc.), saturated hydrocarbons (e.g., hexane, heptane, cyclohexane, etc.), ethers (e.g., diethyl ether, dilsopropyl ether, tetrahydrofuran, dioxane, etc.), nitriles (e.g., acetonitrile, etc.), ketones (e.g., acetone, etc.), sulfoxides (e.g., dimethylsulfoxide, etc.), acid amides (e.g., N,N-dimethylformamide, etc.), esters (e.g., ethyl acetate, etc.), alcohols (e.g., methanol, ethanol, isopropyl alcohol, etc.), water, and so forth. These solvents may be used singly or in mixtures of two or more kinds in appropriate ratios (e.g., 1:1 to 1:100). ratios (e.g., 1:1 to 1:100).

Methods of the "crystallization from vapor" include, for example, a gasification method (sealed tube method, gas stream method), a gas phase reaction method, a chemical transportation method, and so forth.

Methods of the "crystallization from molten form" include, for example, a normal freezing method (pulling-up method, temperature gradient method, Bridgman method), a zone melting method (zone leveling method, float zone method), a special growth method (VLS method, liquid phase epitaxis method), and so forth.

For analyzing the crystal obtained, X-ray diffraction crystallographic analysis is commonly used. In addition, crystal orientation can also be determined by a mechanical method, an optical method, etc.

A thus-obtained crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof (hereinafter also referred to as "crystal of the present invention") is useful as a pharmaceutical because it shows excellent antiulcer action, gastric acid secretion-inhibiting action, mucosa-protecting action, anti-*Helicobacter pylori* action, etc., and because it is of low toxicity. Furthermore, by crystallizing the (R)-isomer, not only its stability is improved but also its handling is facilitated so that it can be prepared as a solid pharmaceutical composition with good reproducibility. In addition, when orally administered, the crystal of the present invention is more absorbable and more rapidly shows its action than the racemate. In addition, when administered, the crystal of the present invention shows a higher Cmax (maximum blood concentration) and a greater AUC (area under the concentration-time curve) than the racemate, and becomes less likely to be metabolized partly because of the increased protein-binding rate, thus showing an extended duration of action. The crystal of the present invention is therefore useful as a pharmaceutical of low dosage and with a low prevalence of adverse reactions.

The crystal of the present invention is useful in mammals (e.g., humans, monkeys, sheep, bovines, horses, dogs, cats, rabbits, rats, mice, etc.) for the treatment and prevention of digestive ulcer (e.g., gastric ulcer, duodenal ulcer, stomal ulcer, Zollinger-Ellison syndrome, etc.), gastritis, reflux esophagitis, NUD (non-ulcer dyspepsia), gastric cancer and gastric MALT lymphoma; *Helicobacter pylori* eradication; suppression of upper gastrointestinal hemorrhage due to digestive ulcer, acute stress ulcer and hemorrhagic gastritis; suppression of upper gastrointestinal hemorrhage due to invasive stress (stress from major surgery necessitating intensive management after surgery, and from cerebral vascular disorder, head trauma, multiple organ failure and extensive bums necessitating intensive treatment); treatment and prevention of ulcer caused by a nonsteroidal anti-inflammatory agent; treatment and prevention of hyperacidity and ulcer due to postoperative stress; pre-anesthetic administration etc.

The crystal of the present invention is of low toxicity and can be safely administered orally or non-orally (e.g., topical, rectal and intravenous administration, etc.), as such or in the form of pharmaceutical compositions formulated with a pharmacologically acceptable carrier, e.g., tablets (including sugar-coated tablets and film-coated tablets), powders, granules, capsules (including soft capsules), orally disintegrating tablets, liquids, injectable preparations, suppositories, sustained-release preparations and patches, in accordance with a commonly known method.

The content of the crystal of the present invention in the pharmaceutical composition of the present invention is about 0.01 to 100% by weight relative to the entire composition. Varying depending on subject of administration, route of administration, target disease etc., its dose is normally about 0.5 to 1,500 mg/day, preferably about 5 to 150 mg/day, based on the active ingredient, for example, when it is orally administered as an antiulcer agent to an adult human (60 kg). The crystal of the present invention may be administered once daily or in 2 to 3 divided portions per day.

Pharmacologically acceptable carriers that may be used to produce the pharmaceutical composition of the present invention include various organic or inorganic carrier substances in common use as pharmaceutical materials, including excipients, lubricants, binders, disintegrants, water-soluble polymers and basic inorganic salts for solid preparations; and solvents, dissolution aids, suspending agents, isotonizing agents, buffers and soothing agents for liquid preparations. Other ordinary pharmaceutical additives such as preservatives, antioxidants, coloring agents, sweetening agents, souring agents, bubbling agents and flavorings may also be used as necessary.

Such "excipients" include, for example, lactose, sucrose, D-mannitol, starch, cornstarch, crystalline cellulose, light silicic anhydride and titanium oxide.

Such "lubricants" include, for example, magnesium stearate, sucrose fatty acid esters, polyethylene glycol, talc and stearic acid.

Such "binders" include, for example, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, crystalline cellulose, α-starch, polyvinylpyrrolidone, gum arabic powder, gelatin, pullulan and low-substitutional hydroxypropyl cellulose.

Such "disintegrants" include (1) crosslinked povidone, (2) what is called super-disintegrants such as crosslinked carmellose sodium (FMC-Asahi Chemical) and carmellose calcium (Gotoku Yakuhin), (3) carboxymethyl starch sodium (e.g., product of Matsutani Chemical), (4) low-substituted hydroxypropyl cellulose (e.g., product of Shin-Etsu Chemical), (5) cornstarch, and so forth. Said "crosslinked povidone" may be any crosslinked polymer having the chemical name 1-ethenyl-2-pyrrolidinone homopolymer, including polyvinylpyrrolidone (PVPP) and 1-vinyl-2-pyrrolidinone homopolymer, and is exemplified by Colidon CL (produced by BASF), Polyplasdon XL (produced by ISP), Polyplasdon XL-10 (produced by ISP) and Polyplasdon INF-10 (produced by ISP).

Such "water-soluble polymers" include, for example, ethanol-soluble water-soluble polymers [e.g., cellulose derivatives such as hydroxypropyl cellulose (hereinafter also referred to as HPC), polyvinylpyrrolidone] and ethanol-insoluble water-soluble polymers [e.g., cellulose derivatives such as hydroxypropylmethyl cellulose (hereinafter also referred to as HPMC), methyl cellulose and carboxymethyl cellulose sodium, sodium polyacrylate, polyvinyl alcohol, sodium alginate, guar gum].

Such "basic inorganic salts" include, for example, basic inorganic salts of sodium, potassium, magnesium and/or calcium. Preferred are basic inorganic salts of magnesium and/or calcium. More preferred are basic inorganic salts of magnesium. Such basic inorganic salts of sodium include, for example, sodium carbonate, sodium hydrogen carbonate, disodium hydrogenphosphate, etc. Such basic inorganic salts of potassium include, for example, potassium carbonate, potassium hydrogen carbonate, etc. Such basic inorganic salts of magnesium include, for example, heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metasilicate aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite [$Mg_6Al_2(OH)_{16}.CO_3.4H_2O$], alumina hydroxide magnesium, and so forth. Among others, preferred is heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, etc. Such basic inorganic salts of calcium include, for example, precipitated calcium carbonate, calcium hydroxide, etc.

Such "solvents" include, for example, water for injection, alcohol, propylene glycol, macrogol, sesame oil, corn oil and olive oil.

Such "dissolution aids" include, for example, polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate and sodium citrate.

Such "suspending agents" include, for example, surfactants such as stearyltriethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride and monostearic glycerol; and hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethyl cellulose sodium, methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose and hydroxypropyl cellulose.

Such "isotonizingagents" include, for example, glucose, D-sorbitol, sodium chloride, glycerol and D-mannitol.

Such "buffers" include, for example, buffer solutions of phosphates, acetates, carbonates, citrates etc.

Such "soothing agents" include, for example, benzyl alcohol.

Such "preservatives" include, for example, p-oxybenzoic acid esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid and sorbic acid.

Such "antioxidants" include, for example, sulfites, ascorbic acid and α-tocopherol.

Such "coloring agents" include, for example, food colors such as Food Color Yellow No. 5, Food Color Red No. 2 and Food Color Blue No. 2; and food lake colors and red oxide.

Such "sweetening agents" include, for example, saccharin sodium, dipotassium glycyrrhetinate, aspartame, stevia and thaumatin.

Such "souring agents" include, for example, citric acid (citric anhydride), tartaric acid and malic acid.

Such "bubbling agents" include, for example, sodium bicarbonate.

Such "flavorings" may be synthetic substances or naturally occurring substances, and include, for example, lemon, lime, orange, menthol and strawberry.

The crystal of the present invention may be prepared as a preparation for oral administration in accordance with a commonly known method, by, for example, compression-shaping it in the presence of an excipient, a disintegrant, a binder, a lubricant, or the like, and subsequently coating it as necessary by a commonly known method for the purpose of

taste masking, enteric dissolution or sustained release. For an enteric preparation, an intermediate layer may be provided by a commonly known method between the enteric layer and the drug-containing layer for the purpose of separation of the two layers.

For preparing the crystal of the present invention as an orally disintegrating tablet, available methods include, for example, a method in which a core containing crystalline cellulose and lactose is coated with the crystal of the present invention and a basic inorganic salt, and is further coated with a coating layer containing a water-soluble polymer, to give a composition, which is coated with an enteric coating layer containing polyethylene glycol, further coated with an enteric coating layer containing triethyl citrate, still further coated with an enteric coating layer containing polyethylene glycol, and still yet further coated with mannitol, to give fine granules, which are mixed with additives and shaped. The above-mentioned "enteric coating layer" includes, for example, aqueous enteric polymer substrates such as cellulose acetate phthalate (CAP), hydroxypropylmethyl cellulose phthalate, hydroxymethyl cellulose acetate succinate, methacrylic acid copolymers (e.g., Eudragit L30D-55 (trade name; produced by Rohm), Colicoat MAE30DP (trade name; produced by BASF), Polyquid PA30 (trade name; produced by San-yo Chemical)), carboxymethylethyl cellulose and shellac; sustained-release substrates such as methacrylic acid polymers (e.g., Eudragit NE30 D (trade name), Eudragit RL30D (trade name), Eudragit RS30D (trade name), etc.); water-soluble polymers; plasticizers such as triethyl citrate, polyethylene glycol, acetylated monoglycerides, triacetin and castor oil; and mixtures thereof. The above-mentioned "additive" includes, for example, water-soluble sugar alcohols (e.g., sorbitol, mannitol, maltitol, reduced starch saccharides, xylitol, reduced palatinose, erythritol, etc.), crystalline cellulose (e.g., Ceolas KG 801, Avicel PH 101, Avicel PH 102, Avicel PH 301, Avicel PH 302, Avicel RC-591 (crystalline cellulose carmellose sodium)), low-substituted hydroxypropyl cellulose (e.g., LH-22, LH-32, LH-23, LH-33 (Shin-Etsu Chemical) and mixtures thereof); binders, souring agents, bubbling agents, sweetening agents, flavorings, lubricants, coloring agents, stabilizers, excipients, disintegrants etc. are also used.

The crystal of the present invention may be used in combination with 1 to 3 other active ingredients.

Such "other active ingredients" include, for example, anti-*Helicobacter pylori* activity substances, imidazole compounds, bismuth salts, quinolone compounds, and so forth. Of these substances, preferred are anti-*Helicobacter pylori* action substances, imidazole compounds etc. Such "anti-*Helicobacter pylori* action substances" include, for example, antibiotic penicillins (e.g., amoxicillin, benzylpenicillin, piperacillin, mecillinam, etc.), antibiotic cefems (e.g., cefixime, cefaclor, etc.), antibiotic macrolides (e.g., erythromycin, clarithromycin. etc.), antibiotic tetracyclines (e.g., tetracycline, minocycline, streptomycin, etc.), antibiotic aminoglycosides (e.g., gentamicin, amikacin, etc.), imipenem. and so forth. Of these substances, preferred are antibiotic penicillins, antibiotic macrolides etc. Such "imidazole compounds" include, for example, metronidazole, miconazole, etc. Such "bismuth salts" include, for example, bismuth acetate, bismuth citrate, etc. Such "quinolone compounds" include, for example, ofloxacin, ciploxacin, etc.

Such "other active ingredients" and the crystal of the present invention may also be used in combination as a mixture prepared as a single pharmaceutical composition [e.g., tablets, powders, granules, capsules (including soft capsules), liquids, injectable preparations, suppositories, sustained-release preparations, etc.], in accordance with a commonly known method, and may also be prepared as separate preparations and administered to the same subject simultaneously or at a time interval.

BEST MODE FOR CARRYING OUT THE INVENTION

The present invention is hereinafter described in more detail by means of, but is not limited to, the following reference examples, examples and experimental examples.

In the following reference examples and examples, the term "room temperature" indicates about 15 to 30 ° C.

Melting points were measured using the Micro Melting Point Apparatus (produced by Yanagimoto Seisakusho), and uncorrected values are shown.

^{1}H-NMR spectra were determined with $CDCl_3$ as the solvent using Varian Gemini-200; data are shown in chemical shift δ (ppm) from the internal standard tetramethylsilane.

IR was determined using SHIMADZU FTIR-8200.

UV was determined using the HITACHI U-3200 spectrophotometer.

Optical rotation $[\alpha]_D$ was determined at 20° C. using the DIP-370 digital polarimeter (produced by JASCO).

Optical purity was determined by HPLC (column: CHIRALCEL OD 4.6mm dia.×250 mm, temperature: about 20° C., mobile phase: hexane/2-propanol=80/20 or hexane/2-propanol=85/15, flow rate: 1.0 ml/min, detection wave length: 285nm) using a chiral column.

Crystal X-ray diffraction data for determining the absolute structure of sulfoxide were obtained by means of a 4-circle diffractometer (RIGAKU AFC5R) using the Cu-Kx_α ray. After the initial phase was determined by the direct method, the fine structure was analyzed using SHELXL-93. X-ray powder diffraction was determined using the X-ray Powder Diffraction meter Rigaku RINT2500 (ultraX18) No. PX-3.

The other symbols used herein have the following definitions:

s: singlet

d: doublet

t: triplet

q: quartet

m: multiplet

bs: broad singlet

J: binding constant

EXAMPLES

Reference Example 1

Isolation of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole)

2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (lansoprazole) (racemate) (3.98 g) was dissolved in the following mobile phase (330 ml) and acetonitrile (37 ml) and fractionated by HPLC (column: CHIRALCEL OD 20 mm dia.×250 mm, temperature: 30° C., mobile phase: hexane/2-propanol/ethanol=255/35/10, flowrate: 16 ml/min, detection wavelength: 285 nm, 1 shot: 20–25 mg). Fractions of optical isomers of shorter retention time were combined and concentrated; the individual lots were combined and dissolved in ethanol and filtered through a 0.45 μm filter; after hexane was added, the filtrate was again evaporated to dryness to yield R(+)-lansoprazole (1.6 g, optical purity>97.6% ee) as an amorphous substance.

The amorphous substance obtained was subjected to fractionation and isolation in the same manner as above to yield R(+)-lansoprazole (1.37 g, optical purity>99.9% ee) as an amorphous substance.

$[\alpha]_D$=+174.3° (c=0.994%, $CHCl_3$)

Reference Example 2

Isolation of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole)

Lansoprazole (racemate) (34.2 g) was dissolved in 2-propanol (1,710 ml) and hexane (1,140 ml) containing triethylamine (0.2%) and fractionated by HPLC (column: CHIRALCEL OD 50 mm dia.×500 mm, temperature: room temperature, mobile phase: hexane/2-propanol=85/15, flow rate: 60 ml/min, detection wavelength: 285 nm, single injection: about 300 mg) to isolate the individual optical isomers. Fractions of an optical isomer of shorter retention time were combined and concentrated; the individual lots were combined and dissolved in ethanol (250 ml); after triethylamine (3 ml) was added, the solution was filtered through a 0.45 μm filter. After the filtrate was concentrated, hexane was added, and the filtrate was again evaporated to dryness to yield R(+)-lansoprazole (9.31 g, optical purity 98.3% ee) as an amorphous substance.

Reference Example 3

Production of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole)

In a nitrogen atmosphere, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]thio]benzimidazole (20.0 g, 0.057 mol), toluene (100 ml), water (55 mg, 0.0031 mol as based on total water content) and diethyl (+) -tartrate (2.12 ml, 0.012 mol) were mixed and stirred at 50 to 55° C. for 30 minutes. After titanium (IV) isopropoxide (1.66 ml, 0.0057 mol) was added to the mixture in a nitrogen atmosphere, the mixture was stirred at 50 to 55° C. for 1 hour. After diisopropylethylamine (3.25 ml, 0.019 mol) was added to the resulting mixed liquor under cooling in a nitrogen atmosphere, cumene hydroperoxide (30.6 ml, content 82%, 0.17 mol) was added at 0 to 5° C., followed by 3.5 hours of stirring at 0 to 5° C., to cause the reaction.

Analysis of the reaction liquor by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected a sulfide at 1.32% and a sulfone at 1.81% as related substances in the reaction liquor, with no other related substances detected. The enantiomer excess rate of the title compound in said reaction liquor was 96.4% ee.

Reference Example 4

Crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole)

(1) In a nitrogen stream, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]thio]benzimidazole (4.5

kg, 12.7 mol, containing 1.89 9 of water), toluene (22 l), water (25 9, 1.39 mol, or 1.49 mol if based on total water content) and diethyl (+)-tartrate (0.958 1, 5.60 mol) were mixed. In a nitrogen stream, titanium (IV) isopropoxide (0.747 1, 2.53 mol) was added to this mixture at 50 to 60° C., and the mixture was stirred at the above temperature for 30 minutes. After diisopropylethylamine (0.733 l, 4.44 mol) was added to the resulting mixed liquor at room temperature in a nitrogen stream, cumene hydroperoxide (6.88 l, content 82%, 37.5 mol) was added at −5 to 5° C., followed by 1.5 hours of stirring at −5 to 5° C., to yield a reaction liquor.

Analysis of the reaction liquor by HPLC (column: Capcell Pak (Shiseido, Co. Ltd.), mobile phase: solvent mixture (acetonitrile/water/ triethylamine=50/50/1); adjusted to pH 7.0 with phosphoric acid, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected a sulfide at 1.87% and a sulfone at 1.59% as related substances in the reaction liquor, with no other related substances detected.

(2) To the reaction liquor obtained in (1) above, a 30% aqueous solution of sodium thiosulfate (17 l) was added, in a nitrogen stream, to decompose the residual cumene hydroperoxide. To the organic layer obtained by liquid separation, water (4.5 l), heptane (13.5 l), t-butyl methyl ether (18 l) and heptane (27 l) were added sequentially in this order, and this mixture was stirred to cause crystallization. The resulting crystal was separated and washed with t-butyl methyl ether-toluene (t-butyl methyl ether:toluene=4:1) (4 l) to yield a wet crystal of (R)-lansoprazole having the following powder X-ray diffraction interplanar spacings (d).

The results of powder X-ray diffraction analysis of this wet crystal are shown below.

The wet crystal yielded a powder X-ray diffraction pattern with characteristic peaks appearing at powder X-ray diffraction interplanar spacings (d) of 5.85, 4.70, 4.35, 3.66 and 3.48 Angstrom.

Analysis of this crystal by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected a sulfone at 0.90% as a related substance in the crystal, with no sulfide or any other related substance detected. The (R)-lansoprazole enantiomer excess rate in this crystal was 100% ee.

(3) With stirring, a suspension in acetone (20 l) of the wet crystal obtained in (2) above was added drop by drop into a mixed liquor of acetone (7 l) and water (34 l), then water (47 l) was added. The precipitated crystal was separated and washed with acetone-water (acetone:water=1:3) (4 l) and water (12 l) to yield a wet crystal of (R)-lansoprazole having the following powder X-ray diffraction interplanar spacings (d).

The results of powder X-ray diffraction analysis of this wet crystal are shown below.

The wet crystal yielded a powder X-ray diffraction pattern with characteristic peaks appearing at powder X-ray diffraction interplanar spacings (d) of 8.33, 6.63, 5.86 and 4.82 Angstrom.

Analysis of this crystal by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected no sulfone, sulfide or any other related substance in the crystal. The (R)-lansoprazole enantiomer excess rate in this crystal was 100% ee.

(4) After the wet crystal obtained in (3) above was dissolved in ethyl acetate (45 l) and water (3 l), this solution was divided into liquid layers. The trace amount of insoluble

matter in the organic layer was filtered off, then triethylamine (0.2 l) was added, after which the filtrate was concentrated under reduced pressure to a liquid volume of about 7 l. To this concentrate, methanol (2.3 l), about 12.5% aqueous ammonia at about 50° C. (23 l) and t-butyl methyl ether at about 50° C. (22 l) were added, and this liquid was divided into layers. To the organic layer, about 12.5% aqueous ammonia (11 l) was added, and this liquid was divided into layers (this operation was repeated once again). The water layers were combined, and ethyl acetate (22 l) was added, and then acetic acid was added drop by drop to reach a pH of about 8 under cooling. The liquid was divided into layers, and the water layer was extracted with ethyl acetate (11 l). The organic layers were combined and washed with about 20% saline (11 l). After triethylamine (0.2 l) was added, the organic layer was concentrated under reduced pressure. Acetone (5 l) was added to the concentrate, and this mixture was concentrated under reduced pressure. The concentrate was dissolved in acetone (9 l), and this solution was added drop by drop into a mixed liquor of acetone (4.5 l) and water (22.5 l), and then water (18 l) was added drop by drop to the mixed liquor obtained. The precipitated crystal was separated and washed sequentially with cold acetone-water (acetone:water=1:3) (3 l) and water (12 l) to yield a wet crystal of (R)-lansoprazole having the following powder X-ray diffraction interplanar spacings (d).

The results of powder X-ray diffraction analysis of this wet crystal are shown below.

The wet crystal yielded a powder X-ray diffraction pattern with characteristic peaks appearing at powder X-ray diffraction interplanar spacings (d) of 8.33, 6.63, 5.86 and 4.82 Angstrom.

Analysis of this crystal by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected no sulfone, sulfide or any other related substance in the crystal. The (R)-lansoprazole enantiomer excess rate in this crystal was 100% ee.

(5) The wet crystal obtained in (4) above was dissolved in ethyl acetate (32 l). The water layer was separated by a liquid separation procedure, and the organic layer obtained was concentrated under reduced pressure to a liquid volume of about 14 l. To the residual liquid, ethyl acetate (36 l) and activated charcoal (270 g) were added, after stirring, the activated charcoal was removed by filtration. The filtrate was concentrated under reduced pressure to a liquid volume of about 14 l. At about 40° C., heptane (90 l) was added drop by drop to the residual liquid. After stirring at the above temperature for about 30 minutes, the resulting crystal was separated, washed with about 40° C. ethyl acetate-heptane (ethyl acetate:heptane=1:8) (6 l), and dried to yield 3.4 kg of the title compound.

The results of powder X-ray diffraction analysis of this crystal are shown below.

The crystal yielded a powder X-ray diffraction pattern with characteristic peaks appearing at powder X-ray diffraction interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

Analysis of this crystal by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected no sulfone, sulfide or any other related substance in the crystal. The (R)-lansoprazole enantiomer excess rate in this crystal was 100% ee.

Example 1

Crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole)

Amorphous R(+)-lansoprazole as obtained in Reference Example 1 (100 mg) was dissolved in acetonitrile (1 ml), which was gradually evaporated at room temperature in a nitrogen stream. After a crystal began to form, diethyl ether (1.5 ml) was added and the container was stoppered and kept standing at room temperature.

The crystal thus formed was subjected to X-ray structural analysis, and the absolute configuration of sulfoxide was found to be the R-configuration by a method using a Flack parameter. The remaining portion of the crystal was collected by filtration, twice washed with diethyl ether (1 ml), and dried under reduced pressure, to yield crystals of R(+)-lansoprazole (38 mg).

m.p.: 144.0–144.5° C. (dec.)

Elemental Analysis

Calculated: C: 52.03, H: 3.82, N: 11.38, S: 8.68, F: 15.43, O:8.66 Found: C: 52.08, H: 3.76, N: 11.58, S: 8.75, F: 15.42

^{1}H-NMR: 2.25(3H,s), 4.40(2H,q,J=7.8 Hz), 4.68(1H,d,J=13.8 Hz), 4.85(1H,d,J=13.8 Hz), 6.69(1H,d,J=6.0 Hz), 7.29–7.39(2H,m), 7.52(1H,m), 7.81(1H,m), 8.37(1H,d,J=6.0 Hz),11.00(1H,bs). IR(ν cm^{-1}): 3081, 3042, 2984, 1586, 1478, 1441, 1306, 1267, 1163.

UVmax ($CHCl_3$): 283.7 nm

$[\alpha]_D$=+199.2° (c=0.202%, $CHCl_3$)

TABLE 1

Crystal Data and Structure Refinement Parameters	
Molecular formula	$C_{16}H_{14}N_3O_2F_3S$
Molecular weight	369.36
Crystal color, habit	Colorless, tabular
Crystal Dimension	0.40 × 0.30 × 0.04 (mm)
Crystal system	Monoclinic
Lattice constants	a = 8.549(1) (Å) b = 23.350(1) (Å) c = 8.720(2) (Å) β = 103.90(1) (°) V = 1,689.8(4) (Å)
Space group	$P2_1$
Z	4
Density (calculated)	1.452 (g/cm^3)
Effective reflection number/parameter number	9.12
R (I ≧ 2σ(I))	0.036
Flack parameter	−0.02(2)

Example 2

Crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole)

Amorphous (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole as obtained in Reference Example 2 (9.17 g) was dissolved in acetone (20 ml), and water (15 ml) was added with gentle heating. After the solution was kept standing at room temperature overnight, water (20 ml) was added, followed by ultrasonication. After being collected by filtration, the solid was washed with water (30 ml, 20 ml), then washed with diisopropyl ether (20 ml), and dried under reduced pressure, to yield a solid (9.10 g). The solid obtained (9.00 g) was dissolved in acetone (30 ml), and after the solution was filtered, diisopropyl ether (50 ml) was added to the filtrate. A crystal seed was placed, and the mixture was kept standing at room temperature overnight. Precipitated crystals were collected by filtration, washed 3 times with diisopropyl ether (10 ml), and dried under reduced pressure, to yield crystals (7.85 g). The crystals obtained (7.80 g) were dissolved under heating in acetone (22.5 ml) and water (30 ml), and this solution was kept standing at room temperature for 1 hour. A precipitated solid was collected by filtration, washed with acetone-water (1:4) (15 ml), and dried under reduced pressure, to yield a solid (3.88 g). The solid obtained (3.88 g) was dissolved under heating in acetone (4 ml) and diisopropyl ether (14 ml) was added. This solution was kept standing at room temperature for 30 minutes. Precipitated crystals were collected by filtration, twice washed with diisopropyl ether (6 ml), and dried under reduced pressure, to yield crystals of R(+)-lansoprazole (3.40 g, optical purity 99.8% ee).

m.p.: 147.0–148.0° C. (dec.)

Elemental Analysis

Calculated: C: 52.03, H: 3.82, N: 11.38, S: 8.68, F: 15.43, O:8.66

Found: C: 51.85, H: 3.92, N: 11.26, S: 8.82, F: 15.22

^{1}H-NMR: 2.24(3H,s), 4.38(2H,q,J=7.8 Hz), 4.74(1H,d,J=13.6 Hz), 4.87(1H,d,J=13.6 Hz), 6.68(1H,d,J=5.8 Hz), 7.26–7.36(2H,m), 7.45(1H,m), 7.78(1H,m), 8.35(1H,d,J=5.8 Hz).

IR (ν cm^{-1}): 3083, 3034, 2975, 1586, 1478, 1441, 1306, 1267, 1163

UVmax ($CHCl_3$): 283.6 nm

$[\alpha]_D$=+180.3° (c=1.004%, $CHCl_3$)

TABLE 2

X-ray Powder Diffraction Data

2θ (°)	Half-value width	d-value (Å)	Relative intensity (%)
7.560	0.141	11.6841	100
13.060	0.165	6.7733	44
15.160	0.141	5.8394	55
15.440	0.141	5.7342	84
20.040	0.165	4.4271	23
21.720	0.165	4.0883	89
22.560	0.141	3.9380	24
22.820	0.141	3.8937	24
24.080	0.165	3.6927	37
26.120	0.118	3.4088	32
28.680	0.165	3.1100	20

Example 3

Crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole) 1.5 hydrate

Amorphous (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole as obtained in Reference Example 1 (100 mg) was dissolved in ethanol (0.15 ml), and water (0.15 ml) was added.

After a seed was placed, the solution was kept standing at room temperature for 1 hour. Precipitated crystals were collected by filtration, twice washed with water (2 ml), and dried under reduced pressure, to yield crystals of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole) 1.5 hydrate (96 mg).

m.p.: 76.0–80.0° C.

Elemental Analysis

Calculated: C: 48.48, H: 4.32, N: 10.60, S: 8.09, F: 14.38, O:14.13 Found: C: 48.52, H: 4.44, N: 10.49

TABLE 3

X-ray Powder Diffraction Data			
2θ (°)	Half-value width	d-value (Å)	Relative intensity (%)
6.680	0.165	13.2212	9
9.200	0.165	9.6046	21
9.960	0.141	8.8734	25
10.980	0.165	8.0513	42
13.380	0.141	6.6120	22
14.960	0.141	5.9170	63
15.680	0.165	5.6469	100
17.640	0.212	5.0237	34
19.760	0.212	4.4892	33
25.420	0.188	3.5010	23
29.800	0.188	2.9957	20

Experimental Example 1

Suppressive action on gastric mucosal injury due to stress of water immersion restraint in rat

Male SD rats (7 weeks of age, weighing 230 to 250 g) were fasted for 24 hours, after which they were stressed by being housed in restraint cages and immersed to below the xiphoid process in a standing position in a 23° C. constant-temperature water chamber. After 5 hours, the rats were removed from the cages and sacrificed using gaseous carbon dioxide, and their stomachs excised. After the lower portion of the esophagus was clipped, a 1% formalin solution (10 ml) was injected into the stomach via the duodenum, which was then occluded, and the stomach was immersed in the same solution. After 10 minutes, an incision was made along the greater curvature, and the length (mm) of each mucosal injury was measured under a stereomicroscope. The overall sum of the injury lengths in each stomach was taken as the gastric mucosal injury index.

The crystals of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole) as obtained in Example 2 were suspended in 0.5% methyl cellulose (pH 9.5) containing 0.05 M $NaHCO_3$ and orally administered at 30 minutes before stressing (dosing volume 2 ml/kg). Each treatment group comprised 9 animals. The control group (solvent administration group) and the drug administration group were compared by Steel's test.

The results are shown in Table 4.

TABLE 4

Sample	Dose (mg/kg)	Gastric mucosal injury index (mm)	Suppression rate (%)
Control	—	10.9 ± 1.9	—
(R)-lansoprazole crystal	3	0.2 ± 0.2*	98.0

Each figure of gastric mucosal injury index is the mean ± standard error for the 9 animals in each group.
*p < 0.01 (versus control group, Steel's test)

Experimental Example 2

The crystals of R(+)-lansoprazole as obtained in Example 2 (about 5 mg) and amorphous R(+)-lansoprazole as obtained in Reference Example 1 (about 5 mg) were each taken in a colorless glass bottle, and their stability during storage at 60° C. (stopper removed) was examined. A 25 ml solution (concentration: about 0.2 mg/ml) of the sample after completion of storage in the mobile phase, along with a standard solution prepared using the initial lot, was analyzed under the HPLC conditions shown below, and the R(+)-lansoprazole content (residual percentage) was calculated from the peak area obtained. The results are shown in Table 5.

HPLC analytical conditions	
Detection wavelength	UV 275 nm
Column	YMC Pro C18, 4.6 × 150 mm
Mobile phase	Fluid prepared by adding phosphoric acid to water/acetonitrile/triethyl amine (63:37:1) to reach pH 7.
Flow rate	1.0 ml/min
Column temperature	40° C.
Sample injection volume	10 μl

TABLE 5

Stability of R(+)-Lansoprazole Crystal and Amorphous			
Sample	Duration of storage	Description	Content (Residual percentage)
Crystal	1 week	Light-brown	97.0
	2 weeks	Brown	93.8
	4 weeks	Brown	91.7
Amorphous	1 week	Brown	70.8
	2 weeks	Blackish brown	57.5

When the sample was stored at 60° C. (exposed), the crystal of Example 2 retained a content exceeding 90% for up to 4 weeks, whereas the amorphous form of Reference Example 1 showed reduction in content to 70.8% after 1 week and 57.5% after 2 weeks. This finding demonstrates that the crystal of R(+)-lansoprazole is more stable and more preferable for use as a pharmaceutical etc. than the amorphous form.

Industrial Applicability

The crystal of the present invention is useful as a pharmaceutical because it shows excellent antiulcer action, gastric acid secretion-inhibiting action, mucosa-protecting action, anti-*Helicobacter pylori* action etc., and because it is of low toxicity. Furthermore, by crystallizing the (R)-isomer, not only its stability is improved but also its handling is facilitated so that it can be prepared as a solid pharmaceutical composition with good reproducibility. In addition, when orally administered, the crystal of the present invention is more absorbable and more rapidly shows its action than the racemate. In addition, when administered, the crystal of the present invention shows a higher Cmax and a greater AUC than the racemate, and becomes less likely to be metabolized partly because of the increased protein-binding rate, thus showing an extended duration of action. The crystal of the present invention is therefore useful as a pharmaceutical of low dosage and with a low prevalence of adverse reactions.

What is claimed is:

1. A crystalline compound of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof.

2. A crystalline compound of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole.

3. A pharmaceutical composition comprising:

a crystalline compound of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof; and

a pharmaceutically acceptable excipient, carrier or diluent.

4. A pharmaceutical composition according to claim 3, which is for treating or preventing digestive ulcer.

5. A method for treating or preventing digestive ulcer in a mammal in need thereof which comprises administering to said mammal an effective amount of a crystalline compound of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof.

6. A method for manufacturing a pharmaceutical composition for treating or preventing digestive ulcer comprising formulating the composition with a crystalline compound of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof.

* * * * *

Exhibit C

US006939971B2

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

(10) **Patent No.: US 6,939,971 B2**
(45) **Date of Patent: *Sep. 6, 2005**

(54) **BENZIMIDAZOLE COMPOUND CRYSTAL**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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(30) **Foreign Application Priority Data**

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(51) **Int. Cl.**[7] **A61K 31/44**; C07D 401/04
(52) **U.S. Cl.** **546/273.7**; 514/338
(58) **Field of Search** 546/273.7; 514/338

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(57) **ABSTRACT**

A novel crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof of the present invention is useful for an excellent antiulcer agent.

17 Claims, No Drawings

BENZIMIDAZOLE COMPOUND CRYSTAL

This application is a continuation of U.S. patent application Ser. No. 10/243,329 filed on Sep. 13, 2002, now issued U.S. Pat. No. 6,664,276, which was a continuation of U.S. patent application Ser. No. 09/674,624 filed on Nov. 3, 2000, now issued U.S. Pat. No. 6,462,058, which application was the National Stage of International Application No. PCT/JP00/03881, filed on Jun. 15, 2000.

TECHNICAL FIELD

The present invention relates to a crystal of a benzimidazole compound showing antiulcer action.

BACKGROUND ART

2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl] methyl]sulfinyl]-1H-benzimidazole or a salt thereof having an antiulcer action is reported in JP-A-61-50978, etc.

There is a demand for a more stable and excellently absorbable antiulcer agent.

DISCLOSURE OF INVENTION

Having chiral sulfur in the molecular structure thereof, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl] sulfinyl]-1H-benzimidazole occurs in two kinds of optical isomers. After extensive exploration, the present inventors succeeded in optically resolving and crystallizing the (R)-isomer of 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole, for the first time found that this crystal serves satisfactorily as a pharmaceutical, made further investigation based on this finding, and developed the present invention.

Accordingly, the present invention relates to:

[1] a crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof;

[2] a crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole;

[3] a crystal according to the above [2] wherein the X-ray powder diffraction analysis pattern has characteristic peaks at interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom;

[4] a pharmaceutical composition which comprises the crystal according to the above [1];

[5] a pharmaceutical composition according to the above [4], which is for treating or preventing digestive ulcer;

[6] a method for treating or preventing digestive ulcer in a mammal in need thereof which comprises administering to said mammal an effective amount of the crystal according to the above [1] with a pharmaceutically acceptable excipient, carrier or diluent;

[7] use of the crystal according to the above [1] for manufacturing a pharmaceutical composition for treating or preventing digestive ulcer, and so forth.

The "salt" of "(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof" includes, for example, metal salts, salts with organic bases, salts with basic amino acids, and so forth. Preferred are physiologically acceptable salts.

Metal salts include, for example, alkali metal salts such as sodium salt and potassium salt; and alkaline earth metal salts such as calcium salt, magnesium salt and barium salt. Salts with organic bases include, for example, salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N-dibenzylethylenediamine, etc. Salts with basic amino acids include, for example, salts with arginine, lysine, etc.

The crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof may be a hydrate or not.

Said "hydrate" includes 0.5 hydrate to 5.0 hydrate. Among others, 0.5 hydrate, 1.0 hydrate, 1.5 hydrate, 2.0 hydrate and 2.5 hydrate are preferred. More preferred is 1.5 hydrate.

The crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof can be produced by subjecting 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl] methyl]sulfinyl]-1H-benzimidazole or a salt thereof to an optical resolution or subjecting 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]thio]-1H-benzimidazole to an asymmetrical oxidization to obtain the (R)-isomer, followed by crystallizing the resultant isomer.

Methods of optical resolution include per se known methods, for example, a fractional recrystallization method, a chiral column method, a diastereomer method, and so forth. Asymmetric oxidation includes per se known methods.

The "fractional recrystallization method" includes a method in which a salt is formed between a racemate and an optically active compound [e.g., (+)-mandelic acid, (−)-mandelic acid, (+)-tartaric acid, (−)-tartaric acid, (+)-1-phenethylamine, (−)-1-phenethylamine, cinchonine, (−)-cinchonidine, brucine, etc.], which salt is separated by fractional recrystallization etc., and, if desired, subjected to a neutralization process, to give a free optical isomer.

The "chiral column method" includes a method in which a racemate or a salt thereof is applied to a column for optical isomer separation (chiral column). In the case of liquid chromatography, for example, optical isomers are separated by adding a racemate to a chiral column such as ENANTIO-OVM (produced by Tosoh Corporation) or the DAICEL CHIRAL series (produced by Daicel Corporation), and developing the racemate in water, a buffer (e.g., phosphate buffer), an organic solvent (e.g., hexane, ethanol, methanol, isopropanol, acetonitrile, trifluoroacetic acid, diethylamine, triethylamine, etc.), or a solvent mixture thereof. In the case of gas chromatography, for example, a chiral column such as CP-Chirasil-DeX CB (produced by GL Science) is used to separate optical isomers.

The "diastereomer method" includes a method in which a racemate and an optically active reagent are reacted (preferably, an optically active reagent is reacted to the 1-position of the benzimidazole group) to give a diastereomer mixture, which is then subjected to ordinary separation means (e.g., fractional recrystallization, chromatography, etc.) to obtain either diastereomer, which is subjected to a chemical reaction (e.g., acid hydrolysis, base hydrolysis, hydrogenolysis, etc.) to cut off the optically active reagent moiety, whereby the desired optical isomer is obtained. Said "optically active reagent" includes, for example, optically active organic acids such as MTPA [α-methoxy-α-(trifluoromethyl)phenylacetic acid] and (−)-menthoxyacetic acid; and optically active alkoxymethyl halides such as (1R-endo)-2-(chloromethoxy)-1,3,3-trimethylbicyclo[2.2.1] heptane, etc.

2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl] methyl]sulfinyl]-1H-benzimidazole or a salt thereof is produced by the methods described in JP-A-61-50978, U.S. Pat. No. 4,628,098 etc. or analogous methods thereto.

Methods of crystallization includes per se known methods, for example, a crystallization from solution, a crystallization from vapor, and a crystallization from molten form.

Methods of the "crystallization from solution" include, for example, a concentration method, a slow cooling method, a reaction method (diffusion method, electrolysis method), a hydrothermal growth method, a fusing agent method, and so forth. Solvents to be used include, for example, aromatic hydrocarbons (e.g., benzene, toluene, xylene, etc.), halogenated hydrocarbons (e.g., dichloromethane, chloroform, etc.), saturated hydrocarbons (e.g., hexane, heptane, cyclohexane, etc.), ethers (e.g., diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, etc.), nitriles (e.g., acetonitrile, etc.), ketones (e.g., acetone, etc.), sulfoxides (e.g., dimethylsulfoxide, etc.), acid amides (e.g., N,N-dimethylformamide, etc.), esters (e.g., ethyl acetate, etc.), alcohols (e.g., methanol, ethanol, isopropyl alcohol, etc.), water, and so forth. These solvents may be used singly or in mixtures of two or more kinds in appropriate ratios (e.g., 1:1 to 1:100).

Methods of the "crystallization from vapor" include, for example, a gasification method (sealed tube method, gas stream method), a gas phase reaction method, a chemical transportation method, and so forth.

Methods of the "crystallization from molten form" include, for example, a normal freezing method (pulling-up method, temperature gradient method, Bridgman method), a zone melting method (zone leveling method, float zone method), a special growth method (VLS method, liquid phase epitaxis method), and so forth.

For analyzing the crystal obtained, X-ray diffraction crystallographic analysis is commonly used. In addition, crystal orientation can also be determined by a mechanical method, an optical method, etc.

A thus-obtained crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof (hereinafter also referred to as "crystal of the present invention") is useful as a pharmaceutical because it shows excellent antiulcer action, gastric acid secretion-inhibiting action, mucosa-protecting action, anti-*Helicobacter pylori* action, etc., and because it is of low toxicity. Furthermore, by crystallizing the (R)-isomer, not only its stability is improved but also its handling is facilitated so that it can be prepared as a solid pharmaceutical composition with good reproducibility. In addition, when orally administered, the crystal of the present invention is more absorbable and more rapidly shows its action than the racemate. In addition, when administered, the crystal of the present invention shows a higher Cmax (maximum blood concentration) and a greater AUC (area under the concentration-time curve) than the racemate, and becomes less likely to be metabolized partly because of the increased protein-binding rate, thus showing an extended duration of action. The crystal of the present invention is therefore useful as a pharmaceutical of low dosage and with a low prevalence of adverse reactions.

The crystal of the present invention is useful in mammals (e.g., humans, monkeys, sheep, bovines, horses, dogs, cats, rabbits, rats, mice, etc.) for the treatment and prevention of digestive ulcer (e.g., gastric ulcer, duodenal ulcer, stomal ulcer, Zollinger-Ellison syndrome, etc.), gastritis, reflux esophagitis, NUD (non-ulcer dyspepsia), gastric cancer and gastric MALT lymphoma; *Helicobacter pylori* eradication; suppression of upper gastrointestinal hemorrhage due to digestive ulcer, acute stress ulcer and hemorrhagic gastritis; suppression of upper gastrointestinal hemorrhage due to invasive stress (stress from major surgery necessitating intensive management after surgery, and from cerebral vascular disorder, head trauma, multiple organ failure and extensive burns necessitating intensive treatment); treatment

and prevention of ulcer caused by a nonsteroidal anti-inflammatory agent; treatment and prevention of hyperacidity and ulcer due to postoperative stress; pre-anesthetic administration etc.

The crystal of the present invention is of low toxicity and can be safely administered orally or non-orally (e.g., topical, rectal and intravenous administration, etc.), as such or in the form of pharmaceutical compositions formulated with a pharmacologically acceptable carrier, e.g., tablets (including sugar-coated tablets and film-coated tablets), powders, granules, capsules (including soft capsules), orally disintegrating tablets, liquids, injectable preparations, suppositories, sustained-release preparations and patches, in accordance with a commonly known method.

The content of the crystal of the present invention in the pharmaceutical composition of the present invention is about 0.01 to 100% by weight relative to the entire composition. Varying depending on subject of administration, route of administration, target disease etc., its dose is normally about 0.5 to 1,500 mg/day, preferably about 5 to 150 mg/day, based on the active ingredient, for example, when it is orally administered as an antiulcer agent to an adult human (60 kg). The crystal of the present invention may be administered once daily or in 2 to 3 divided portions per day.

Pharmacologically acceptable carriers that may be used to produce the pharmaceutical composition of the present invention include various organic or inorganic carrier substances in common use as pharmaceutical materials, including excipients, lubricants, binders, disintegrants, water-soluble polymers and basic inorganic salts for solid preparations; and solvents, dissolution aids, suspending agents, isotonizing agents, buffers and soothing agents for liquid preparations. Other ordinary pharmaceutical additives such as preservatives, antioxidants, coloring agents, sweetening agents, souring agents, bubbling agents and flavorings may also be used as necessary.

Such "excipients" include, for example, lactose, sucrose, D-mannitol, starch, cornstarch, crystalline cellulose, light silicic anhydride and titanium oxide.

Such "lubricants" include, for example, magnesium stearate, sucrose fatty acid esters, polyethylene glycol, talc and stearic acid.

Such "binders" include, for example, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, crystalline cellulose, α-starch, polyvinylpyrrolidone, gum arabic powder, gelatin, pullulan and low-substitutional hydroxypropyl cellulose.

Such "disintegrants" include (1) crosslinked povidone, (2) what is called super-disintegrants such as crosslinked carmellose sodium (FMC-Asahi Chemical) and carmellose calcium (Gotoku Yakuhin), (3) carboxymethyl starch sodium (e.g., product of Matsutani Chemical), (4) low-substituted hydroxypropyl cellulose (e.g., product of Shin-Etsu Chemical), (5) cornstarch, and so forth. Said "crosslinked povidone" may be any crosslinked polymer having the chemical name 1-ethenyl-2-pyrrolidinone homopolymer, including polyvinylpyrrolidone (PVPP) and 1-vinyl-2-pyrrolidinone homopolymer, and is exemplified by Colidon CL (produced by BASF), Polyplasdon XL (produced by ISP), Polyplasdon XL-10 (produced by ISP) and Polyplasdon INF-10 (produced by ISP).

Such "water-soluble polymers" include, for example, ethanol-soluble water-soluble polymers [e.g., cellulose derivatives such as hydroxypropyl cellulose (hereinafter also referred to as HPC), polyvinylpyrrolidone] and ethanol-insoluble water-soluble polymers [e.g., cellulose derivatives such as hydroxypropylmethyl cellulose (hereinafter also referred to as HPMC), methyl cellulose and carboxymethyl cellulose sodium, sodium polyacrylate, polyvinyl alcohol, sodium alginate, guar gum].

Such "basic inorganic salts" include, for example, basic inorganic salts of sodium, potassium, magnesium and/or calcium. Preferred are basic inorganic salts of magnesium and/or calcium. More preferred are basic inorganic salts of magnesium. Such basic inorganic salts of sodium include, for example, sodium carbonate, sodium hydrogen carbonate, disodium hydrogenphosphate, etc. Such basic inorganic salts of potassium include, for example, potassium carbonate, potassium hydrogen carbonate, etc. Such basic inorganic salts of magnesium include, for example, heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metasilicate aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite $[Mg_6Al_2(OH)_{16}.CO_3.4H_2O]$, alumina hydroxide magnesium, and so forth. Among others preferred is heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, etc. Such basic inorganic salts of calcium include, for example, precipitated calcium carbonate, calcium hydroxide, etc.

Such "solvents" include, for example, water for injection, alcohol, propylene glycol, macrogol, sesame oil, corn oil and olive oil.

Such "dissolution aids" include, for example, polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate and sodium citrate.

Such "suspending agents" include, for example, surfactants such as stearyltriethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride and monostearic glycerol; and hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethyl cellulose sodium, methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose and hydroxypropyl cellulose.

Such "isotonizing agents" include, for example, glucose, D-sorbitol, sodium chloride, glycerol and D-mannitol.

Such "buffers" include, for example, buffer solutions of phosphates, acetates, carbonates, citrates etc.

Such "soothing agents" include, for example, benzyl alcohol.

Such "preservatives" include, for example, p-oxybenzoic acid esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid and sorbic acid.

Such "antioxidants" include, for example, sulfites, ascorbic acid and α-tocopherol.

Such "coloring agents" include, for example, food colors such as Food Color Yellow No. 5, Food Color Red No. 2 and Food Color Blue No. 2; and food lake colors and red oxide.

Such "sweetening agents" include, for example, saccharin sodium, dipotassium glycyrrhetinate, aspartame, stevia and thaumatin.

Such "souring agents" include, for example, citric acid (citric anhydride), tartaric acid and malic acid.

Such "bubbling agents" include, for example, sodium bicarbonate.

Such "flavorings" may be synthetic substances or naturally occurring substances, and include, for example, lemon, lime, orange, menthol and strawberry.

The crystal of the present invention may be prepared as a preparation for oral administration in accordance with a commonly known method, by, for example, compression-shaping it in the presence of an excipient, a disintegrant, a binder, a lubricant, or the like, and subsequently coating it as necessary by a commonly known method for the purpose of taste masking, enteric dissolution or sustained release. For an enteric preparation, an intermediate layer may be provided by a commonly known method between the enteric layer and the drug-containing layer for the purpose of separation of the two layers.

For preparing the crystal of the present invention as an orally disintegrating tablet, available methods include, for example, a method in which a core containing crystalline cellulose and lactose is coated with the crystal of the present invention and a basic inorganic salt, and is further coated with a coating layer containing a water-soluble polymer, to give a composition, which is coated with an enteric coating layer containing polyethylene glycol, further coated with an enteric coating layer containing triethyl citrate, still further coated with an enteric coating layer containing polyethylene glycol, and still yet further coated with mannitol, to give fine granules, which are mixed with additives and shaped. The above-mentioned "enteric coating layer" includes, for example, aqueous enteric polymer substrates such as cellulose acetate phthalate (CAP), hydroxypropylmethyl cellulose phthalate, hydroxymethyl cellulose acetate succinate, methacrylic acid copolymers (e.g., Eudragit L30D-55 (trade name; produced by Rohm), Colicoat MAE30DP (trade name; produced by BASF), Polyquid PA30 (trade name; produced by San-yo Chemical)), carboxymethylethyl cellulose and shellac; sustained-release substrates such as methacrylic acid polymers (e.g., Eudragit NE30 D (trade name), Eudragit RL30D (trade name), Eudragit RS30D (trade name), etc.); water-soluble polymers; plasticizers such as triethyl citrate, polyethylene glycol, acetylated monoglycerides, triacetin and castor oil; and mixtures thereof. The above-mentioned "additive" includes, for example, water-soluble sugar alcohols (e.g., sorbitol, mannitol, maltitol, reduced starch saccharides, xylitol, reduced palatinose, erythritol, etc.), crystalline cellulose (e.g., Ceolas KG 801, Avicel PH 101, Avicel PH 102, Avicel PH 301, Avicel PH 302, Avicel RC-591 (crystalline cellulose carmellose sodium)), low-substituted hydroxypropyl cellulose (e.g., LH-22, LH-32, LH-23, LH-33 (Shin-Etsu Chemical) and mixtures thereof); binders, souring agents, bubbling agents, sweetening agents, flavorings, lubricants, coloring agents, stabilizers, excipients, disintegrants etc. are also used.

The crystal of the present invention may be used in combination with 1 to 3 other active ingredients.

Such "other active ingredients" include, for example, anti-*Helicobacter pylori* activity substances, imidazole compounds, bismuth salts, quinolone compounds, and so forth. Of these substances, preferred are anti-*Helicobacter pylori* action substances, imidazole compounds etc. Such "anti-*Helicobacter pylori* action substances" include, for example, antibiotic penicillins (e.g., amoxicillin, benzylpenicillin, piperacillin, mecillinam, etc.), antibiotic cefems (e.g., cefixime, cefaclor, etc.), antibiotic macrolides (e.g., erythromycin, clarithromycin. etc.), antibiotic tetracyclines (e.g., tetracycline, minocycline, streptomycin, etc.), antibiotic aminoglycosides (e.g., gentamicin, amikacin, etc.), imipenem and so forth. Of these substances, preferred are antibiotic penicillins, antibiotic macrolides etc. Such "imidazole compounds" include, for example, metronidazole, miconazole, etc. Such "bismuth salts" include, for example, bismuth acetate, bismuth citrate, etc. Such "quinolone compounds" include, for example, ofloxacin, ciploxacin, etc.

Such "other active ingredients" and the crystal of the present invention may also be used in combination as a mixture prepared as a single pharmaceutical composition [e.g., tablets, powders, granules, capsules (including soft capsules), liquids, injectable preparations, suppositories, sustained-release preparations, etc.], in accordance with a commonly known method, and may also be prepared as separate preparations and administered to the same subject simultaneously or at a time interval.

BEST MODE FOR CARRYING OUT THE INVENTION

The present invention is hereinafter described in more detail by means of, but is not limited to, the following reference examples, examples and experimental examples.

In the following reference examples and examples, the term "room temperature" indicates about 15 to 30° C.

Melting points were measured using the Micro Melting Point Apparatus (produced by Yanagimoto Seisakusho), and uncorrected values are shown.

^{1}H-NMR spectra were determined with $CDCl_3$ as the solvent using Varian Gemini-200; data are shown in chemical shift δ (ppm) from the internal standard tetramethylsilane.

IR was determined using SHIMADZU FTIR-8200.

UV was determined using the HITACHI U-3200 spectrophotometer.

Optical rotation $[\alpha]_D$ was determined at 20° C. using the DIP-370 digital polarimeter (produced by JASCO).

Optical purity was determined by HPLC (column: CHIRALCEL OD 4.6 mm dia.×250 mm, temperature: about 20° C., mobile phase: hexane/2-propanol=80/20 or hexane/2-propanol=85/15, flow rate: 1.0 ml/min, detection wavelength: 285 nm) using a chiral column.

Crystal X-ray diffraction data for determining the absolute structure of sulfoxide were obtained by means of a 4-circle diffractometer (RIGAKU AFC5R) using the Cu-Kα ray. After the initial phase was determined by the direct method, the fine structure was analyzed using SHELXL-93. X-ray powder diffraction was determined using the X-ray Powder Diffraction meter Rigaku RINT2500 (ultraX18) No. PX-3.

The other symbols used herein have the following definitions:

s: singlet

d: doublet

t: triplet

q: quartet

m: multiplet

bs: broad singlet

J: binding constant

EXAMPLES

Reference Example 1

Isolation of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole)

2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl] methyl]sulfinyl]-1H-benzimidazole (lansoprazole) (racemate) (3.98 g) was dissolved in the following mobile phase (330 ml) and acetonitrile (37 ml) and fractionated by HPLC (column: CHIRALCEL OD 20 mm dia.×250 mm, temperature: 30° C., mobile phase: hexane/2-propanol/ethanol=255/35/10, flowrate: 16 ml/min, detection wavelength: 285 nm, 1 shot: 20–25 mg). Fractions of optical isomers of shorter retention time were combined and concentrated; the individual lots were combined and dissolved in ethanol and filtered through a 0.45 μm filter; after hexane was added, the filtrate was again evaporated to dryness to yield R(+)-lansoprazole (1.6 g, optical purity>97.6% ee) as an amorphous substance.

The amorphous substance obtained was subjected to fractionation and isolation in the same manner as above to yield R(+)-lansoprazole (1.37 g, optical purity>99.9% ee) as an amorphous substance.

$[\alpha]_D$=+174.3° (c=0.994%, $CHCl_3$)

Reference Example 2

Isolation of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole)

Lansoprazole (racemate) (34.2 g) was dissolved in 2-propanol (1,710 ml) and hexane (1,140 ml) containing triethylamine (0.2%) and fractionated by HPLC (column: CHIRALCEL OD 50 mm dia.×500 mm, temperature: room temperature, mobile phase: hexane/2-propanol=85/15, flow rate: 60 ml/mm, detection wavelength: 285 nm, single injection: about 300 mg) to isolate the individual optical isomers. Fractions of an optical isomer of shorter retention time were combined and concentrated; the individual lots were combined and dissolved in ethanol (250 ml); after triethylamine (3 ml) was added, the solution was filtered through a 0.45 μm filter. After the filtrate was concentrated, hexane was added, and the filtrate was again evaporated to dryness to yield R(+)-lansoprazole (9.31 g, optical purity 98.3% ee) as an amorphous substance.

Reference Example 3

Production of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole)

In a nitrogen atmosphere, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]thio]benzimidazole (20.0 g, 0.057 mol), toluene (100 ml), water (55 mg, 0.0031 mol as based on total water content) and diethyl (+)-tartrate (2.12 ml, 0.012 mol) were mixed and stirred at 50 to 55° C. for 30 minutes. After titanium (IV) isopropoxide (1.66 ml, 0.0057 mol) was added to the mixture in a nitrogen atmosphere, the mixture was stirred at 50 to 55° C. for 1 hour. After diisopropylethylamine (3.25 ml, 0.019 mol) was added to the resulting mixed liquor under cooling in a nitrogen atmosphere, cumene hydroperoxide (30.6 ml, content 82%, 0.17 mol) was added at 0 to 5° C., followed by 3.5 hours of stirring at 0 to 5° C., to cause the reaction.

Analysis of the reaction liquor by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected a sulfide at 1.32% and a sulfone at 1.81% as related substances in the reaction liquor, with no other related substances detected. The enantiomer excess rate of the title compound in said reaction liquor was 96.4% ee.

Reference Example 4

Crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole)

(1) In a nitrogen stream, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]thio]benzimidazole (4.5

kg, 12.7 mol, containing 1.89 g of water), toluene (22 l), water (25 g, 1.39 mol, or 1.49 mol if based on total water content) and diethyl (+)-tartrate (0.958 l, 5.60 mol) were mixed. In a nitrogen stream, titanium (IV) isopropoxide (0.747 l, 2.53 mol) was added to this mixture at 50 to 60° C., and the mixture was stirred at the above temperature for 30 minutes. After diisopropylethylamine (0.733 l, 4.44 mol) was added to the resulting mixed liquor at room temperature in a nitrogen stream, cumene hydroperoxide (6.88 l, content 82%, 37.5 mol) was added at −5 to 5° C., followed by 1.5 hours of stirring at −5 to 5° C., to yield a reaction liquor.

Analysis of the reaction liquor by HPLC (column: Capcell Pak (Shiseido, Co. Ltd.), mobile phase: solvent mixture (acetonitrile/water/triethylamine=50/50/1); adjusted to pH 7.0 with phosphoric acid, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected a sulfide at 1.87% and a sulfone at 1.59% as related substances in the reaction liquor, with no other related substances detected.

(2) To the reaction liquor obtained in (1 l) above, a 30% aqueous solution of sodium thiosulfate (17 l) was added, in a nitrogen stream, to decompose the residual cumene hydroperoxide. To the organic layer obtained by liquid separation, water (4.5 l), heptane (13.5 l), t-butyl methyl ether (18 l) and heptane (27 l) were added sequentially in this order, and this mixture was stirred to cause crystallization. The resulting crystal was separated and washed with t-butyl methyl ether-toluene (t-butyl methyl ether:toluene=4:1) (4 l) to yield a wet crystal of (R)-lansoprazole having the following powder X-ray diffraction interplanar spacings (d).

The results of powder X-ray diffraction analysis of this wet crystal are shown below.

The wet crystal yielded a powder X-ray diffraction pattern with characteristic peaks appearing at powder X-ray diffraction interplanar spacings (d) of 5.85, 4.70, 4.35, 3.66 and 3.48 Angstrom.

Analysis of this crystal by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected a sulfone at 0.90% as a related substance in the crystal, with no sulfide or any other related substance detected. The (R)-lansoprazole enantiomer excess rate in this crystal was 100% ee.

(3) With stirring, a suspension in acetone (20 l) of the wet crystal obtained in (2) above was added drop by drop into a mixed liquor of acetone (7 l) and water (34 l), then water (47 l) was added; The precipitated crystal was separated and washed with acetone-water (acetone:water=1:3) (4 l) and water (12 l) to yield a wet crystal of (R)-lansoprazole having the following powder X-ray diffraction interplanar spacings (d).

The results of powder X-ray diffraction analysis of this wet crystal are shown below.

The wet crystal yielded a powder X-ray diffraction pattern with characteristic peaks appearing at powder X-ray diffraction interplanar spacings (d) of 8.33, 6.63, 5.86 and 4.82 Angstrom.

Analysis of this crystal by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected no sulfone, sulfide or any other related substance in the crystal. The (R)-lansoprazole enantiomer excess rate in this crystal was 100% ee.

(4) After the wet crystal obtained in (3) above was dissolved in ethyl acetate (45 l) and water (3 l), this solution was divided into liquid layers. The trace amount of insoluble matter in the organic layer was filtered off, then triethylamine (0.2 l) was added, after which the filtrate was concentrated under reduced pressure to a liquid volume of about 7 l. To this concentrate, methanol (2.3 l), about 12.5% aqueous ammonia at about 50° C. (23 l) and t-butyl methyl ether at about 50° C. (22 l) were added, and this liquid was divided into layers. To the organic layer, about 12.5% aqueous ammonia (11 l) was added, and this liquid was divided into layers (this operation was repeated once again). The water layers were combined, and ethyl acetate (22 l) was added, and then acetic acid was added drop by drop to reach a pH of about 8 under cooling. The liquid was divided into layers, and the water layer was extracted with ethyl acetate (11 l). The organic layers were combined and washed with about 20% saline (11 l). After triethylamine (0.2 l) was added, the organic layer was concentrated under reduced pressure. Acetone (5 l) was added to the concentrate, and this mixture was concentrated under reduced pressure. The concentrate was dissolved in acetone (9 l), and this solution was added drop by drop into a mixed liquor of acetone (4.5 l) and water (22.5 l), and then water (18 l) was added drop by drop to the mixed liquor obtained. The precipitated crystal was separated and washed sequentially with cold acetone-water (acetone:water=1:3) (3 l) and water (12 l) to yield a wet crystal of (R)-lansoprazole having the following powder X-ray diffraction interplanar spacings (d).

The results of powder X-ray diffraction analysis of this wet crystal are shown below.

The wet crystal yielded a powder X-ray diffraction pattern with characteristic peaks appearing at powder X-ray diffraction interplanar spacings (d) of 8.33, 6.63, 5.86 and 4.82 Angstrom.

Analysis of this crystal by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected no sulfone, sulfide or any other related substance in the crystal. The (R)-lansoprazole enantiomer excess rate in this crystal was 100% ee.

(5) The wet crystal obtained in (4) above was dissolved in ethyl acetate (32 l). The water layer was separated by a liquid separation procedure, and the organic layer obtained was concentrated under reduced pressure to a liquid volume of about 14 l. To the residual liquid, ethyl acetate (36 l) and activated charcoal (270 g) were added, after stirring, the activated charcoal was removed by filtration. The filtrate was concentrated under reduced pressure to a liquid volume of about 14 l. At about 40° C., heptane (90 l) was added drop by drop to the residual liquid. After stirring at the above temperature for about 30 minutes, the resulting crystal was separated, washed with about 40° C. ethyl acetate-heptane (ethyl acetate:heptane=1:8) (6 l), and dried to yield 3.4 kg of the title compound.

The results of powder X-ray diffraction analysis of this crystal are shown below.

The crystal yielded a powder X-ray diffraction pattern with characteristic peaks appearing at powder X-ray diffraction interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

Analysis of this crystal by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected no sulfone, sulfide or any other related substance in the crystal. The (R)-lansoprazole enantiomer excess rate in this crystal was 100% ee.

Example 1

Crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole)

Amorphous R(+)-lansoprazole as obtained in Reference Example 1 (100 mg) was dissolved in acetonitrile (1 ml), which was gradually evaporated at room temperature in a nitrogen stream. After a crystal began to form, diethyl ether (1.5 ml) was added and the container was stoppered and kept standing at room temperature.

The crystal thus formed was subjected to X-ray structural analysis, and the absolute configuration of sulfoxide was found to be the R-configuration by a method using a Flack parameter. The remaining portion of the crystal was collected by filtration, twice washed with diethyl ether (1 ml), and dried under reduced pressure, to yield crystals of R(+)-lansoprazole (38 mg).

m.p.: 144.0–144.5° C. (dec.) Elemental analysis Calculated: C: 52.03, H: 3.82, N: 11.38, S: 8.68, F: 15.43, O: 8.66 Found: C: 52.08, H: 3.76, N: 11.58, S: 8.75, F: 15.42 ^{1}H-NMR: 2.25(3H, s), 4.40(2H, q, J=7.8 Hz), 4.68(1H, d, J=13.8 Hz), 4.85(1H, d, J=13.8 Hz), 6.69(1H, d, J=6.0 Hz), 7.29–7.39(2H, m), 7.52(1H, m), 7.81(1H, m), 8.37(1H, d, J=6.0 Hz), 11.00(1H, bs).

IR(νcm^{-1}): 3081, 3042, 2984, 1586, 1478, 1441, 1306, 1267, 1163. UVmax($CHCl_3$): 283.7 nm $[\alpha]_D$=+199.2° (c=0.202%, $CHCl_3$)

TABLE 1

Crystal Data and Structure Refinement Parameters	
Molecular formula	$C_{16}H_{14}N_3O_2F_3S$
Molecular weight	369.36
Crystal color, habit	Colorless, tabular
Crystal Dimension	0.40 × 0.30 × 0.04 (mm)
Crystal system	Monoclinic
Lattice constants	a = 8.549(1) (Å)
	b = 23.350(1) (Å)
	c = 8.720(2) (Å)
	β = 103.90(1) (°)
	V = 1,689.8(4) (Å)
Space group	$P2_1$
Z	4
Density (calculated)	1.452 (g/cm^3)
Effective reflection number/parameter number	9.12
R (I ≥ 2σ (I))	0.036
Flack parameter	−0.02(2)

Example 2

Crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole)

Amorphous (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole as obtained in Reference Example 2 (9.17 g) was dissolved in acetone (20 ml), and water (15 ml) was added with gentle heating. After the solution was kept standing at room temperature overnight, water (20 ml) was added, followed by ultrasonication. After being collected by filtration, the solid was washed with water (30 ml, 20 ml), then washed with diisopropyl ether (20 ml), and dried under reduced pressure, to yield a solid (9.10 g). The solid obtained (9.00 g) was dissolved in acetone (30 ml), and after the solution was filtered, diisopropyl ether (50 ml) was added to the filtrate. A crystal seed was placed, and the mixture was kept standing at room temperature overnight. Precipitated crystals were collected by filtration, washed 3 times with diisopropyl ether (10 ml), and dried under reduced pressure, to yield crystals (7.85 g). The crystals obtained (7.80 g) were dissolved under heating in acetone (22.5 ml) and water (30 ml), and this solution was kept standing at room temperature for 1 hour. A precipitated solid was collected by filtration, washed with acetone-water (1:4) (15 ml), and dried under reduced pressure, to yield a solid (3.88 g). The solid obtained (3.88 g) was dissolved under heating in acetone (4 ml) and diisopropyl ether (14 ml) was added. This solution was kept standing at room temperature for 30 minutes. Precipitated crystals were collected by filtration, twice washed with diisopropyl ether (6 ml), and dried under reduced pressure, to yield crystals of R(+)-lansoprazole (3.40 g, optical purity 99.8% ee).

m.p.: 147.0–148.0° C. (dec.) Elemental analysis Calculated: C: 52.03, H: 3.82, N: 11.38, S: 8.68, F: 15.43, O: 8.66 Found: C: 51.85, H: 3.92, N: 11.26, S: 8.82, F: 15.22 ^{1}H-NMR: 2.24(3H, s), 4.38(2H, q, J=7.8 Hz), 4.74(1H, d, J=13.6 Hz), 4.87(1H, d, J=13.6 Hz), 6.68(1H, d, J=5.8 Hz), 7.26–7.36(2H, m), 7.45(1H, m), 7.78(1H, m), 8.35(1H, d, J=5.8 Hz). IR(νcm^{-1}): 3083, 3034, 2975, 1586, 1478, 1441, 1306, 1267, 1163 UVmax ($CHCl_3$): 283.6 nm $[\alpha]_D$=+180.3° (c=1.004%, $CHCl_3$)

TABLE 2

X-ray Powder Diffraction Data

2θ (°)	Half-value width	d-value (Å)	Relative intensity (%)
7.560	0.141	11.6841	100
13.060	0.165	6.7733	44
15.160	0.141	5.8394	55
15.440	0.141	5.7342	84
20.040	0.165	4.4271	23
21.720	0.165	4.0883	89
22.560	0.141	3.9380	24
22.820	0.141	3.8937	24
24.080	0.165	3.6927	37
26.120	0.118	3.4088	32
28.680	0.165	3.1100	20

Example 3

Crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole) 1.5 hydrate

Amorphous (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole as obtained in Reference Example 1 (100 mg) was dissolved in ethanol (0.15 ml), and water (0.15 ml) was added. After a seed was placed, the solution was kept standing at room temperature for 1 hour. Precipitated crystals were collected by filtration, twice washed with water (2 ml), and dried under reduced pressure, to yield crystals of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole) 1.5 hydrate (96 mg).

m.p.: 76.0–80.0° C. Elemental analysis Calculated: C: 48.48, H: 4.32, N: 10.60, S: 8.09, F: 14.38, O: 14.13 Found: C: 48.52, H: 4.44, N: 10.49

TABLE 3

X-ray Powder Diffraction Data

2θ (°)	Half-value width	d-value (Å)	Relative intensity (%)
6.680	0.165	13.2212	9
9.200	0.165	9.6046	21
9.960	0.141	8.8734	25
10.980	0.165	8.0513	42
13.380	0.141	6.6120	22

TABLE 3-continued

X-ray Powder Diffraction Data			
2θ (°)	Half-value width	d-value (Å)	Relative intensity (%)
14.960	0.141	5.9170	63
15.680	0.165	5.6469	100
17.640	0.212	5.0237	34
19.760	0.212	4.4892	33
25.420	0.188	3.5010	23
29.800	0.188	2.9957	20

Experimental Example 1

Suppressive action on gastric mucosal injury due to stress of water immersion restraint in rat

Male SD rats (7 weeks of age, weighing 230 to 250 g) were fasted for 24 hours, after which they were stressed by being housed in restraint cages and immersed to below the xiphoid process in a standing position in a 23° C. constant-temperature water chamber. After 5 hours, the rats were removed from the cages and sacrificed using gaseous carbon dioxide, and their stomachs excised. After the lower portion of the esophagus was clipped, a 1% formalin solution (10 ml) was injected into the stomach via the duodenum, which was then occluded, and the stomach was immersed in the same solution. After 10 minutes, an incision was made along the greater curvature, and the length (mm) of each mucosal injury was measured under a stereomicroscope. The overall sum of the injury lengths in each stomach was taken as the gastric mucosal injury index.

The crystals of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole) as obtained in Example 2 were suspended in 0.5% methyl cellulose (pH 9.5) containing 0.05 M $NaHCO_3$ and orally administered at 30 minutes before stressing (dosing volume 2 ml/kg). Each treatment group comprised 9 animals. The control group (solvent administration group) and the drug administration group were compared by Steel's test.

The results are shown in Table 4.

TABLE 4

Sample	Dose (mg/kg)	Gastric mucosal injury index (mm)	Suppression rate (%)
Control	—	10.9 ± 1.9	—
(R)-lansoprazole crystal	3	0.2 ± 0.2*	98.0

Each figure of gastric mucosal injury index is the mean ± standard error for the 9 animals in each group. *p < 0.01 (versus control group, Steel's test)

Experimental Example 2

The crystals of R(+)-lansoprazole as obtained in Example 2 (about 5 mg) and amorphous R(+)-lansoprazole as obtained in Reference Example 1 (about 5 mg) were each taken in a colorless glass bottle, and their stability during storage at 60° C. (stopper removed) was examined. A 25 ml solution (concentration: about 0.2 mg/ml) of the sample after completion of storage in the mobile phase, along with a standard solution prepared using the initial lot, was analyzed under the HPLC conditions shown below, and the R(+)-lansoprazole content (residual percentage) was calculated from the peak area obtained. The results are shown in Table 5.

HPLC analytical conditions	
Detection wavelength	UV 275 nm
Column	YMC Pro C18, 4.6 × 150 mm
Mobile phase	Fluid prepared by adding phosphoric acid to water/acetonitrile/triethyl amine (63:37:1) to reach pH 7.
Flow rate	1.0 ml/min
Column temperature	40° C.
Sample injection volume	10 μl

TABLE 5

Stability of R(+)-Lansoprazole Crystal and Amorphous			
Sample	Duration of storage	Description	Content (Residual percentage)
Crystal	1 week	Light-brown	97.0
	2 weeks	Brown	93.8
	4 weeks	Brown	91.7
Amorphous	1 week	Brown	70.8
	2 weeks	Blackish brown	57.5

When the sample was stored at 60° C. (exposed), the crystal of Example 2 retained a content exceeding 90% for up to 4 weeks, whereas the amorphous form of Reference Example 1 showed reduction in content to 70.8% after 1 week and 57.5% after 2 weeks. This finding demonstrates that the crystal of R(+)-lansoprazole is more stable and more preferable for use as a pharmaceutical etc. than the amorphous form.

INDUSTRIAL APPLICABILITY

The crystal of the present invention is useful as a pharmaceutical because it shows excellent antiulcer action, gastric acid secretion-inhibiting action, mucosa-protecting action, anti-*Helicobacter pylori* action etc., and because it is of low toxicity. Furthermore, by crystallizing the (R)-isomer, not only its stability is improved but also its handling is facilitated so that it can be prepared as a solid pharmaceutical composition with good reproducibility. In addition, when orally administered, the crystal of the present invention is more absorbable and more rapidly shows its action than the racemate. In addition, when administered, the crystal of the present invention shows a higher Cmax and a greater AUC than the racemate, and becomes less likely to be metabolized partly because of the increased protein-binding rate, thus showing an extended duration of action. The crystal of the present invention is therefore useful as a pharmaceutical of low dosage and with a low prevalence of adverse reactions.

What is claimed is:

1. A method of treating Zollinger-Ellison syndrome in a mammal in need thereof which comprises administering to said mammal an effective amount of a crystalline compound of (R)-2-(((3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl) methyl)sulfinyl)-1H-benzimidazole or a salt thereof and a pharmaceutically acceptable excipient, carrier or diluent.

2. The method of claim **1** wherein said crystalline compound is (R)-2-(((3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole.

3. The method of claim **2** wherein said crystalline compound has an X-ray powder diffraction analysis pattern with characteristic peaks at interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

4. The method of claim **1** wherein said crystalline compound is (R)-2-(((3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole 1.5 hydrate and has an X-ray powder diffraction analysis pattern with characteristic peaks at interplanar spacings (d) of 13.22, 9.60, 8.87, 8.05, 6.61, 5.92, 5.65, 5.02, 4.49, 3.50 and 3.00 Angstrom.

5. A method of treating reflux esophagitis in a mammal in need thereof which comprises administering to said mammal an effective amount of a crystalline compound of (R)-2-(((3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole or a salt thereof and a pharmaceutically acceptable excipient, carrier or diluent.

6. The method of claim **5** wherein said crystalline compound is (R)-2-(((3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole.

7. The method of claim **6** wherein said crystalline compound has an X-ray powder diffraction analysis pattern with characteristic peaks at interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

8. The method of claim **5** wherein said crystalline compound is (R)-2-(((3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole 1.5 hydrate and has an X-ray powder diffraction analysis pattern with characteristic peaks at interplanar spacings (d) of 13.22, 9.60, 8.87, 8.05, 6.61, 5.92, 5.65, 5.02, 4.49, 3.50 and 3.00 Angstrom.

9. A method of eradicating *Helicobacter pylori* in a mammal in need thereof which comprises administering to said mammal an effective amount of a crystalline compound of (R)-2-(((3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole or a salt thereof and a pharmaceutically acceptable excipient, carrier or diluent.

10. The method of claim **9** further comprising administering one to three other active ingredients.

11. The method of claim **10** wherein said crystalline compound and said other active ingredient are administered simultaneously or in intervals.

12. The method of claim **10** wherein said other active ingredient is selected from the group consisting of an anti-*Helicobacter pylori* action substance, an imidazole compound, a bismuth salt, a quinoline compound and combinations thereof.

13. The method of claim **12** wherein said anti-*Helicobacter pylori* action substance is selected from the group consisting of antibiotic penicillins, antibiotic macrolides and combinations thereof.

14. The method of claim **12** wherein said imidazole compound is metronidazole.

15. The method of claim **9** wherein said crystalline compound is (R)-2-(((3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole.

16. The method of claim **15** wherein said crystalline compound has an X-ray powder diffraction analysis pattern with characteristic peaks at interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

17. The method of claim **9** wherein said crystalline compound is (R)-2-(((3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole 1.5 hydrate and has an X-ray powder diffraction analysis pattern with characteristic peaks at interplanar spacings (d) of 13.22, 9.60, 8.87, 8.05, 6.61, 5.92, 5.65, 5.02, 4.49, 3.50 and 3.00 Angstrom.

* * * * *

Exhibit D

US007285668B2

(12) United States Patent
Hashimoto et al.

(10) Patent No.: US 7,285,668 B2
(45) Date of Patent: *Oct. 23, 2007

(54) **PROCESS FOR THE CRYSTALLIZATION OF (R)- OR (S)-LANSOPRAZOLE**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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C07D 401/12 (2006.01)

(52) **U.S. Cl.** **546/273.7**

(58) **Field of Classification Search** 546/273.7; 514/338

See application file for complete search history.

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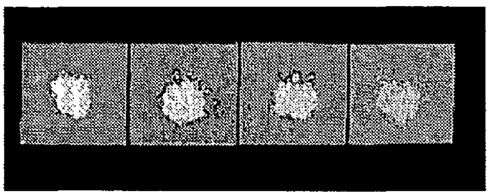
(57) **ABSTRACT**

The present invention relates to a production method of a crystal of (R)-lansoprazole or (S)-lansoprazole, which includes crystallization at a temperature of about 0° C. to about 35° C. from a C_{1-4} alkyl acetate solution containing (R)-lansoprazole or (S)-lansoprazole at a concentration of about 0.1 g/mL to about 0.5 g/mL and the like. According to the production method of the present invention, a crystal of (R)-lansoprazole or (S)-lansoprazole superior in preservation stability can be produced efficiently on an industrial large scale.

13 Claims, 1 Drawing Sheet

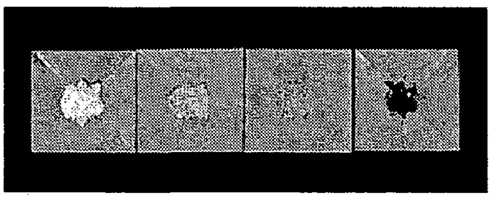
FIG. 1



Initial 40°C 2W 50°C 2W 60°C 2W

Method of present invention

(melting start temperature: about 134°C)



Initial 40°C 2W 50°C 2W 60°C 2W

Conventional method

(melting start temperature: about 130°C)

PROCESS FOR THE CRYSTALLIZATION OF (R)- OR (S)-LANSOPRAZOLE

This application is the National Phase filing of International Patent Application No. PCT/JP01/10462, filed 30 Nov. 2001.

TECHNICAL FIELD

The present invention relates to production methods of an optically active sulfoxide compound having an antiulcer activity, a crystal of an optically active sulfoxide compound having remarkably improved stability, and the like.

BACKGROUND ART

As a method for producing (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole [hereinafter sometimes to be referred to as (R)-lansoprazole] or (S)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole [hereinafter sometimes to be referred to as (S)-lansoprazole] having an antiulcer activity, for example, JP-A-11-508590 (WO 97/02261) describes a method for optically purifying a compound product adjusted to contain an enriched enantiomer and crystallization method by removing the solvent, which comprises treating a compound containing either (+)-enantiomer or (−)-enantiomer in a greater amount, namely, a compound enriched in one enantiomer, with a solvent, selectively precipitating a racemic compound from the solvent utilizing the crystallinity of the racemate, filtering off the precipitated racemic compound and removing the solvent to give a single enantiomer of the compound having an increased optical purity, which corresponds to lansoprazole and the like.

JP-A-10-504290 (WO 96/02535) describes a production method of an optically active sulfoxide compound, which comprises subjecting a thio compound to an oxidation reaction, and crystallization (Example 11) of omeprazole, which comprises concentrating an acetonitrile solution and the like.

Lansoprazole is now on the market worldwide as a pharmaceutical product having a superior antiulcer activity. The crystal of lansoprazole is a racemate and is superior in preservation stability.

A crystal of optically active (R)-lansoprazole and (S)-lansoprazole obtained according to the above-mentioned conventional method does not necessarily satisfy the preservation stability, with the undeniable possibility of decreased purity, increased amounts of analogous materials, coloring and the like during preservation.

Therefore, there is a demand for a production method of the crystal of (R)-lansoprazole or (S)-lansoprazole sufficiently superior in the preservation stability.

DISCLOSURE OF INVENTION

As a result of various studies of the production methods of crystals of (R)-lansoprazole and (S)-lansoprazole, the present inventors have unexpectedly found for the first time that crystallization of (R)-lansoprazole and (S)-lansoprazole under specific conditions produces an extremely stable crystal and that this method is sufficiently satisfactory on an industrial scale, and completed the present invention.

Accordingly, the present invention provides the following:

[1] a method for producing a crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or (S)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole, which comprises crystallizing at a temperature of about 0° C. to about 35° C. from a C_{1-4} alkyl acetate solution containing (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or (S)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole at a concentration of about 0.1 g/mL to about 0.5 g/mL;

[2] a method for producing a crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or (S)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole, which comprises crystallizing at a temperature of about 0° C. to about 35° C. from a C_{1-4} alkyl acetate solution containing (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or (S)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole at a concentration of about 0.1 g/mL to about 0.5 g/mL, and adding dropwise to the C_{1-4} alkyl acetate solution, at the same temperature, C_{5-8} hydrocarbon in an amount of not more than 7 times the amount of the C_{1-4} alkyl acetate solution;

[3] the method of the above-mentioned [1] or [2], wherein the crystallization temperature is about 20° C. to about 30° C.;

[4] the method of the above-mentioned [1] or [2] wherein the crystallization is conducted for about 30 minutes to about 4 hours;

[5] the method of the above-mentioned [1] or [2], wherein the C_{1-4} alkyl acetate is ethyl acetate or propyl acetate;

[6] the method of the above-mentioned [2], wherein the C_{5-8} hydrocarbon is added in an amount of not more than 5 times the amount of the C_{1-4} alkyl acetate solution;

[7] the method of the above-mentioned [2], wherein the C_{5-8} hydrocarbon is heptane or hexane;

[8] the method of the above-mentioned [2], wherein the C_{5-8} hydrocarbon is added dropwise over about 15 minutes to about 4 hours;

[9] a crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or (S)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole produced according to the method of the above-mentioned [1] or [2];

[10] a crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole produced according to the method of the above-mentioned [1] or [2];

[11] a crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or (S)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole having a melting start temperature of not lower than about 131° C.;

[12] the crystal of the above-mentioned [11], wherein the melting start temperature is about 135° C.;

[13] a pharmaceutical composition containing the crystal of the above-mentioned [9] or [11];

[14] the pharmaceutical composition of the above-mentioned [13], which is for the prophylaxis or treatment of digestive ulcer, gastritis, reflux esophagitis, NUD (Non Ulcer Dyspepsia), gastric cancer, gastric MALT lymphoma, upper gastrointestinal hemorrhage, ulcer caused by a nonsteroidal anti-inflammatory agent, hyperacidity and ulcer due to postoperative stress, or a disease due to *Helicobacter pylori;*

[15] a method of preventing or treating digestive ulcer, gastritis, reflux esophagitis, NUD (Non Ulcer Dyspepsia), gastric cancer, gastric MALT lymphoma, upper gas-

trointestinal hemorrhage, ulcer caused by a nonsteroidal anti-inflammatory agent, hyperacidity and ulcer due to postoperative stress, or a disease due to *Helicobacter pylori,* which comprises administering the crystal of the above-mentioned [9] or [11] to human;

[16] use of the crystal of the above-mentioned [9] or [11] for the production of a pharmaceutical composition for the prophylaxis or treatment of digestive ulcer, gastritis, reflux esophagitis, NUD (Non Ulcer Dyspepsia), gastric cancer, gastric MALT lymphoma, upper gastrointestinal hemorrhage, ulcer caused by a nonsteroidal anti-inflammatory agent, hyperacidity and ulcer due to postoperative stress, or a disease due to *Helicobacter pylori;*

[17] a method for stabilizing a crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or (S)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole, which comprises crystallizing at a temperature of about 0° C. to about 35° C. from a C_{1-4} alkyl acetate solution containing (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or (S)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole at a concentration of about 0.1 g/mL to about 0.5 g/mL; and the like.

BRIEF DESCRIPTION OF DRAWINGS

FIG. **1** shows the appearance of a crystal (Example 1) having a melting start temperature of about 134° C. and a crystal (Reference Example 6) having a melting start temperature of about 130° C., before stability test (initial) and after stability test at 40° C. for 2 weeks, 50° C. for 2 weeks and 60° C. for 2 weeks.

DETAILED DESCRIPTION OF THE INVENTION

The "(R)-lansoprazole" or "(S)-lansoprazole" used as a starting material in the crystal production method of the present invention can be produced according to a method known per se, such as the method described in JP-A-10-504290 (WO 96/02535) or a method analogous thereto, or the method described in the following production method 1 or 2.

(1) Production Method 1

2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]thio]-1H-benzimidazole and an excess amount (about 1.5-10 molar equivalents) of an oxidant (e.g., peroxide such as hydrogen peroxide, tert-butyl hydroperoxide, cumene hydroperoxide, etc.) are reacted in the presence of a catalyst for asymmetric induction (e.g., optically active diol, complex of titanium(IV) alkoxide and water, etc.), an organic solvent [e.g., alcohols such as methanol, ethanol, propanol, isopropanol etc.; aromatic hydrocarbons such as benzene, toluene, xylene etc.; ethers such as diethyl ether, diisopropyl ether, butyl methyl ether, dioxane, tetrahydrofuran etc.; esters such as ethyl acetate, methyl acetate etc.; ketones such as acetone, methyl isobutyl ketone etc.; halogenated hydrocarbons such as chloroform, dichloromethane, ethylene dichloride, carbon tetrachloride etc.; amides such as N,N-dimethylformamide etc.; sulfoxides such as dimethylsulfoxide etc.; acetic acid and the like] and a base [such as an inorganic base (e.g., alkali metal carbonates (potassium carbonate, sodium carbonate etc.), alkali metal hydroxides (sodium hydroxide, potassium hydroxide etc.), alkali metal hydrides (sodium hydride, potassium hydride etc.) etc.); an organic base such as alkali metal alkoxides (sodium methoxide, sodium ethoxide, etc.), alkali metal carboxylates (sodium acetate, etc.), amines (piperidine, piperazine, pyrrolidine, morpholine, triethylamine, tripropylamine, tributylamine, trioctylamine, diisopropylethylamine, dimethylphenylamine, etc.), pyridines (pyridine, dimethylaminopyridine, etc.) and the like; a basic amino acid (e.g., arginine, lysin, ornithine etc.) and the like], at about −20° C. to 20° C. for about 0.1 to 50 hours.

The obtained compound can be isolated by a separation and purification method known per se, such as concentration, solvent extraction, crystallization, redissolution, chromatography or a combination thereof.

(2) Production Method 2

2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole is subjected to optical resolution to give an isomer.

The method of optical resolution includes a method known per se, for example, a fractional recrystallization method, a chiral column method, a diastereomer method, and so forth.

The "fractional recrystallization method" includes a method in which a salt is formed between a racemate and an optically active compound [e.g., (+)-mandelic acid, (−)-mandelic acid, (+)-tartaric acid, (−)-tartaric acid, (+)-1-phenethylamine, (−)-1-phenethylamine, cinchonine, (−)-cinchonidine, brucine, etc.], which salt is separated by fractional recrystallization etc., and, if desired, subjected to a neutralization process, to give a free optical isomer.

The "chiral column method" includes a method in which a racemate or a salt thereof is applied to a column for separation of optical isomer (chiral column). In the case of liquid chromatography, for example, optical isomers are separated by adding a racemate to a chiral column such as ENANTIO-OVM (produced by Tosoh Corporation) or the DAICEL CHIRAL series (produced by Daicel Corporation), and developing the racemate in water, a buffer (e.g., phosphate buffer), an organic solvent (e.g., hexane, ethanol, methanol, isopropanol, acetonitrile, trifluoroacetic acid, diethylamine, triethylamine, etc.), or a solvent mixture thereof. In the case of gas chromatography, for example, a chiral column, such as CP-Chirasil-DeX CB (produced by GL Science), is used to separate optical isomers.

The "diastereomer method" includes a method in which a racemate and an optically active reagent are reacted (preferably, an optically active reagent is reacted with the 1-position of the benzimidazole group) to give a diastereomer mixture, which is then subjected to ordinary separation methods (e.g., fractional recrystallization, chromatography, etc.) to obtain either diastereomer, which is subjected to a chemical reaction (e.g., acid hydrolysis, base hydrolysis, hydrogenolysis, etc.) to cut off the optically active reagent moiety, whereby the desired optical isomer is obtained. Said "optically active reagent" includes, for example, optically active organic acids such as MTPA [α-methoxy-α-(trifluoromethyl)phenylacetic acid] and (−)-menthoxyacetic acid; and optically active alkoxymethyl halides such as (1R-endo)-2-(chloromethoxy)-1,3,3-trimethylbicyclo[2.2.1]heptane and the like.

The above-mentioned 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]thio]-1H-benzimidazole can be produced according to the method described in JP-A-61-50978, U.S. Pat. No. 4,628,098, JP-A-10-195068, WO 98/21201 and the like or a method analogous thereto.

2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole is produced by the method described in JP-A-61-50978, U.S. Pat. No. 4,628,098 etc. or a method analogous thereto.

The (R)-lansoprazole or (S)-lansoprazole produced by the above-mentioned method may be a solid (crystal, amorphous) or an oily substance and may not be isolated or purified.

The crystal of (R)-lansoprazole or (S)-lansoprazole may or may not be a hydrate.

The "hydrate" includes 0.5 hydrate to 5.0 hydrate. Among others, 0.5 hydrate, 1.0 hydrate, 1.5 hydrate, 2.0 hydrate and 2.5 hydrate are preferred. More preferred is 0.5 hydrate, 1.0 hydrate and 1.5 hydrate.

When the (R)-lansoprazole or (S)-lansoprazole obtained according to the above-mentioned method as, for example, a crystal (hereinafter sometimes to be referred to as crystal (I)) and then subjected to the crystal production method of the present invention, the method of crystallization of crystal (I) includes methods known per se, for example, crystallization from a solution, crystallization from vapor, and crystallization from a molten form.

The method of the "crystallization from a solution" include, for example, a concentration method, a slow cooling method, a reaction method (diffusion method, electrolysis method), a hydrothermal growth method, a fusing agent method, and so forth. The solvents to be used include, for example, aromatic hydrocarbons (e.g., benzene, toluene, xylene, etc.), halogenated hydrocarbons (e.g., dichloromethane, chloroform, etc.), saturated hydrocarbons (e.g., hexane, heptane, cyclohexane, etc.), ethers (e.g., diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, etc.), nitrites (e.g., acetonitrile, etc.), ketones (e.g., acetone, etc.), sulfoxides (e.g., dimethylsulfoxide, etc.), acid amides (e.g., N,N-dimethylformamide, etc.), esters (e.g., ethyl acetate, etc.), alcohols (e.g., methanol, ethanol, isopropyl alcohol. etc.), water, and so forth. These solvents may be used singly or in a mixture of two or more kinds at appropriate ratios (e.g., 1:1 to 1:100).

The method of the "crystallization from vapor" includes, for example, a gasification method (sealed tube method, gas stream method), a gas phase reaction method, a chemical transportation method, and so forth.

The method of the "crystallization from a molten form" includes, for example, a normal freezing method (pulling-up method, temperature gradient method, Bridgman method), a zone melting method (zone leveling method, float zone method), a special growth method (VLS method, liquid phase epitaxis method), and so forth.

Examples of the crystal of (R)-lansoprazole or (S)-lansoprazole to be used as a starting material in the crystal production method of the present invention include the following:

(1) a crystal showing an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings (d) of 5.88, 4.70, 4.35, 3.66 and 3.48 Angstrom in an X-ray powder diffraction of wet crystal;

(2) a crystal showing an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings (d) of 8.33, 6.63, 5.86 and 4.82 Angstrom in an X-ray powder diffraction of wet crystal;

(3) a mixture of the crystals of the aforementioned (1) and (2); and

(4) a crystal showing an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

The enantiomeric excess of (R)-lansoprazole or (S)-lansoprazole to be applied to the crystal production method of the present invention is, for example, not less than about 80% ee, preferably not less than about 90% ee.

More preferable (R)-lansoprazole does not contain (S)-lansoprazole substantially. By "does not contain substantially" is meant (R)-lansoprazole containing (S)-lansoprazole in 0-3%, preferably 0-1%. More preferably, (S)-lansoprazole does not contain (R)-lansoprazole substantially. By "does not contain substantially" here is meant (S)-lansoprazole containing (R)-lansoprazole in 0-3%, preferably 0-1%.

It is preferable that (R)-lansoprazole or (S)-lansoprazole obtained by the above-mentioned production method be subjected to the step to be mentioned below for improving the optical purity.

For an increased optical purity of the (R)-lansoprazole or (S)-lansoprazole obtained by the above-mentioned production method, for example, the method described in JP-A-11-508590 (WO 97/02261) or a method analogous thereto, or the following method [1] or [2] is employed.

[1] A crystal of (R)-lansoprazole is selectively crystallized from a solution containing (R)-lansoprazole in a greater amount than (S)-lansoprazole and the precipitated crystal is separated to give a crystal of (R)-lansoprazole substantially free of (S)-lansoprazole.

[2] A crystal of (S)-lansoprazole is selectively crystallized from a solution containing (S)-lansoprazole in a greater amount than (R)-lansoprazole and the precipitated crystal is separated to give a crystal of (S)-lansoprazole substantially free of (R)-lansoprazole.

It is also possible to separate the precipitated crystal after the above-mentioned [1] or [2] and subject the crystal to recrystallization once or more.

The methods for "selective crystallization" include, for example, a method of stirring a solution, a method of adding a seed crystal to a solution, a method of changing the temperature of a solution, a method of changing the solvent composition of a solution, a method of decreasing the liquid amount of a solution, or a method consisting of two or more of these methods in combination and the like.

The "method of stirring a solution" includes, for example, stirring a solution containing one of (R)-lansoprazole and (S)-lansoprazole in a greater amount than the other at about −80° C. to 120° C., preferably at about −20° C. to 60° C., for about 0.01 to 100 hours, preferably for about 0.1 to 10 hours.

The "method of adding a seed crystal to a solution" include, for example, adding (1) a crystal showing an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings(d) of 5.88, 4.70, 4.35, 3.66 and 3.48 Angstrom; (2) a crystal showing an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings(d) of 8.33, 6.63, 5.86 and 4.82 Angstrom; (3) a mixture of the crystals of the aforementioned (1) and (2) or (4) in a solution, a solid that transforms to the aforementioned (1)-(3) (e.g., a crystal showing an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings(d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom; a crystal showing an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings(d) of 8.86, 8.01, 6.58, 5.91, 5.63, 5.02 and 4.48 Angstrom; a crystal showing an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings(d) of 8.37, 4.07, 5.65, 5.59, 5.21, 4.81 and 4.21 Angstrom; a crystal showing an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings(d) of 11.68, 6.78, 5.85, 5.73, 4.43, 4.09, 3.94, 3.90, 3.69, 3.41 and 3.11 Angstrom, etc.) to a solution containing one of (R)-lansoprazole and (S)-lansoprazole in a greater amount than the other as a seed crystal.

The "method of changing the temperature of a solution" includes, for example, changing the temperature of a solution containing one of (R)-lansoprazole and (S)-lansoprazole in a greater amount than the other, preferably by cooling (e.g., lower the liquid temperature by 5-100° C.).

The "method of changing the solvent composition of a solution" includes, for example, adding water, a low polar organic solvent (e.g., esters, ethers, aromatic hydrocarbons, hydrocarbons, halogenated hydrocarbons or a mixture of two or more of these etc.) or a mixture of two or more of these to a solution containing one of (R)-lansoprazole and (S)-lansoprazole in a greater amount than the other.

The "method of decreasing the liquid amount of a solution" includes, for example, distilling away or evaporating the solvent from a solution containing one of (R)-lansoprazole and (S)-lansoprazole in a greater amount than the other and the like.

Of these, preferred are:

(i) a method of stirring a solution,

(ii) a method comprising a method of stirring a solution and a method of adding a seed crystal to a solution,

(iii) a method comprising a method of stirring a solution and a method of changing the temperature of a solution,

(iv) a method comprising a method of stirring a solution and a method of changing the solvent composition of a solution,

(v) a method comprising a method of stirring a solution and a method of decreasing the liquid amount of a solution,

(vi) a method comprising a method of stirring a solution, a method of changing the temperature of a solution and a method of adding a seed crystal to a solution,

(vii) a method comprising a method of stirring a solution, a method of changing the solvent composition of a solution and a method of adding a seed crystal to a solution,

(viii) a method comprising a method of stirring a solution, a method of decreasing the liquid amount of a solution and a method of adding a seed crystal to a solution,

(ix) a method comprising a method of stirring a solution, a method of changing the temperature of a solution and a method of changing the solvent composition of a solution,

(x) a method comprising a method of stirring a solution, a method of changing the temperature of a solution, a method of changing the solvent composition of a solution and a method of adding a seed crystal to a solution,

(xi) a method comprising a method of stirring a solution, a method of changing the temperature of a solution and a method of decreasing the liquid amount of a solution, and

(xii) a method comprising a method of stirring a solution, a method of changing the temperature of a solution, a method of decreasing the liquid amount of a solution and a method of adding a seed crystal to a solution.

The precipitated crystal can be separated by, for example, filtration, centrifugation and the like.

The thus-obtained crystal may be used as it is, or dried, where necessary, or may be subjected to a recrystallization step, where necessary.

The "drying" includes, for example, vacuum drying, through-flow drying, drying by heating, air drying and the like.

When, for example, (R)-lansoprazole or (S)-lansoprazole obtained by asymmetric synthesis is used, it is applied to the method of the above-mentioned [1] or [2], or where necessary, recrystallization once or more times to reduce the amount of analogous materials (e.g., 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]thio]-1H-benzimidazole and/or 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfonyl]-1H-benzimidazole, etc.) in the precipitated crystals.

To be specific, the obtained crystal or a dry crystal thereof is dissolved in a solvent (e.g., water, esters, ketones, phenols, alcohols, ethers, aromatic hydrocarbons, amides, sulfoxides, hydrocarbons, nitrites, halogenated hydrocarbons, pyridines or a mixture of two or more of these), applied to a dehydration step where necessary, and crystallized.

The "dehydrating" is performed by a conventional dehydration method, such as a concentration method, a method using a dehydrating agent [e.g., anhydrous magnesium sulfate, anhydrous sodium sulfate, molecular sieve (trade name)] and the like.

Examples of the "crystallization" method include the aforementioned crystallization method.

The crystal obtained after the above-mentioned recrystallization is exemplified by:

(1) a crystal showing an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings (d) of 5.88, 4.70, 4.35, 3.66 and 3.48 Angstrom in an X-ray powder diffraction of wet crystal,

(2) a crystal showing an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings (d) of 8.33, 6.63, 5.86 and 4.82 Angstrom in an X-ray powder diffraction of wet crystal,

(3) a mixture of the crystals of the aforementioned (1) and (2), and

(4) a crystal showing an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

The amount of the analogous materials in the crystal is less than 1 wt %, preferably less than 0.4 wt %.

The crystal precipitated in the recrystallization step can be separated by, for example, filtration, centrifugation and the like.

The thus-obtained crystal may be used as it is, or dried, where necessary, or may be subjected to a second recrystallization step, where necessary.

The "drying" is done by a method similar to the above-mentioned "drying".

To be specific, the obtained crystal is dissolved in a solvent (e.g., water, esters, ketones, phenols, alcohols, ethers, aromatic hydrocarbons, amides, sulfoxides, hydrocarbons, nitrites, halogenated hydrocarbons, pyridines or a mixture of two or more of these etc.), applied to a dehydration step where necessary, crystallized, separated and dried.

The "dehydrating" is performed by a method such as the above-mentioned "dehydration method".

Examples of the "crystallization" method include the aforementioned crystallization method.

The crystal obtained in the above-mentioned second recrystallization step is exemplified by a crystal of (R)- or (S)-lansoprazole, which shows an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings(d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

The crystal obtained in the second recrystallization step may be separated by, for example, filtration, centrifugation and the like.

The separated crystal can be dried by, for example, vacuum drying, through-flow drying, drying by heating, air drying and the like.

The "esters" include, for example, methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, ethyl formate and the like.

The "ketones" include, for example, acetone, methyl ethyl ketone, methyl isopropyl ketone, methyl butyl ketone, methyl isobutyl ketone and the like.

The "phenols" include, for example, anisole and the like.

The "alcohols" include, for example, methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, 2-methyl-1-propanol, pentanol, 3-methyl-1-butanol, 2-methoxyethanol, 2-ethoxyethanol, ethylene glycol and the like.

The "ethers" include, for example, t-butyl methyl ether, diethyl ether, 1,1-diethoxypropane, 1,1-dimethoxypropane, 2,2-dimethoxypropane, isopropyl ether, tetrahydrofuran, methyltetrahydrofuran and the like.

The "aromatic hydrocarbons" include, for example, chlorobenzene, toluene, xylene, cumene and the like.

The "amides" include, for example, formamide, N,N-dimethylacetamide, N,N-dimethylformamide, N-methylpyrrolidone and the like.

The "sulfoxides" include, for example, dimethylsulfoxide and the like.

The "hydrocarbons" include, for example, propane, hexane, pentane, octane, isooctane and the like.

The "nitriles" include, for example, acetonitrile and the like.

The "halogenated hydrocarbons" include, for example, chloroform, dichloromethane, dichloroethene, trichloroethene and the like.

The "pyridines" include, for example, pyridine and the like.

The crystal obtained by crystallization by the above-mentioned method and dry crystal thereof do not substantially contain the other enantiomer.

(R)-Lansoprazole or (S)-lansoprazole obtained by the above-mentioned various methods is applied to the crystal production method of the present invention.

The crystal production method of the present invention is described in detail in the following.

(1) Step for Crystallization at a Temperature of About 0° C. to About 35° C. from C_{1-4} Alkyl Acetate Solution Containing (R)-lansoprazole or (S)-lansoprazole at a Concentration of About 0.1 g/mL to About 0.5 g/mL

First, (R)-lansoprazole or (S)-lansoprazole is made to be present in C_{1-4} alkyl acetate at a concentration of about 0.1 g/mL to about 0.5 g/mL (preferably about 0.1 g/mL to about 0.35 g/mL, more preferably about 0.2 g/mL to about 0.3 g/mL, particularly preferably about 0.25 g/mL to about 0.28 g/mL).

For example, an excess C_{1-4} alkyl acetate is added to (R)-lansoprazole or (S)-lansoprazole, and the mixture is heated where necessary at about 30° C. to 60° C. to dissolve same and concentrated under reduced pressure to achieve a given concentration (about 0.1 g/mL to about 0.5 g/mL).

As used herein, the concentration is measured according to an area comparison method with a standard product solution using high performance liquid chromatography. The measurement method is explained in detail in the following.

Measurement Conditions

Column: Shiseido CAPCELL PAK C18 SG120 5 μm 4.6×250 mm

Column Temp.: 25° C.

Mobile phase: H_2O:CH_3CN:Et_3N=50:50:1 (adjusted to pH 7.0 with phosphoric acid)

Flow rate: 1.0 mL/min.

Inject. Vol.: 10 μl

Wavelength: 285 nm

Sample Preparation

Standard solution: standard product (about 75 mg) is precisely weighed and mobile phase is added to make the amount 100 mL.

Sample solution: mobile phase is added to ethyl acetate solution (1 mL) to make the amount 100 mL.

Concentration Measurement Method

Standard solution (10 μl) and sample solution (10 μl) are tested by liquid chromatography under the aforementioned HPLC conditions and peak area A_S of (R)-lansoprazole or (S)-lansoprazole in the Standard solution, and the peak area A_T of (R)-lansoprazole or (S)-lansoprazole in the sample solution are measured by automatic integration, based on which the concentration of (R)-lansoprazole or (S)-lansoprazole is calculated from the following formula:

$$(A_T/A_S)\times(W_S/1000)$$

W_S: standard product sample amount (mg)

The concentration can be made to fall within the optimal range for the selected solvent, wherein the state of saturation or per-saturation (R)-lansoprazole or (S)-lansoprazole is preferable for crystallization.

The C_{1-4} alkyl acetate includes methyl acetate, ethyl acetate, propyl acetate, butyl acetate and the like, of which preferably used are ethyl acetate and propyl acetate.

The crystallization is performed by standing or stirring a C_{1-4} alkyl acetate solution containing the above-mentioned (R)-lansoprazole or (S)-lansoprazole according to a method known per se at a crystallization temperature of about 0° C. to about 35° C.

The lower limit of crystallization temperature is preferably about 10° C., more preferably about 15° C., most preferably about 20° C. The upper limit of crystallization temperature is preferably about 30° C. Particularly, crystallization temperature is preferably about 20° C. to about 30° C.

The crystallization time is about 30 minutes to about 10 hours, preferably about 30 minutes to about 4 hours, particularly preferably about 1 hour to about 2 hours.

In this step, a seed crystal may be added to the solution. Examples of the seed crystal include one that may be added to the solution before or during dropwise addition of C_{5-8} hydrocarbon to be mentioned below.

This step is carried out in an atmosphere or under an inert gas atmosphere, or in an inert gas stream. As the "inert gas", one usable for dropwise addition of C_{5-8} hydrocarbon to be mentioned below is employed.

The crystal obtained by this step can be separated by a method such as filtration, centrifugation and the like.

The separated crystal may be washed, where necessary, with a (1:0-1:10) mixture of C_{1-4} alkyl acetate-C_{5-8} hydrocarbon, and the like. The C_{1-4} alkyl acetate here is exemplified by those mentioned above, and the C_{5-8} hydrocarbon is exemplified by those mentioned below. The separated crystal can be dried by, for example, vacuum drying, through-flow drying, drying by heating, air drying and the like.

The crystal obtained by this step is superior in preservation stability and can be used as the pharmaceutical product to be mentioned below. By the following step (2), the objective crystal superior in preservation stability can be obtained in a high yield.

(2) Step for Adding Dropwise C_{5-8} Hydrocarbon in an Amount of Not More Than 7 Times the Amount of the C_{1-4} Alkyl Acetate Solution at the Same Temperature After Step (1)

By applying this step to the crystal obtained by the above-mentioned step (1) after separation or without separation, the crystal can be obtained in greater amounts.

This step is preferably applied after precipitation of the crystal in the above-mentioned step (1). It is preferably applied after precipitation of a crystal in at least about 20 wt %, more preferably about 30 wt % to about 90 wt %, particularly preferably about 50 wt % to about 90 wt %, of (R)-lansoprazole or (S)-lansoprazole added as a starting material.

The crystallization temperature in this step is the same as in step (1).

Examples of C_{5-8} hydrocarbon include straight chain or branched C_{5-8} aliphatic hydrocarbon, such as pentane, isopentane, neopentane, hexane, isohexane, 3-methylpentane, neohexane, 2,3-dimethylbutane, heptane, 2-methylhexane, 3-methylhexane, 3-ethylpentane, 2,2-dimethylpentane, 2,3-dimethylpentane, 2,4-dimethylpentane, 3,3-dimethylpentane, 2,2,3-trimethylbutane, octane, isooctane and the like, and C_{7-8} aromatic hydrocarbon, such as toluene, xylene and the like. Preferably, heptane and straight chain C_{5-8} aliphatic hydrocarbon such as hexane and the like, are used.

The amount of dropwise addition of C_{5-8} hydrocarbon is not more than 7 times, preferably not more than 5 times, more preferably 1 to 3 times, the amount of the C_{1-4} alkyl acetate solution containing (R)-lansoprazole or (S)-lansoprazole in step (1).

The dropwise addition includes sequential dropwise addition of almost the same amount over, for example, about 15 minutes to about 4 hours (preferably about 1 hour to about 2 hours) while standing or stirring the solution.

The temperature during dropwise addition is preferably adjusted to the above-mentioned crystallization temperature.

In this step, a seed crystal may be added to the solution before or during the dropwise addition of C_{5-8} hydrocarbon.

The seed crystal includes, for example,

(1) a crystal showing an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings (d) of 5.88, 4.70, 4.35, 3.66 and 3.48 Angstrom,

(2) a crystal showing an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings (d) of 8.33, 6.63, 5.86 and 4.82 Angstrom X-ray powder diffraction,

(3) a crystal showing an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom,

(4) a crystal showing an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings (d) of 8.86, 8.01, 6.58, 5.91, 5.63, 5.02 and 4.48 Angstrom,

(5) a crystal showing an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings (d) of 8.37, 4.07, 5.65, 5.59, 5.21, 4.81 and 4.21 Angstrom,

(6) a crystal showing an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings (d) of 11.68, 6.78, 5.85, 5.73, 4.43, 4.09, 3.94, 3.90, 3.69, 3.41 and 3.11 Angstrom,

(7) a mixture of two or more crystals from the aforementioned (1)-(6) and

(8) a solid that transforms into the aforementioned (1)-(6) in a solution.

After the dropwise addition, the mixture may be stood or stirred on demand for about 1 hour to about 3 hours.

This step is applied in an atmosphere or under an inert gas atmosphere, or in an inert gas stream. The "inert gas" includes, for example, nitrogen, helium, neon, argon and the like.

The crystal obtained by this step can be separated by filtration, centrifugation and the like.

The separated crystal may be washed, where necessary, with a C_{1-4} alkyl acetate —C_{5-8} hydrocarbon (1:0-1:10) mixture and the like. As used herein, the C_{1-4} alkyl acetate and C_{5-8} hydrocarbon are exemplified by those mentioned above. The separated crystal can be dried by, for example, vacuum drying, through-flow drying, drying by heating, air drying and the like.

The obtained crystal can be analyzed generally by crystal analysis by X-ray diffraction. The orientation of the crystal can be determined by a mechanical method, optical method and the like.

The crystal obtained by the above-mentioned production method (step (1) alone, or step (2) after step (1)) has the following melting start temperature by DSC measurement (temperature rise rate 0.5° C./min). As used herein, the "melting start temperature" refers to the temperature at which crystals start to melt when heated under, for example, the DSC measurement conditions to be mentioned below. The crystal has the melting start temperature of not less than about 131° C., preferably about 131° C. to about 137° C., more preferably about 132° C. to about 135° C., most preferably about 133° C. to about 135° C., particularly preferably about 135° C. For example, the melting start temperature of the crystal obtained in the above-mentioned step (1) can be about 135° C. In addition, the melting start temperature of the crystal obtained by step (2) after applying the above-mentioned step (1) can be about 132° C. to about 135° C.

The melting start temperature of the crystal obtained by a conventional method is less than about 131° C. For example, the melting start temperature of the crystal obtained by the method of Reference Example 3 mentioned below was about 125° C. to about 130° C.

The crystal having a melting start temperature of not less than about 131° C., which is obtained by the production method of the present invention, has extremely superior preservation stability as compared to the crystal having a melting start temperature of less than about 131° C., which is obtained by a prior art method. In the stability test (40° C.—one month residual ratio, 60° C.—one month residual ratio) to be mentioned below, for example, the crystal obtained by the production method of the present invention showed a residual ratio of not less than 99%, but the ratio of the crystal obtained by a conventional method was less than 94%. Moreover, the crystal obtained by a conventional method showed noticeable coloring during preservation.

The crystal having a melting start temperature of not less than about 131° C., which is obtained by the production method of the present invention, has such superior preservation stability and can be used advantageously as a pharmaceutical product, as compared to the crystal having a melting start temperature of less than about 131° C., which is obtained by a prior art method.

The crystal of (R)-lansoprazole or (S)-lansoprazole obtained by the crystal production method of the present invention is useful as a pharmaceutical product because it shows excellent antiulcer activity, gastric acid secretion-inhibiting action, mucosa-protecting action, anti-*Helicobacter pylori* action, etc., and because it is of low toxicity. The dry crystal of (R)-lansoprazole or (S)-lansoprazole is stabler than a precipitated crystal (wet crystal) of (R)-lansoprazole or (S)-lansoprazole, and when it is used as a pharmaceutical product, a dry crystal of (R)-lansoprazole or (S)-lansoprazole is preferably used.

The crystal or dry crystal obtained by the method of the present invention is useful for mammals (e.g., humans, monkeys, sheep, bovines, horses, dogs, cats, rabbits, rats, mice, etc.) in the treatment and prevention of digestive ulcer (e.g., gastric ulcer, duodenal ulcer, stomach ulcer, Zollinger-Ellison syndrome, etc.), gastritis, reflux esophagitis, NUD (non-ulcer dyspepsia), gastric cancer (inclusive of gastric cancer caused by promotion of interleukin-1β production due to genetic polymorphism of interleukin-1) and gastric MALT lymphoma; *Helicobacter pylori* eradication; suppression of upper gastrointestinal hemorrhage due to digestive ulcer, acute stress ulcer and hemorrhagic gastritis; suppression of upper gastrointestinal hemorrhage due to invasive stress (stress from major surgery necessitating intensive management after surgery, and from cerebral vascular disorder, head trauma, multiple organ failure and extensive burn necessitating intensive treatment); treatment and prevention of ulcer caused by a nonsteroidal anti-inflammatory agent; treatment and prevention of hyperacidity and ulcer due to postoperative stress; pre-anesthetic administration and the like. For eradication of *Helicobacter pylori,* the crystal or dry crystal obtained by the method of the present invention and antibiotic penicillins (e.g., amoxicillin etc.) and antibiotic erythromycins (e.g., clarithromycin, etc.) are preferably used.

For the above-mentioned various pharmaceutical uses, the crystal of (R)-lansoprazole is preferably used.

The crystal of the present invention can be safely administered orally or non-orally (e.g., topical, rectal and intravenous administration, etc.), as such or in the form of pharmaceutical compositions formulated with a pharmacologically acceptable carrier, e.g., tablets (including sugar-coated tablets and film-coated tablets), powders, granules, capsules (including soft capsules), orally disintegrating tablets, liquids, injectable preparations, suppositories, sustained-release preparations and patches, in accordance with a commonly known method.

The content of the crystal of the present invention in the pharmaceutical composition of the present invention is about 0.01 to 100 wt % relative to the entire composition. Varying depending on subject of administration, route of administration, target disease etc., its dose is normally about 0.5 to 1,500 mg/day, preferably about 5 to 150 mg/day, based on the active ingredient, when, for example, it is orally administered as an antiulcer agent to an adult human (60 kg). The crystal of the present invention may be administered once daily or in 2 to 3 divided portions per day.

Pharmacologically acceptable carriers that may be used to produce the pharmaceutical composition of the present invention include various organic or inorganic carrier substances in common use as pharmaceutical materials, including excipients, lubricants, binders, disintegrants, water-soluble polymers and basic inorganic salts for solid preparations; and solvents, dissolution aids, suspending agents, isotonicity agents, buffers and soothing agents for liquid preparations. Other ordinary pharmaceutical additives such as preservatives, antioxidants, coloring agents, sweetening agents, souring agents, bubbling agents and flavorings may also be used as necessary.

Such “excipients” include, for example, lactose, sucrose, D-mannitol, starch, cornstarch, crystalline cellulose, light silicic anhydride, titanium oxide and the like.

Such “lubricants” include, for example, magnesium stearate, sucrose fatty acid esters, polyethylene glycol, talc, stearic acid and the like.

Such “binders” include, for example, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, crystalline cellulose, α-starch, polyvinylpyrrolidone, gum arabic powder, gelatin, pullulan, low-substituted hydroxypropyl cellulose and the like.

Such “disintegrants” include (1) crosslinked povidone, (2) what is called super-disintegrants such as crosslinked carmellose sodium (FMC-Asahi Chemical) and carmellose calcium (Gotoku Yakuhin), (3) carboxymethyl starch sodium (e.g., product of Matsutani Chemical), (4) low-substituted hydroxypropyl cellulose (e.g., product of Shin-Etsu Chemical), (5) cornstarch, and so forth. Said “crosslinked povidone” may be any crosslinked polymer having the chemical name 1-ethenyl-2-pyrrolidinone homopolymer, including, what is called, polyvinylpyrrolidone (PVPP) and 1-vinyl-2-pyrrolidinone homopolymer, and is exemplified by Colidon CL (produced by BASF), Polyplasdon XL (produced by ISP), Polyplasdon XL-10 (produced by ISP), Polyplasdon INF-10 (produced by ISP) and the like.

Such “water-soluble polymers” include, for example, ethanol-soluble water-soluble polymers [e.g., cellulose derivatives such as hydroxypropyl cellulose (hereinafter also referred to as HPC), polyvinylpyrrolidone etc.], ethanol-insoluble water-soluble polymers [e.g., cellulose derivatives such as hydroxypropylmethyl cellulose (hereinafter also referred to as HPMC), methyl cellulose and carboxymethyl cellulose sodium, sodium polyacrylate, polyvinyl alcohol, sodium alginate, guar gum etc.] and the like.

Such “basic inorganic salts” include, for example, basic inorganic salts of sodium, potassium, magnesium and/or calcium. Preferred are basic inorganic salts of magnesium and/or calcium. More preferred are basic inorganic salts of magnesium. Such basic inorganic salts of sodium include, for example, sodium carbonate, sodium hydrogen carbonate, disodium hydrogenphosphate, etc. Such basic inorganic salts of potassium include, for example, potassium carbonate, potassium hydrogen carbonate, etc. Such basic inorganic salts of magnesium include, for example, heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metasilicate aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite $[Mg_6Al_2(OH)_{16}.CO_3.4H_2O]$, alumina hydroxide magnesium, and so forth. Among others, preferred is heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, etc. Such basic inorganic salts of calcium include, for example, precipitated calcium carbonate, calcium hydroxide and the like.

Such “solvents” include, for example, water for injection, alcohol, propylene glycol, macrogol, sesame oil, corn oil, olive oil and the like.

Such “dissolution aids” include, for example, polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate and the like.

Such “suspending agents” include, for example, surfactants such as stearyltriethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride and monostearic glycerol; and hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethyl cellulose sodium, methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose and hydroxypropyl cellulose.

Such “isotonicity agents” include, for example, glucose, D-sorbitol, sodium chloride, glycerol, D-mannitol and the like.

Such “buffers” include, for example, buffer solutions of phosphates, acetates, carbonates, citrates and the like.

Such “soothing agents” include, for example, benzyl alcohol and the like.

Such “preservatives” include, for example, p-oxybenzoic acid esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid and the like.

Such “antioxidants” include, for example, sulfites, ascorbic acid, α-tocopherol and the like.

Such “coloring agents” include, for example, foodcolors such as Food Color Yellow No. 5, Food Color Red No. 2 and Food Color Blue No. 2; and food lake colors, Bengal and the like.

Such “sweetening agents” include, for example, saccharin sodium, dipotassium glycyrrhetinate, aspartame, stevia, thaumatin and the like.

Such “souring agents” include, for example, citric acid (citric anhydride), tartaric acid, malic acid and the like.

Such “bubbling agents” include, for example, sodium bicarbonate and the like.

Such “flavorings” may be synthetic substances or naturally occurring substances, and include, for example, lemon, lime, orange, menthol, strawberry and the like.

The crystal of the present invention may be prepared as a preparation for oral administration in accordance with a commonly known method, by, for example, compression-shaping it in the presence of an excipient, a disintegrant, a binder, a lubricant or the like, and subsequently coating it as necessary by a commonly known method for the purpose of taste masking, enteric dissolution or sustained release. For an enteric preparation, an intermediate layer may be provided by a commonly known method between the enteric layer and the drug-containing layer for the purpose of separation of the two layers.

For preparing the crystal of the present invention as an orally disintegrating tablet, available method include, for example, a method in which a core containing crystalline cellulose and lactose is coated with the crystal of the present invention and a basic inorganic salt, and is further coated with a coating layer containing a water-soluble polymer, to give a composition, which is coated with an enteric coating layer containing polyethylene glycol, further coated with an enteric coating layer containing triethyl citrate, still further coated with an enteric coating layer containing polyethylene glycol, and still yet further coated with mannitol, to give fine granules, which are mixed with additives and shaped. The above-mentioned "enteric coating layer" includes, for example, aqueous enteric polymer substrates such as cellulose acetate phthalate (CAP), hydroxypropylmethyl cellulose phthalate, hydroxymethyl cellulose acetate succinate, methacrylic acid copolymers [e.g., Eudragit L30D-55 (trade name; produced by Rohm), Colicoat MAE30DP (trade name; produced by BASF), Polykid PA30 (trade name; produced by San-yo Chemical) etc.], carboxymethylethyl cellulose and shellac; sustained-release substrates such as methacrylic acid polymers [e.g., Eudragit NE30D (trade name), Eudragit RL30D (trade name), Eudragit RS30D (trade name), etc.]; water-soluble polymers; plasticizers such as triethyl citrate, polyethylene glycol, acetylated monoglycerides, triacetine and castor oil; and mixtures of one or more thereof. The above-mentioned "additive" includes, for example, water-soluble sugar alcohols (e.g., sorbitol, mannitol, multitol, reduced starch saccharides, xylitol, reduced paratinose, erythritol. etc.), crystalline cellulose [e.g. Ceolas KG 801, Avicel PH 101, Avicel PH 102, Avicel PH 301, Avicel PH 302, Avicel RC-591 (crystalline cellulose carmellose sodium) etc.], low-substituted hydroxypropyl cellulose [e.g., LH-22, LH-32, LH-23, LH-33 (Shin-Etsu Chemical) and mixtures thereof etc.] etc.; binders, souring agents, bubbling agents, sweetening agents, flavorings, lubricants, coloring agents, stabilizers, excipients, disintegrants etc. are also used.

The crystal of the present invention may be used in combination with 1 to 3 other active ingredients.

Such "other active ingredients" include, for example, anti-*Helicobacter pylori* activity substances, imidazole compounds, bismuth salts, quinolone compounds, and so forth. Of these substances, preferred are anti-*Helicobacter pylori* action substances, imidazole compounds etc. Such "anti-*Helicobacter pylori* action substances" include, for example, antibiotic penicillins (e.g., amoxicillin, benzylpenicillin, piperacillin, mecillinam, etc.), antibiotic cefems (e.g., cefixime, cefaclor, etc.), antibiotic macrolides (e.g., erythromycin. clarithromycin, etc.), antibiotic tetracyclines (e.g., tetracycline, minocycline, streptomycin. etc.), antibiotic aminoglycosides (e.g., gentamicin, amikacin, etc.), imipenem, and so forth. Of these substances, preferred are antibiotic penicillins, antibiotic macrolides etc. Especially preferred is a triple therapy of an antibiotic penicillins, anantibiotic macrolide and the crystal of (R)-lansoprazole or (S)-lansoprazole. Such "imidazole compounds" include, for example, metronidazole, miconazole, etc. Such "bismuth salts" include, for example, bismuth acetate, bismuth citrate, etc. Such "quinolone compounds" include, for example, ofloxacin, ciploxacin, etc.

Such "other active ingredients" and the crystal of the present invention may also be used in combination as a mixture prepared as a single pharmaceutical composition [e.g., tablets. powders, granules, capsules (including soft capsules), liquids, injectable preparations, suppositories, sustained-release preparations, etc.], in accordance with a commonly known method. and may also be prepared as separate preparations and administered to the same subject simultaneously or at a time interval.

While the present invention is explained in detail in the following by referring to Reference Examples and Examples, the present invention is not limited by these Examples.

The X-ray powder diffraction was measured using X-ray Diffractometer RINT Ultima+ (Rigaku).

The melting start temperature was measured using DSC (differential scanning calorimeter SEIKO DSC220C) under the following measurement conditions.

DSC Measurement Conditions;

temperature range: room temperature to 220° C.

temperature rise rate: 0.5° C./min.

sample container: aluminum pan (without cover)

atmosphere: nitrogen gas (100 mL/min)

Enantiomeric excess (% ee) was measured by high performance liquid chromatography using an optically active column for the following conditions (A).

The amounts of sulfide and sulfone present were measured by high performance liquid chromatography using an optically active column for the following conditions (A) or high performance liquid chromatography under the conditions (B).

High Performance Liquid Chromatography Conditions (A);

Column: CHIRALCEL OD (4.6×250 mm; DAICEL CHEMICAL INDUSTRIES, LTD.)

Mobile phase: hexane/ethanol=90/10

Flow rate: 1.0 mL/min

Detection: UV 285 nm

High Performance Liquid Chromatography Conditions (B);

Column: CAPCELL PAK C18 SG120 5 μm 4.6×250 mm (Shiseido Co., Ltd.)

Mobile Phase: acetonitrile:water:triethylamine mixture (50:50:1) adjusted to pH 7.0 with phosphoric acid

Flow rate: 1.0 mL/min

Detection: UV 285 nm

Reference Example 1

Production of Solution Containing (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole by Asymmetric Oxidation

2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]thio]-1H-benzimidazole monohydrate (6 kg, 16.2 mol) was dried in vacuo at 80° C. for 21 hours to give 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]thio]-1H-benzimidazole (5.73 kg, water content 0.0364%). 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]thio]-1H-benzimidazole (5.00 kg, 14.1 mol, containing water 1.82 g), toluene (25 L), water (13.18 g, 0.732 mol, as total water content 0.833 mol) and (+)-diethyl tartrate (531 mL, 3.10 mol) were mixed under a nitrogen gas stream. Titanium(IV) isopropoxide (414 mL, 1.40 mol) was added at 50-60° C. under a nitrogen gas stream, and the mixture was stirred at the same temperature for 30 min. Diisopropylethylamine (815 mL, 4.68 mol) was added under a nitrogen gas stream at 15-25° C., and cumene hydroperoxide (7.65 L, content 82%, 42.7 mol) was added at −10° C. to 5° C. and the mixture was stirred at −8° C. to 2° C. for 3 hours to allow reaction.

The analysis results of the reaction mixture by high performance liquid chromatography (conditions (A)) are as follows.

The enantiomeric excess of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole in the reaction mixture was 96.9% ee.

As a result of the analysis of the reaction mixture by high performance liquid chromatography (conditions (B)), analogous materials in the reaction mixture were found to be sulfide 1.0% and sulfone 1.7% alone.

Reference Example 2

Purification Method of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole

(1) To the reaction mixture obtained in the above-mentioned Reference Example 1 was added 30% aqueous sodium thiosulfate solution (13.5 kg) under a nitrogen gas stream, and the remaining cumene hydroperoxide was decomposed. The mixture was concentrated under reduced pressure until the liquid amount became about 25 L. Heptane-t-butyl methyl ether (heptane:t-butyl methyl ether=1:1, 20 L) was added dropwise while maintaining the mixture at 0-10° C. and heptane (70 L) was added dropwise. The precipitated crystals were separated, and washed with cooled t-butyl methyl ether-toluene (t-butyl methyl ether: toluene=4:1, 5 L).

As a result of the analysis of the crystal by high performance liquid chromatography (conditions (A)), the enantiomeric excess of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole in the crystal was found to be 98.3% ee.

As a result of the analysis of the reaction mixture by high performance liquid chromatography (conditions (B)), analogous materials in the reaction mixture were found to be sulfide 0.45% and sulfone 1.8% alone.

(2) A suspension of the wet crystal obtained in the above-mentioned (1) in acetone (20 L) was added dropwise to a mixture of acetone (7.5 L) and water (37.5 L), and water (52.5 L) was added. The precipitated crystals were separated and washed with cooled acetone-water (acetone: water=1:3, 5 L) and water (6.5 L).

As a result of the analysis of the crystal by high performance liquid chromatography (conditions (A)), the enantiomeric excess of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole in the crystal was found to be 100% ee.

As a result of the analysis of the crystal by high performance liquid chromatography (conditions (B)), analogous materials in the crystal were found to be sulfide 0.19% and sulfone 0.08% alone.

(3) The wet crystal obtained in the above-mentioned (2) was suspended in ethyl acetate (50 L) and magnesium sulfate (2.5 kg) was added. Magnesium sulfate was separated and the residue was washed with ethyl acetate (3.5 L). After addition of triethylamine (250 mL), the mixture was concentrated under reduced pressure until the liquid amount became about 10 L. To the concentrate were added methanol (2.5 L), about 12.5% aqueous ammonia (25.5 L, about 50° C.) and t-butyl methyl ether (24.5 L, about 50° C.) for partitioning. About 12.5% aqueous ammonia (12 L, about 50° C.) was added to the organic layer and the mixture was partitioned (this step was repeated once). The aqueous layers were combined, ethyl acetate (24.5 L) was added, and acetic acid was added dropwise at not more than 20° C. to adjust the pH to about 8. After partitioning, the aqueous layer was extracted with ethyl acetate (24.5 L). The organic layers were combined and washed with about 20% brine (24.5 L). After addition of triethylamine (250 mL), the organic layer was concentrated under reduced pressure. Acetone (5.55 L) was added to the concentrate and the mixture was concentrated under reduced pressure. The concentrate was dissolved in acetone (10 L) and the solution was added dropwise to a mixture of acetone (5 L) and water (25 L). Water (20 L) was added dropwise to the obtained mixture. The precipitated crystal was separated and successively washed with cooled acetone-water (1:3, 4 L) and water (13 L).

As a result of the analysis of the crystal by high performance liquid chromatography (conditions (A)), the enantiomeric excess of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole in the crystal was found to be 100% ee.

As a result of the analysis of the crystal by high performance liquid chromatography (conditions (B)), analogous materials in the crystal were found to be sulfide 0.018% and sulfone 0.016% alone.

Reference Example 3

Purification Method of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole

The wet crystal obtained by the method of the above-mentioned Reference Example 2 was dissolved in ethyl acetate (43 L). The separated aqueous layer was partitioned and the obtained organic layer was concentrated under reduced pressure until the liquid amount became about 19 L. Ethyl acetate (48 L) was added to the concentrate, and the mixture was concentrated under reduced pressure until the liquid amount became about 19 L. Ethyl acetate (48 L) and activated carbon (360 g) were added to the concentrate and the mixture was stirred and the activated carbon was filtered off. The filtrate was concentrated under reduced pressure until the liquid amount became about 19 L. Heptane (150 L) was added dropwise to the concentrate at about 40° C. The mixture was stirred at the same temperature for about 30 minutes and the crystal was separated and washed with ethyl acetate-heptane (1:8, 8 L, about 40° C.) and dried to give the title compound (4.5 kg).

The analysis results of the crystal by X-ray powder diffraction are as follows.

The crystal showed an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings(d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

As a result of the analysis of the crystal by high performance liquid chromatography (conditions (A)), analogous materials in the crystal were found to be sulfone 0.02% alone, and other analogous materials such as sulfide and the like were not found. The enantiomeric excess of (R)-lansoprazole in the crystal was 100% ee.

The melting start temperature of the crystal was 127.5° C.

Reference Example 4

Production of (S)-lansoprazole

(1) 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]thio]-1H-benzimidazole (50.0 g, 0.14 mol, containing water 20 mg), toluene (250 mL), water (130 mg, 0.0072 mol, total water content 0.0083 mol) and (−)-diethyl tartrate (5.31 mL, 0.031 mol) were mixed under a nitrogen atmosphere. Titanium(IV) isopropoxide (4.14 mL, 0.014 mol) was added to the mixture at 50° C. and the mixture was stirred at 50-55° C. for 1 hour under a nitrogen atmosphere. Diisopropylethylamine (8.13 mL,

0.047 mol) was added to the obtained mixture under a nitrogen atmosphere and cooling, and cumene hydroperoxide (76.50 mL, content 82%, 0.42 mol) was added at −10° C. to 0° C. The mixture was stirred at −5° C. to 5° C. for 3.5 hours to give a reaction mixture.

As a result of the analysis of the reaction mixture by high performance liquid chromatography (conditions (A)), the enantiomeric excess of (S)-lansoprazole in the reaction mixture was 96.5% ee.

As a result of the analysis of the reaction mixture by high performance liquid chromatography (conditions (B)), analogous materials in the reaction mixture were found to be sulfone 1.90% and sulfide 1.50% alone.

(2) To the reaction mixture obtained in the above-mentioned (1) was added 30% aqueous sodium thiosulfate solution (180 mL) under a nitrogen gas stream, and the remaining cumene hydroperoxide was decomposed. The mixture was partitioned, and water (50 mL), heptane (150 mL), t-butyl methyl ether (200 mL) and heptane (300 mL) were successively added to the obtained organic layer to allow crystallization. The crystal was separated and washed with t-butyl methyl ether-toluene (t-butyl methyl ether: toluene=4:1, 45 mL) to give (S)-lansoprazole having interplanar spacings(d) in the following X-ray powder diffraction, as a wet crystal.

As a result of the analysis of the crystal by X-ray powder diffraction, the wet crystal showed an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings(d) of 5.88, 4.70, 4.35, 3.66 and 3.48 Angstrom.

As a result of the analysis of the crystal by high performance liquid chromatography (conditions (A)), the enantiomeric excess of the crystal was 100% ee.

As a result of the analysis of the crystal by high performance liquid chromatography (conditions (B)), the analogous material in the crystal was sulfone 0.72% and other analogous materials such as sulfide and the like were not found.

(3) A suspension of the wet crystal obtained in the above-mentioned (2) in acetone (220 mL) was added dropwise to a mixture of acetone (75 mL) and water (370 mL), and then water (520 mL) was added. The precipitated crystal was separated and washed with acetone-water (acetone: water=1:3, 44 mL) and water (130 mL) to give a wet crystal of (S)-lansoprazole having interplanar spacings(d) in the following X-ray powder diffraction.

As a result of the analysis of the wet crystal by X-ray powder diffraction, the crystal showed an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings(d) of 8.33, 6.63, 5.86 and 4.82 Angstrom.

As a result of the analysis of the crystal by high performance liquid chromatography (conditions (A)), the enantiomeric excess of the crystal was 100% ee.

As a result of the analysis of the crystal by high performance liquid chromatography (conditions (B)), analogous materials such as sulfone, sulfide and the like were not found.

Reference Example 5

Production of (S)-lansoprazole

The wet crystal (containing the title compound 35.37 g, content of analogous materials: 0%, enantiomeric excess: 100% ee) obtained according to Reference Example 4 was dissolved in ethyl acetate (340 mL). The aqueous layer was separated by partitioning and the obtained organic layer was concentrated under reduced pressure until the liquid amount became about 100 mL. Ethyl acetate (400 mL) and activated carbon (3 g) were added to the concentrate and the mixture was stirred. The activated carbon was removed by filtration. The filtrate was concentrated under reduced pressure until the liquid amount became about 100 mL. Heptane (1000 mL) was added dropwise to the concentrate at about 40° C. The mixture was stirred at the same temperature for about 30 minutes, and the crystal was separated and washed with ethyl acetate-heptane (1:8, 63 mL, about 40° C.). The crystal was dried to give the title compound (35.08 g, yield: 99.2%).

As a result of the analysis of the crystal by X-ray powder diffraction, the crystal showed an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings(d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

As a result of the analysis of the crystal by high performance liquid chromatography (conditions (A)), analogous materials such as sulfone, sulfide and the like were not found in the crystal. The enantiomeric excess of (S)-lansoprazole in the crystal was 100% ee.

The melting start temperature of the crystal was 127.0° C.

Reference Example 6

The crystal (1.5 g, 4.06 mmol) of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole was dissolved in ethyl acetate (30 mL) and concentrated to 6 mL under reduced pressure at an outer temperature of about 25° C. Heptane (24 mL) was added dropwise at about −5° C. for about 30 minutes. After stirring for about 2.5 hours, the precipitated crystal was separated and dried to give the title compound (1.46 g, yield: 97.3%).

As a result of the analysis of the crystal by X-ray powder diffraction, the crystal showed an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings(d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

As a result of the analysis of the crystal by high performance liquid chromatography (conditions (A)), analogous materials such as sulfone, sulfide and the like were not found in the crystal. The enantiomeric excess of (R)-lansoprazole in the crystal was 100% ee.

The melting start temperature of the crystal was 130.0° C.

Reference Example 7

The crystal (1.5 g, 4.06 mmol) of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole was dissolved in ethyl acetate (30 mL) and concentrated to 20 mL under reduced pressure at an outer temperature of about 25° C. Heptane (90 mL) was added dropwise at about 25° C. for about 30 minutes. After stirring for about 2.5 hours, the precipitated crystal was separated and dried to give the title compound (1.40 g, yield: 93.3%).

As a result of the analysis of the crystal by X-ray powder diffraction, the crystal showed an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings(d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

As a result of the analysis of the crystal by high performance liquid chromatography (conditions (A)), analogous materials such as sulfone, sulfide and the like were not found in the crystal. The enantiomeric excess of (R)-lansoprazole in the crystal was 100% ee.

The melting start temperature of the crystal was 128.5° C.

EXAMPLE 1

Production Method of High Melting Point Crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole

The wet crystal obtained according to the method of the above-mentioned Reference Example 2 was dissolved in ethyl acetate (50 L). The mixture was partitioned and the organic layer was concentrated under reduced pressure until the liquid amount became about 25 L. Ethyl acetate (30 L) was added to the concentrate, and the mixture was concentrated under reduced pressure until the liquid amount became about 15 L. Ethyl acetate (30 L) and activated carbon (150 g) were added to the concentrate. The activated carbon was removed and the mixture was washed with ethyl acetate (1.5 L). The filtrate was concentrated under reduced pressure until the concentration of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole became about 0.28 g/mL (12.5 L). The mixture was stirred under a nitrogen gas stream, at about 25° C. for about 2 hours, and after confirmation of crystal precipitation, heptane (25 L) was dropwise added over about 1.5 hours, and the mixture was stirred for about 1.5 hours. The precipitated crystal was separated, washed with ethyl acetate-heptane (ethyl acetate:heptane=1:5, 6 L) and dried to give the title compound (3.66 kg, yield: 70% based on 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]thio]-1H-benzimidazole).

As a result of the analysis of the crystal by X-ray powder diffraction, the crystal showed an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings(d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

As a result of the analysis of the crystal by high performance liquid chromatography (conditions (A)), the enantiomeric excess of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole in the crystal was 100% ee.

As a result of the analysis of the crystal by high performance liquid chromatography (conditions (B)), the analogous material was sulfone 0.01% alone, and sulfide and the like were not found. The melting start temperature of the crystal was 134.0° C.

EXAMPLE 2

The crystal (3 g, 8.12 mmol) of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole was dissolved in ethyl acetate (12 mL) at about 50° C. and the solution was stirred at about 25° C. for about 6 hours. The precipitated crystal was separated, washed with ethyl acetate-heptane (ethyl acetate:heptane=1:5, 3 mL) and dried to give the title compound (1.55 g, yield: 52%).

As a result of the analysis of the crystal by X-ray powder diffraction, the crystal showed an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings(d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

As a result of the analysis of the crystal by high performance liquid chromatography (conditions (A)), analogous materials such as sulfone, sulfide and the like were not

found. The enantiomeric excess of (R)-lansoprazole in the crystal was 100% ee.

The melting start temperature of the crystal was 135.0° C.

EXAMPLE 3

The crystal (1.5 g, 4.06 mmol) of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole was dissolved in n-propyl acetate (30 mL) and concentrated to 6 mL under reduced pressure at an outer temperature of about 25° C. After stirring for about 2.5 hours, the precipitated crystal was separated and dried to give the title compound (0.94 g, yield: 63%).

The melting start temperature of the crystal was 134.5° C.

EXAMPLE 4

The crystal (3.0 g, 8.12 mmol) of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole was dissolved in ethyl acetate (12 mL) at about 50° C. The mixture was stirred at about 25° C. for about 2.5 hours, and after confirmation of crystal precipitation, heptane (60 mL) was dropwise added over about 15 minutes. The precipitated crystal was separated, washed with ethyl acetate-heptane (ethyl acetate:heptane=1:5, 3 mL) and dried to give the title compound (2.84 g, yield: 95%).

The melting start temperature of the crystal was 133.5° C.

EXAMPLE 5

The crystal (3.0 g, 8.12 mmol) of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole was dissolved in ethyl acetate (12 mL) at about 50° C. The mixture was stirred at about 25° C. for about 2 hours, and after confirmation of crystal precipitation, hexane (24 mL) was dropwise added over about 20 minutes. The precipitated crystal was separated, washed with ethyl acetate-hexane (ethyl acetate:hexane=1:5, 3 mL) and dried to give the title compound.

The melting start temperature of the crystal was 133.5° C.

EXAMPLE 6

The crystal (2.0 g, 5.41 mmol) of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole was dissolved in n-propyl acetate (30 mL) at about 30° C. The mixture was concentrated to 8 mL under reduced pressure at an outer temperature of about 25° C. After stirring for about 1.5 hours, crystal precipitation was confirmed, and heptane (16 mL) was dropwise added over about 20 minutes. The precipitated crystal was separated, washed twice with n-propyl acetate-heptane (n-propyl acetate:heptane=1:5, 6 mL) and dried to give the title compound (1.86 g, yield: 93%).

The melting start temperature of the crystal was 134.0° C.

EXAMPLE 7

The crystal (2.0 g, 5.41 mmol) of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole was dissolved in i-propyl acetate (40 mL) at about 35° C. The mixture was concentrated to 8 mL under reduced pressure at an outer temperature of about 35° C. After stirring for about 1.5 hours, crystal precipitation was confirmed, and heptane (16 mL) was dropwise added over about 20 minutes. The precipitated crystal was separated, washed twice with i-propyl acetate-heptane (i-propyl acetate:heptane=1:5, 6 mL) and dried to give the title compound (1.89 g, yield: 95%).

The melting start temperature of the crystal was 133.0° C.

EXAMPLE 8

The crystal (2.0 g, 5.41 mmol) of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole was dissolved in n-butyl acetate (40 mL) at about 35° C. The mixture was concentrated to 8 mL under reduced pressure at an outer temperature of about 35° C. After stirring for about 1 hour, crystal precipitation was confirmed, and heptane (16 mL) was dropwise added over about 20 minutes. The precipitated crystal was separated, washed twice with n-butyl acetate-heptane (n-butyl acetate:heptane=1:5, 6 mL) and dried to give the title compound (1.87 g, yield: 93%).

The melting start temperature of the crystal was 133.0° C.

EXAMPLE 9

The crystal (2.0 g, 5.41 mmol) of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole was dissolved in methyl acetate (15 mL). The mixture was concentrated to 8 mL under reduced pressure at an outer temperature of about 25° C. After stirring for about 1.5 hours, crystal precipitation was confirmed, and heptane (16 mL) was dropwise added over about 20 minutes. The precipitated crystal was separated, washed twice with methyl acetate-heptane (methyl acetate:heptane=1:5, 6 mL) and dried to give the title compound (1.71 g, yield: 86%).

The melting start temperature of the crystal was 134.0° C.

EXAMPLE 10

The wet crystal obtained according to the method of the above-mentioned Reference Example 4 was dissolved in ethyl acetate (50 L). The mixture was partitioned and the organic layer was concentrated under reduced pressure until the liquid amount became about 27 L. Ethyl acetate (30 L) was added to the concentrate, and the mixture was concentrated under reduced pressure until the liquid amount became about 16 L. Ethyl acetate (30 L) and activated carbon (150 g) were added to the concentrate. The activated carbon was removed and the mixture was washed with ethyl acetate (1.5 L). The filtrate was concentrated under reduced pressure until the concentration of (S)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole became about 0.27 g/mL (12.5 L). After stirring at about 25° C. for about 2 hours under a nitrogen gas stream, crystal precipitation was confirmed, and heptane (25 L) was dropwise added over about 1.5 hours. The mixture was stirred for about 1.5 hours. The precipitated crystal was separated, washed with ethyl acetate-heptane (ethyl acetate:heptane=1:5, 6 L) and dried to give the title compound (3.76 kg, yield: 72% based on 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]thio]-1H-benzimidazole).

As a result of the analysis of the crystal by X-ray powder diffraction, the crystal showed an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings(d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

As a result of the analysis of the crystal by high performance liquid chromatography (conditions (A)), the enantiomeric excess of (S)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole in the crystal was 100% ee.

As a result of the analysis of the crystal by high performance liquid chromatography (conditions (B)), analogous materials in the crystal, such as sulfone, sulfide and the like were not found.

The melting start temperature of the crystal was 133.5° C.

EXAMPLE 11

The crystal (1.5 g, 4.06 mmol) of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole was dissolved in ethyl acetate (30 mL). The mixture was concentrated to 6 mL under reduced pressure at an outer temperature of about 25° C. The mixture was stirred for about 2 hours at the same temperature, and precipitation of the crystal was confirmed. Heptane (24 mL) was dropwise added over about 30 minutes. The mixture was stirred for about 2.5 hours, and the precipitated crystal was separated and dried to give the title compound (1.46 g, yield: 97.3%).

The melting start temperature of the crystal was 133.5° C.

Experimental Example: Stability Test (Relationship Between Melting Start Temperature and Stability)

Various (R)-lansoprazole crystals obtained in the above-mentioned Reference Examples and Examples were subjected to a stability test at 60° C. for one month. The partial results are shown in Table 1 below.

TABLE 1

production method	melting start temperature	60° C. one month residual ratio
present invention (1) (Example 2)	135.0° C.	100%
present invention (2) (Example 1)	134.0° C.	99.7%
present invention (3) (Example 6)	134.0° C.	99.2%
conventional method (A) (Reference Example 6)	130.0° C.	93.8%
conventional method (B) (Reference Example 3)	127.5° C.	89.8%

The crystal obtained by the method of the present invention shows a residual ratio of not less than 99% in a 60° C. one month stability test. The crystal obtained by a conventional method shows a residual ratio decreased to about 90-94%.

The crystal of (R)-lansoprazole was subjected to a 40° C. one month stability test. The partial results are shown in the following Table 2.

TABLE 2

production method	present invention (Example 11)	conventional method (Reference Example 7)
melting start temperature	133.5° C.	128.5° C.
initial		
appearance	almost white	almost white
content	99.5%	99.6%
analogous material content	0.2%	0.1%
40° C. one month		
appearance	almost white	brown
content	99.7%	93.8%
analogous material content	0.2%	4.6%

By the method of the present invention, decomposition was not found in the 40° C. one month stability test, but the appearance was degraded, the content decreased and the analogous material content increased by the conventional method.

In FIG. **1**, the appearance of a crystal (Example 1) having a melting start temperature of about 134° C. and a crystal (Reference Example 6) having a melting start temperature of about 130° C. before stability test and after stability tests (40° C. 2 weeks, 50° C. 2 weeks and 60° C. 2 weeks) is shown. The crystal having a melting start temperature of about 134° C. did not show changes in the appearance but the crystal having a melting start temperature of about 130° C. showed appreciably degraded appearance.

From the foregoing results, it is apparent that there exists a clear relationship between melting start temperature and stability in the case of the crystals of (R)-lansoprazole and (S)-lansoprazole, and that the crystal having a melting start temperature of not lower than about 131° C. is stable but the crystal having a melting start temperature of less than about 131° C. is unstable.

Formulation Example 1

Production of Capsule

Capsules (15 mg) were obtained according to the charge amount-1 in the following Table 3 and the following method (in Table 4, amounts per capsule are shown). (1) The crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (hereinafter to be referred to as compound A) obtained in Example 1 and the ingredients (3) to (6) were thoroughly mixed to give a dusting powder. In a centrifugal fluidized coating granulator was charged (2) Nonpareil and the above-mentioned dusting powder was coated while spraying an aqueous solution of (7) hydroxypropyl cellulose in purified water. The spherical granules were dried in vacuo at 40° C. for 16-20 hours and passed through a sieve (600 µm, 1180 µm) to give base granules. The base granules were placed in a roll flow type coating machine and coated with a suspension of (8) methacrylic acid copolymer LD-(12) polysorbate 80 in purified water. The coated granules were passed through a sieve (710 µm, 1400 µm) and dried in vacuo at 40° C. for 16-20 hours to give enteric coated granules. To the enteric coated granules were added (13) talc and (14) light silicic anhydride and mixed granules were produced in a tumbler mixer. The mixed granules were filled in (17) HPMC Capsule No. 2 by a capsule filling machine to give 15 mg capsules.

By controlling the amount to be filled of the above-mentioned mixed granules, 20 mg and 10 mg capsules were produced.

TABLE 3

Charge amount-1		
ingredients		15 mg capsule
[base granule]		
(1)	compound A	450.0 g
(2)	sucrose · starch spherical granule (Nonpareil)	1650.0
(3)	magnesium carbonate	336.0
(4)	purified sucrose	897.0
(5)	cornstarch	546.0
(6)	low-substituted hydroxypropyl cellulose	600.0
(7)	hydroxypropyl cellulose	21.0
	purified water	1029.0
	subtotal	4500.0 g
[enteric coated granule]		
	base granule	3600.0 g
(8)	methacrylic acid copolymer LD (Eudragit L30D-55[TR])	535.2
(9)	talc	160.8
(10)	macrogol 6000	52.8
(11)	titanium oxide	52.8
(12)	polysorbate 80	24.0
	purified water	2054.4
	subtotal	4425.6 g
[mixed granule]		
	enteric coated granule	3688.0 g
(13)	talc	6.0
(14)	light silicic anhydride	2.0
	subtotal	3696.0 g
[capsule]		
	mixed granule	924.0 g
(15)	HPMC Capsule No. 2	5000.0 cap.

TABLE 4

Formulation per capsule		
ingredients		15 mg capsule
[base granule]		
(1)	compound A	15.00 mg
(2)	sucrose · starch spherical granule (Nonpareil)	55.00
(3)	magnesium carbonate	11.20
(4)	purified sucrose	29.90
(5)	cornstarch	18.20
(6)	low-substituted hydroxypropyl cellulose	20.00
(7)	hydroxypropyl cellulose	0.70
	subtotal	150.00 mg
[enteric coated granule]		
	base granule	150.00 mg
(8)	methacrylic acid copolymer LD (Eudragit L30D-55[TR])	22.30
(9)	talc	6.70
(10)	macrogol 6000	2.20
(11)	titanium oxide	2.20
(12)	polysorbate 80	1.00
	subtotal	184.40 mg

TABLE 4-continued

ingredients		Formulation per capsule 15 mg capsule
[mixed granule]		
	enteric coated granule	184.40 mg
(13)	talc	0.30
(14)	light silicic anhydride	0.10
	subtotal	184.80 mg
[capsule]		
	mixed granule	184.80 mg
(15)	HPMC Capsule No. 2	62.00
	subtotal	246.80 mg

Formulation Example 2

Production of Capsule

Capsules (15 mg) were obtained according to the charge amount-2 in the following Table 5 and the following method (in Table 6, amounts per capsule are shown). (1) Compound A and the ingredients (3) to (6) were thoroughly mixed to give a main drug dusting powder. The ingredients (7) to (9) were thoroughly mixed to give a cover coating agent. In a centrifugal fluidized coating granulator was charged (2) Nonpareil and the above-mentioned main drug dusting powder and the cover coating agent were successively coated while spraying an aqueous solution of (10) hydroxypropyl cellulose in purified water. The spherical granules were dried in vacuo at 40° C. for 16-20 hours and passed through a sieve (600 μm, 1180 μm) to give base granules. The base granules were placed in a roll flow type coating machine and coated with a suspension of (11) methacrylic acid copolymer LD-(15) polysorbate 80 in purified water. The coated granules were passed through a sieve (710 μm, 1400 μm) and dried in vacuo at 40° C. for 16-20 hours to give enteric-coated granules. To the enteric coated granules were added (16) talc and (17) light silicic anhydride and mixed granules were produced in a tumbler mixer. The mixed granules were filled in (18) HPMC Capsule No. 2 by a capsule filling machine to give 15 mg capsules.

TABLE 5

ingredients		Charge amount-2
[base granule]		
(1)	compound A	450.0 g
(2)	sucrose · starch spherical granule (Nonpareil)	1650.0
(3)	magnesium carbonate	336.0
(4)	purified sucrose	597.0
(5)	cornstarch	300.0
(6)	low-substituted hydroxypropyl cellulose	354.0
(7)	purified sucrose	300.0
(8)	cornstarch	246.0
(9)	low-substituted hydroxypropyl cellulose	246.0
(10)	hydroxypropyl cellulose	21.0
	purified water	1029.0
	subtotal	4500.0 g
[enteric coated granule]		

TABLE 5-continued

ingredients		Charge amount-2
granule]		
	base granule	3600.0 g
(11)	methacrylic acid copolymer LD (Eudragit L30D-55[TR])	535.2
(12)	talc	160.8
(13)	macrogol 6000	52.8
(14)	titanium oxide	52.8
(15)	polysorbate 80	24.0
	purified water	2054.4
	subtotal	4425.6 g
[mixed granule]		
	enteric coated granule	3688.0 g
(16)	talc	6.0
(17)	light silicic anhydride	2.0
	subtotal	3696.0 g
[capsule]		
	mixed granule	924.0 g
(18)	HPMC Capsule No. 2	5000.0 cap.

TABLE 6

ingredients		Formulation per capsule 15 mg capsule
[base granule]		
(1)	compound A	15.0 mg
(2)	sucrose · starch spherical granule (Nonpareil)	55.0
(3)	magnesium carbonate	11.2
(4)	purified sucrose	19.9
(5)	cornstarch	10.0
(6)	low-substituted hydroxypropyl cellulose	11.8
(7)	purified sucrose	10.0
(8)	cornstarch	8.2
(9)	low-substituted hydroxypropyl cellulose	8.2
(10)	hydroxypropyl cellulose	0.7
	subtotal	150.0 mg
[enteric coated granule]		
	base granule	150.0 mg
(11)	methacrylic acid copolymer LD (Eudragit L30D-55[TR])	22.3
(12)	talc	6.7
(13)	macrogol 6000	2.2
(14)	titanium oxide	2.2
(15)	polysorbate 80	1.0
	subtotal	184.4 mg
[mixed granule]		
	enteric coated granule	184.4 mg
(16)	talc	0.3
(17)	light silicic anhydride	0.1
	subtotal	184.8 mg

TABLE 6-continued

ingredients		Formulation per capsule 15 mg capsule
[capsule]		
	mixed granule	184.8 mg
(18)	HPMC Capsule No. 2	62.0
	subtotal	246.8 mg

INDUSTRIAL APPLICABILITY

According to the production method of the present invention, a crystal of (R)-lansoprazole or (S)-lansoprazole superior in preservation stability can be produced efficiently on an industrial large scale.

This application is based on patent application No. 2000-367757 filed in Japan, the contents of which are hereby incorporated by reference.

The invention claimed is:

1. A method for producing a crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or (S)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole, which comprises crystallizing at a temperature of about 0° C. to about 35° C. from a C_{1-4} alkyl acetate solution containing (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or (S)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole at a concentration of about 0.1 g/mL to about 0.5 g/mL.

2. A method for producing a crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or (S)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole, which comprises crystallizing at a temperature of about 0° C. to about 35° C. from a C_{1-4} alkyl acetate solution containing (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or (S)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole at a concentration of about 0.1 g/mL to about 0.5 g/mL, and adding dropwise to the C_{1-4} alkyl acetate solution, at the same temperature, C_{5-8} hydrocarbon in an amount of not more than 7 times the amount of the C_{1-4} alkyl acetate solution.

3. The method of claim **1**, wherein the crystallization temperature is about 20° C. to about 30° C.

4. The method of claim **1**, wherein the crystallization is conducted for about 30 minutes to about 4 hours.

5. The method of claim **1**, wherein the C_{1-4} alkyl acetate is ethyl acetate or propyl acetate.

6. The method of claim **2**, wherein the C_{5-8} hydrocarbon is added in an amount of not more than 5 times the amount of the C_{1-4} alkyl acetate solution.

7. The method of claim **2**, wherein the C_{5-8} hydrocarbon is heptane or hexane.

8. The method of claim **2**, wherein the C_{5-8} hydrocarbon is added dropwise over about 15 minutes to about 4 hours.

9. A crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or (S)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole having a melting start temperature of not lower than about 131° C.

10. The crystal of claim **9**, wherein the melting start temperature is about 135° C.

11. The method of claim **2**, wherein the crystallization temperature is about 20° C. to about 30° C.

12. The method of claim **2**, wherein the crystallization is conducted for about 30 minutes to about 4 hours.

13. The method of claim **2**, wherein the C_{1-4} alkyl acetate is ethyl acetate or acetate.

* * * * *

Exhibit E

US007790755B2

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

(10) **Patent No.: US 7,790,755 B2**
(45) **Date of Patent: Sep. 7, 2010**

(54) **CONTROLLED RELEASE PREPARATION**

(75) Inventors: **Yohko Akiyama**, Osaka (JP); **Takashi Kurasawa**, Osaka (JP); **Hiroto Bando**, Osaka (JP); **Naoki Nagahara**, Osaka (JP)

(73) Assignee: **Takeda Pharmaceutical Company Limited**, Osaka (JP)

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(21) Appl. No.: **10/531,069**

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(86) PCT No.: **PCT/JP03/13155**

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A61K 31/4439 (2006.01)
C07D 401/02 (2006.01)

(52) **U.S. Cl.** **514/339**; 546/273.7

(58) **Field of Classification Search** 546/273.7; 514/339

See application file for complete search history.

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(57) **ABSTRACT**

A controlled release preparation wherein the release of active ingredient is controlled, which releases an active ingredient for an extended period of time by staying or slowly migrating in the gastrointestinal tract, is provided by means such as capsulating a tablet, granule or fine granule wherein the release of active ingredient is controlled and a gel-forming polymer. Said tablet, granule or fine granule has a release-controlled coating-layer formed on a core particle containing an active ingredient.

9 Claims, No Drawings

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CONTROLLED RELEASE PREPARATION

This application is the National Phase filing of International Patent Application No. PCT/JP03/013155, filed Oct. 15, 2003.

TECHNICAL FIELD

The present invention relates to a controlled release preparation, in particular a capsule comprising a tablet, granule or fine granule wherein the release of active ingredient is controlled and a gel-forming polymer which delays the migration speed in the gastrointestinal tract.

BACKGROUND ART

An oral formulation is a dosage form which is used most frequently among pharmaceutical agents. Lots of preparations for oral administration wherein the drug efficacy thereof is sustained with the administration of once or twice a day have been developed from the viewpoint of improving QOL in these years. The compound having a kinetics of sustained drug efficacy with the administration of once or twice a day is tried to synthesize in the synthetic stage of compound itself, while quite a lot of attempts to modify the kinetics are made with designing controlled release preparation by contriving formulation. As the dosage form of oral controlled release preparation, various release-controlled systems such as a release control by a release-controlled coating-layer or a diffusion control of compound by a matrix, a release control of compound by erosion of matrix (base material), a pH-dependent release control of compound and a time-dependent release control wherein the compound is released after a certain lag time, are developed and applied. It is considered that a further extension of sustainability becomes possible by combining the above-mentioned release-controlled system with a control of migration speed in the gastrointestinal tract.

The preparation containing a medicament having an acid-labile property as an active ingredient such as a benzimidazole compound having a proton pump inhibitor (hereinafter sometimes referred to as PPI) action needs to be enteric-coated. That is, a composition containing a benzimidazole compound having a proton pump inhibitor action is needed to disintegrate rapidly in the small intestine, so the composition is preferred to formulate into a granule or fine granule which has a broader surface area than a tablet and is easy to disintegrate or dissolve rapidly. In the case of a tablet, it is desirable to reduce the size of tablet (for example, see JP-A 62-277322).

After administered orally, the tablet, granule or fine granule migrates through gastrointestinal tract with releasing an active ingredient to stomach, duodenum, jejunum, ileum and colon sequentially. And in the meantime, the active ingredient is absorbed at the each absorption site. A controlled release preparation is designed to control the absorption by delaying the release of active ingredient in some way. It is considered that a further extension of sustainability becomes possible by combining a release-controlled system with a function to control the migration speed in gastrointestinal tract such as adherability, floatability etc. These prior arts are disclosed in WO 01/89483, JP-A 2001-526213, U.S. Pat. Nos. 6,274,173, 6,093,734, 4,045,563, 4,686,230, 4,873,337, 4,965,269, 5,021,433 and the like.

DISCLOSURE OF INVENTION

(Object of the Invention)

An object of the present invention is to provide a controlled release preparation wherein the release of active ingredient of drug is controlled, which releases an active ingredient for an extended period of time with staying or slowly migrating in the gastrointestinal tract.

SUMMARY OF THE INVENTION

That is, the present invention provides:

(1) A capsule comprising a tablet, granule or fine granule and a gel-forming polymer wherein a release of an active ingredient is controlled;

(2) The capsule according to the above-mentioned (1), wherein the release of active ingredient is controlled by a release-controlled coating-layer formed on a core particle containing an active ingredient;

(3) The capsule according to the above-mentioned (2), wherein the release-controlled coating-layer contains a pH-dependently soluble polymer;

(4) The capsule according to the above-mentioned (2), wherein the release-controlled coating-layer is a diffusion-controlled layer;

(5) The capsule according to the above-mentioned (1), wherein the release of active ingredient is controlled by dispersing an active ingredient into a release-controlled matrix composing tablet, granule or fine granule;

(6) The capsule according to the above-mentioned (3) or (4), wherein the tablet, granule or fine granule in which the release of active ingredient is controlled has a disintegrant layer containing disintegrant formed on the core particle containing an active ingredient and a release-controlled coating-layer formed on said disintegrant layer, and the release of active ingredient is initiated after a certain lag time;

(7) The capsule according to any one of the above-mentioned (3) to (6), wherein the tablet, granule or fine granule in which the release of active ingredient is controlled is coated with a gel-forming polymer;

(8) The capsule according to the above-mentioned (7) which further contains a gel-forming polymer;

(9) The capsule according to any one of the above-mentioned (1) to (7), which comprises two kinds of tablet, granule or fine granule having different release properties of active ingredient;

(10) The capsule according to the above-mentioned (9), which comprises a tablet, granule or fine granule having an enteric coat that releases an active ingredient at the pH of about 5.5 and a tablet, granule or fine granule having a release-controlled coating-layer that releases an active ingredient at the pH of about 6.0 or above;

(11) The capsule according to the above-mentioned (1), (7) or (8), wherein the gel-forming polymer is a polymer whose viscosity of 5% aqueous solution is about 3,000 mPa·s or more at 25° C.;

(12) The capsule according to the above-mentioned (1), (7) or (8), wherein the gel-forming polymer is a polymer having molecular weight of 400,000 to 10,000,000;

(13) The capsule according to any one of the above-mentioned (2) to (4) or (6), wherein the release-controlled coating-layer is a layer containing one or more kinds of polymeric substances selected from the group consisting of hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, carboxymethylethyl cellulose, methyl methacrylate-methacrylic acid copolymer, methacrylic acid-ethyl acrylate

copolymer, ethyl acrylate-methyl methacrylate-trimethylammoniumethyl methacrylate chloride copolymer, methyl methacrylate-ethyl acrylate copolymer, methacrylic acid-methyl acrylate-methyl methacrylate copolymer, hydroxypropyl cellulose acetate succinate and polyvinyl acetate phthalate;

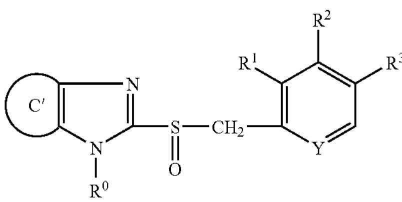
(14) The capsule according to the above-mentioned (13), wherein the release-controlled coating-layer is comprised of 2 or more kinds of layers;

(15) The capsule according to the above-mentioned (1), wherein the release-controlled granule or fine granule has a particle size of about 100-1,500 μm;

(16) The capsule according to the above-mentioned (1), wherein the active ingredient is a proton pump inhibitor (PPI);

(17) The capsule according to (16), wherein the PPI is an imidazole compound represented by the formula (I'):

(I')



wherein ring C' is an optionally substituted benzene ring or an optionally substituted aromatic monocyclic heterocyclic ring, R^0 is a hydrogen atom, an optionally substituted aralkyl group, acyl group or acyloxy group, R^1, R^2 and R^3 are the same or different and are a hydrogen atom, an optionally substituted alkyl group, an optionally substituted alkoxy group or an optionally substituted amino group, and Y represents a nitrogen atom or CH; or a salt thereof or an optically active isomer thereof;

(18) The capsule according to the above-mentioned (17), wherein the imidazole compound is lansoprazole;

(19) The capsule according to the above-mentioned (17), wherein PPI is an optically active R-isomer of lansoprazole;

(20) The capsule according to any one of the above-mentioned (1), (7) or (8), wherein the gel-forming polymer is one or more kinds of substances selected from the group consisting of polyethylene oxide (PEO, molecular weight: 400,000-10,000,000), hydroxypropylmethyl cellulose (HPMC), carboxymethyl cellulose (CMC-Na), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose and carboxyvinyl polymer;

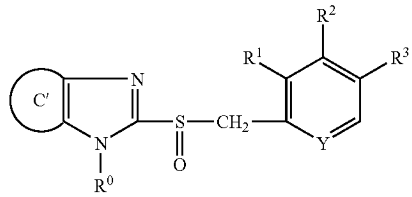
(21) The capsule according to any one of the above-mentioned (1), (7) or (8), wherein the gel-forming polymer is polyethylene oxide (molecular weight: 400,000-10,000,000);

(22) The capsule according to the above-mentioned (1) or (8), wherein the gel-forming polymer is added as a powder, fine granule or granule;

(23) The capsule according to the above-mentioned (3), wherein the pH-dependently soluble polymer is methyl methacrylate-methacrylic acid copolymer;

(24) A tablet, granule or fine granule wherein the release of active ingredient is controlled, said tablet, granule or fine granule comprising a core particle containing an imidazole compound represented by the formula (I'):

(I')



wherein ring C' is an optionally substituted benzene ring or an optionally substituted aromatic monocyclic heterocyclic ring, R^0 is a hydrogen atom, an optionally substituted aralkyl group, acyl group or acyloxy group, R^1, R^2 and R^3 are the same or different and are a hydrogen atom, an optionally substituted alkyl group, an optionally substituted alkoxy group or an optionally substituted amino group, and Y represents a nitrogen atom or CH; or a salt thereof or an optically active isomer thereof as an active ingredient, and

a pH-dependently soluble release-controlled coating-layer which comprises one kind of polymeric substance or a mixture of two or more kinds of polymeric substances having different release properties selected from the group consisting of hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, carboxymethylethyl cellulose, methyl methacrylate-methacrylic acid copolymer, methacrylic acid-ethyl acrylate copolymer, methacrylic acid-methyl acrylate-methyl methacrylate copolymer, hydroxypropyl cellulose acetate succinate, polyvinyl acetate phthalate and shellac, and said polymeric substance is soluble in the pH range of 6.0 to 7.5;

(25) The tablet, granule or fine granule according to the above-mentioned (24), wherein the pH-dependently soluble release-controlled coating-layer is formed on an intermediate layer which is formed on a core particle;

(26) The capsule comprising the tablet, granule or fine granule according to the above-mentioned (24);

(27) The capsule comprising the tablet, granule or fine granule according to the above-mentioned (24) and an enteric-coated tablet, granule or fine granule containing a compound represented by the formula (II);

(28) The tablet, granule or fine granule according to the above-mentioned (24), wherein the active ingredient is lansoprazole;

(29) The tablet, granule or fine granule according to the above-mentioned (24), wherein the active ingredient is an optically active R-isomer of lansoprazole;

(30) The tablet, granule or fine granule according to the above-mentioned (24), wherein the active ingredient is an optically active S-isomer of lansoprazole;

(31) The tablet, granule or fine granule according to the above-mentioned (24), wherein the active ingredient is a derivative of lansoprazole;

(32) The tablet, granule or fine granule according to the above-mentioned (24), wherein the active ingredient is a derivative of optically active R-isomer of lansoprazole;

(33) The tablet, granule or fine granule according to any one of the above-mentioned (24), (25) or (28) to (32), comprising having an enteric coat on the core particle containing an active ingredient, a disintegrant layer containing disintegrant on said enteric coat and a release-controlled coating-layer on said disintegrant layer;

(34) The tablet, granule or fine granule according to any one of the above-mentioned (28) to (33), which is coated with a gel-forming polymer;

(35) An extended release capsule comprising the tablet, granule or fine granule according to any one of the above-mentioned (28) to (32) and a gel-forming polymer;

(36) A tablet, granule or fine granule according to the above-mentioned (24) wherein the release of active ingredient is controlled by two or more kinds of release-controlled coating-layers, and the outermost release-controlled coating-layer is soluble at higher pH than the inner release-controlled coating-layer;

(37) The tablet, granule or fine granule according to the above-mentioned (36), wherein the inner release-controlled coating-layer is soluble in the pH range of 6.0-7.0 and the outermost release-controlled coating-layer is soluble at the pH of 7.0 or above;

(38) The tablet, granule or fine granule according to the above-mentioned (36), wherein the inner release-controlled coating-layer is soluble in the pH range of 6.5-7.0 and the outermost release-controlled coating-layer is soluble at the pH of 7.0 or above;

(39) The tablet, granule or fine granule according to the above-mentioned (36), wherein the thickness of the outermost release-controlled coating-layer is 100 µm or less;

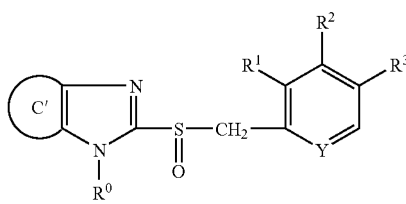
(40) The granule or fine granule according to the above-mentioned (36), wherein the release-controlled granule or fine granule has a particle size of about 100-1,500 µm;

(41) A capsule comprising

(i) a tablet, granule or fine granule in which the release of active ingredient is controlled; said tablet, granule or fine granule comprises

a core particle containing an imidazole compound represented by the formula (I'):

(I')



wherein ring C' is an optionally substituted benzene ring or an optionally substituted aromatic monocyclic heterocyclic ring, R^0 is a hydrogen atom, an optionally substituted aralkyl group, acyl group or acyloxy group, R^1, R^2 and R^3 are the same or different and are a hydrogen atom, an optionally substituted alkyl group, an optionally substituted alkoxy group or an optionally substituted amino group, and Y represents a nitrogen atom or CH; or a salt thereof or an optically active isomer thereof as an active ingredient, and

a pH-dependently soluble release-controlled coating-layer which comprises one kind of polymeric substance or a mixture of two or more kinds of polymeric substances having different release properties selected from the group consisting of hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, carboxymethylethyl cellulose, methyl methacrylate-methacrylic acid copolymer, methacrylic acid-ethyl acrylate copolymer, methacrylic acid-methyl acrylate-methyl methacrylate copolymer, hydroxypropyl cellulose acetate succinate, polyvinyl acetate phthalate and shellac; said polymeric substance is soluble in the pH range of 6.0 to 7.5, and

(ii) a tablet, granule or fine granule comprising a core particle containing an active ingredient and enteric coat which is dissolved, thereby an active ingredient being released in the pH range of no less than 5.0, nor more than 6.0;

(42) The capsule according to the above-mentioned (41), wherein the pH-dependently soluble release-controlled coating-layer is formed on an intermediate layer which is formed on the core particle containing an active ingredient;

(43) The capsule according to the above-mentioned (41), wherein the active ingredient is lansoprazole;

(44) The capsule according to the above-mentioned (41), wherein the active ingredient is an optically active R-isomer of lansoprazole;

(45) The capsule according to the above-mentioned (41), wherein the active ingredient is an optically active S-isomer of lansoprazole;

(46) The capsule according to the above-mentioned (41), wherein the core particle containing an active ingredient contains a stabilizer of basic inorganic salt;

(47) The capsule according to the above-mentioned (41), wherein the pH-dependently soluble release-controlled coating-layer of the tablet, granule or fine granule in which the release of an active ingredient is controlled is a layer soluble in the pH range of no less than 6.5, nor more than 7.0;

(48) The capsule according to the above-mentioned (47), wherein the pH-dependently soluble release-controlled coating-layer contains a mixture of two or more kinds of methyl methacrylate-methacrylic acid copolymers having different release properties; and

(49) The capsule according to the above-mentioned (41), which further contains a gel-forming polymer.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a pharmaceutical composition containing a tablet, granule or fine granule, wherein the release of active ingredients is controlled, or a pharmaceutical composition containing these tablet, granule or fine granule and a gel-forming polymer, which delays digestive tract migration speed. The pharmaceutical composition of the present invention may be these tablet, granule or fine granule itself, or a form of a mixture of a tablet, granule or fine granule and a gel-forming polymer, or a capsule form in which the pharmaceutical composition is filled, but the capsule form is preferred in particular. It has been cleared that the persistence of blood levels after oral administration is remarkably prolonged by these combinations.

The release control of active ingredient in "a tablet, granule or fine granule wherein the release of active ingredient is controlled" of the present invention is performed by coating the active ingredient in a tablet, granule or fine granule with a layer controlling the release of active ingredient, or by dispersing the active ingredient in release-controlled matrices. Further, the "tablet, granule or fine granule wherein the release of active ingredient is controlled" of the present invention include also a tablet, granule or fine granule which is coated with a usual enteric coat which is dissolved at a pH of about 5.5, and tablets containing these granules or fine granules.

On the other hand, when the "release-controlled coating-layer" is mentioned in the present specification, it indicates a coating-layer having a function of further delaying or extending the release of active ingredient, such as a pH-dependently soluble layer which is dissolved at a higher pH region than a usual enteric coating which is dissolved at a pH of about 5.5, and a diffusion-controlled layer whose layer itself is not dissolved and which releases an active ingredient through pores which are formed in the layer. It does not include a usual enteric coat and layer which is dissolved at a pH of about 5.5, rapidly dissolved in the intestinal juice and release an active ingredient. Further, the pH mentioned here means a pH of the Mcilvaine solution or Clark-Lubs solution. Hereinafter, the pH of a pH-dependently soluble layer means the pH of these solutions.

The coating-layer of the "release-controlled coating-layer" inlcudes coating layers in a film form and those having larger thickness. Also, the coating-layer includes not only a coating-layer which entirely coats the inner core or layer but also the coating layers in which a part of the inner core or layer is not covered but most of the inner core or layer is coated (coating-layer which covers at least about 80% or more of the surface of the inner core or layer, and preferably covers the surface entirely).

The absorption from the digestive tract of the active ingredient from the pharmaceutical composition of the present invention is controlled by two kind of systems utilizing (1) a release control of active ingredient by a controlled release tablet, granule or fine granule and (2) retentive prolongation in the digestive tract of a tablet, granule or fine granule by a gel-forming polymer, or their combinations. Among the pharmaceutical composition of the present invention, the composition containing a gel-forming polymer forms adhesive gels by rapidly absorbing water by the gel-forming polymer in the digestive tract when orally administrated, and the tablet, granule or fine granule is retained on the surface of gels or in the gels to be gradually migrated through the digestive tract. The release of active ingredient is controlled in the meanwhile, the active ingredient is released continuously or in a pulsatile manner from the tablet, granule or fine granule by a controlled system, and as a result, the incidences of prolonged absorption and drug efficacy are attained.

The above-mentioned system enabling the persistence of therapeutic effective levels by controlling the release over a long time has advantages of therapeutic effectiveness at a low dose and reduction of side effects caused by initial rise of blood level and the like, as well as the reduction of administration times.

The gel-forming polymer may be a polymer which rapidly forms highly viscous gels by contacting with water and prolongs the retention time in the digestive tract. Such gel-forming polymer is preferably a polymer having a viscosity of about 3000 mPa·s or more for 5% aqueous solution at 25° C. Further, the gel-forming polymer is preferably a polymer usually having a molecular weight of about 400000 to 10000000 in general. As the gel-forming polymer, powder, granular or fine granular polymer is preferable for producing formulations. The gel-forming polymer includes a polyethylene oxide (PEO, for example, Polyox WSR 303 (molecular weight: 7000000), Polyox WSR Coagulant (molecular weight: 5000000), Polyox WSR 301 (molecular weight: 4000000), Polyox WSR N-60K (molecular weight: 2000000), and Polyox WSR 205 (molecular weight: 600000); manufactured by Dow Chemical Co., Ltd.), hydroxypropyl methylcellulose (HPMC, Metlose 90SH10000, Metlose 90SH50000, and Metlose 90SH30000; manufactured by Shin-Etsu Chemical Co., Ltd.), carboxymethylcellulose (CMC-Na, Sanlose F-1000MC), hydroxypropyl cellulose (HPC, for example, HPC-H, manufactured by Nippon Soda Co., Ltd.), hydroxyethyl cellulose (HEC), carboxyvinyl polymer (HIVISWAKO (R) 103, 104 and 105 manufactured by Wako Pure Chemical Industries Ltd.; CARBOPOL 943 manufactured by Goodrich Co., Ltd.), chitosan, sodium alginate, pectin and the like. These may be used alone or as a mixture of at least 2 or more of powders by mixing at an appropriate proportion. In particular, PEO, HPMC, HPC, CMC-Na, carboxyvinyl polymer and the like are preferably used as a gel-forming polymer.

One preferable form of a tablet, granule or fine granule wherein the release of active ingredient is controlled includes a tablet, granule or fine granule wherein a core particle containing at least one active ingredient is coated with a release-controlled coating-layer and a tablet containing these granules or fine granules. In order to prepare such core-possessing tablet, granule or fine granule, as a core particle can be used the tablet, granule or fine granule wherein an active ingredient is coated on a core which is an inactive carrier such as NONPAREIL (NONPAREIL-101 (particle diameter: 850-710, 710-500, and 500-355), NONPAREIL-103 (particle diameter: 850-710, 710-500, and 500-355), NONPAREIL-105 (particle diameter: 710-500, 500-355 and 300-180); manufactured by Freund Industrial Co., Ltd.) and Celphere (CP-507 (particle diameter: 500-710), and CP-305 (particle diameter: 300-500); manufactured by Asahi Kasei Corporation); or the tablet prepared by using these granules or fine granules; or the particle obtained by granulation using an active ingredient and an excipient usually used for formulation. For example, they can be produced by the method disclosed in JP-A 63-301816. For example, when a core particle is prepared by coating an active ingredient on a core of an inactive carrier, core particles containing an active ingredient can be produced by wet granulation, using, for example, a centrifugal fluid-bed granulator (CF-mini, CF-360, manufactured by Freund Industrial Co., Ltd.) or a centrifugal fluidized coating granulator (POWREX MP-10), or the like. Further, coating may be carried out by dusting an active ingredient while adding a solution containing a binder and the like on the core of an inactive carrier with spray and the like. The production apparatuses are not limited and for example, it is preferable in the latter coating to produce them using a centrifugal fluid-bed granulator and the like. An active ingredient may be coated at two steps by carrying out the coating using the above-mentioned two apparatuses in combination. When an inactive carrier core is not used, a core particle can be produced by granulating excipient such as lactose, white sugar, mannitol, corn starch and crystalline cellulose and an active ingredient, using binders such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, methyl cellulose, a polyvinyl alcohol, Macrogol, Pullronic F68, gum arabic, gelatin and starch, if necessary, adding disintegrants such as sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, sodium cross carboxymethyl cellulose (Ac-Di-Sol, manufactured by FMC International Co., Ltd.), polyvinyl pyrrolidone and low substituted hydroxypropyl cellulose, with a stirring granulator, a wet extruding granulator, a fluidized bed granulator and the like.

Particles having desired sizes can be obtained by sieving the granules or fine granules obtained. The core particle may be prepared by dry granulation with a roller compactor and the like. Particles having a particle size of 50 μm to 5 mm, preferably 100 μm to 3 mm and more preferably 100 μm to 2 mm are used.

The active ingredient-containing core particle thus obtained may be further coated to provide an intermediate coating layer, and the particle may be used as a core particle. It is preferable from the viewpoint of improving the stability of drugs that the intermediate coating layer is provided to intercept the direct contact of active ingredient-containing core particle with the release-controlled coating-layer when the active ingredient is an unstable drug against an acid, such as PPI and the like, etc. The intermediate coating layer may be formed by a plural number of layers.

The coating materials for the intermediate coating layer include those obtained by appropriately compounding polymeric materials such as low substituted hydroxypropyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose (for example, TC-5 and the like), polyvinylpyrrolidone, polyvinyl alcohol, methylcellulose and hydroxyethyl methylcellulose with saccharides such as sucrose [purified sucrose (pulverized (powdered sugar), not pulverized) and the like], starch saccharide such as corn starch, lactose, sugar alcohol (D-mannitol, erythritol and the like). Excipients (for example, masking agents (titanium oxide and the like) and antistatic agents (titanium oxide, talc and the like) may be suitably added to the intermediate coating layer for the preparations mentioned below, if necessary.

The coating amount of the intermediate coating layer is usually about 0.02 part by weight to about 1.5 parts by weight based on 1 part by weight of granules containing an active ingredient, and preferably about 0.05 part by weight to about 1 part by weight. The coating can be carried out by conventional methods. For example, preferably, the components of the intermediate coating layer are diluted with purified water and sprayed to coat in liquid form. Then, it is preferable to carry out the coating while spraying a binder such as hydroxypropyl cellulose.

As the controlled release tablet, granule or fine granule contained in the pharmaceutical composition of the present invention, it is preferable to coat the above-mentioned core particle with a coating material which is pH-dependently dissolved/eluted to control the release, and to prepare the tablet, granule or fine granule having a release-controlled coating-layer, or the tablet containing these controlled release granules or fine granules. Herein, the "pH-dependently" means that the coating material is dissolved/eluted under the circumstances of more than a certain pH value to release an active ingredient. A usual enteric coat is eluted at a pH of about 5.5 to initiate the release of drug, while the coating material of the present invention is preferably a substance which is dissolved at a higher pH (preferably a pH of 6.0 or above and 7.5 or below, and more preferably a pH of 6.5 or above and below 7.2) and controls more favorably the release of drug in the stomach.

As a coating material for controlling pH-dependently the release of medical active ingredient, polymers such as hydroxypropyl methylcellulose phthalate (HP-55, HP-50 manufactured by Shin-Etsu Chemical Co., Ltd.), cellulose acetate phthalate, carboxymethyl ethylcellulose (CMEC manufactured by Freund Industrial Co., Ltd.), methyl methacrylate-methacrylic acid copolymer (Eudragit L100 (methacrylic acid copolymer L) or Eudragit S100 (methacrylic acid copolymer S); manufactured by Rohm Co.), methacrylic acid-ethyl acrylate copolymer (Eudragit L100-55 (dried methacrylic acid copolymer LD) or Eudragit L30D-55 (methacrylic acid copolymer LD); manufactured by Rohm Co.), methacrylic acid-methyl acrylate-methyl methacrylate copolymer (Eudragit FS30D manufactured by Rohm Co.), hydroxypropyl cellulose acetate succinate (HPMCAS manufactured by Shin-Etsu Chemical Co., Ltd.), polyvinyl acetate phthalate and shellac are used. The tablet, granule or fine granule may be those having two or more kinds of release-controlled coating-layers which have different release properties of active ingredient. The polymer as the above-mentioned coating material may be used alone or at least 2 or more kinds of the polymers may be used to coat in combination, or at least 2 or more kinds of the polymers may be coated sequentially to prepare multi-layers. It is desirable that the coating material is used alone or, if necessary, in combination so that the polymer is dissolved preferably at a pH of 6.0 or above, more preferably at a pH of 6.5 or above, and further more preferably at a pH of 6.75 or above. Further, more desirably, a polymer soluble at a pH of 6.0 or above and a polymer soluble at a pH of 7.0 or above are used in combination, and furthermore desirably, a polymer soluble at a pH of 6.0 or above and a polymer soluble at a pH of 7.0 or above are used in combination at a ratio of 1:0.5 to 1:5.

Further, plasticizers such as a polyethylene glycol, dibutyl sebacate, diethyl phthalate, triacetin and triethyl citrate, stabilizers and the like may be used for coating, if necessary. The amount of coating material is 5% to 200% based on the core particle, preferably 20% to 100% and more preferably 30% to 60%. The rate of elution of active ingredient from the active ingredient release-controlled tablet, granule or fine granule thus obtained is desirably 10% or less for 5 hours in a solution of pH 6.0, and 5% or less for one hour and 60% or more for 8 hours in a solution of pH 6.8.

The controlled release tablet, granule or fine granule (hereinafter, sometimes referred to simply as a controlled release granule) may be a tablet, granule or fine granule wherein a material which becomes viscous by contact with water, such as polyethylene oxide (PEO, for example, Polyox WSR 303 (molecular weight: 7000000), Polyox WSR Coagulant (molecular weight: 5000000), Polyox WSR 301 (molecular weight: 4000000), Polyox WSR N-60K (molecular weight: 2000000), and Polyox WSR 205 (molecular weight: 600000); manufactured by Dow Chemical Co., Ltd.), hydroxypropyl methylcellulose (HPMC, Metlose 90SH10000, Metlose 90SH50000, Metlose 90SH30000; manufactured by Shin-Etsu Chemical Co., Ltd.), carboxymethyl cellulose (CMC-Na, Sanlose F-1000MC), hydroxypropyl cellulose (HPC, for example, HPC-H manufactured by Nippon Soda Co., Ltd.), hydroxyethyl cellulose (HEC), carboxyvinyl polymer (HIVISWAKO (R) 103, 104, 105: manufactured by Wako Pure Chemical Industries Ltd.; CARBOPOL 943 manufactured by Goodrich Co., Ltd.), chitosan, sodium alginate and pectin, is coated on the active ingredient release-controlled tablet, granule or fine granule thus obtained.

The controlled release granule may be a form in which the core particle containing an active ingredient is coated with a diffusion-controlled layer having an action of controlling the release of active ingredient by diffusion. The materials for these diffusion-controlled layer include ethyl acrylate-methyl methacrylate-trimethylammoniumethyl methacrylate chloride copolymer (Eudragit RS (aminoalkyl methacrylate copolymer RS) or Eudragit RL (aminoalkyl methacrylate copolymer RL); manufactured by Rohm Co.), methyl methacrylate-ethyl acrylate copolymer (Eudragit NE30D manufactured by Rohm Co.), ethyl cellulose and the like. Further, these materials for layer may be mixed at an appropriate ratio, and can be used by mixing with hydrophilic pore forming substances such as HPMC, HPC, carboxyvinyl polymer, polyethylene glycol 6000, lactose, mannitol and organic acid at a fixed ratio.

Further, in order to prepare the tablet, granule or fine granule wherein the release of active ingredient is controlled to initiate after a fixed lag time, a disintegrant layer is provided between the core particle containing an active ingredient and the release-controlled coating-layer by coating a swelling substance such as a disintegrant previously before coating the above-mentioned diffusion-controlled layer. For example, preferably, a swelling substance such as cross carmelose sodium (Ac-Di-Sol, manufactured by FMC International Co.), carmelose calcium (ECG 505, manufactured by Gotoku Chemicals Co.), CROSSPOVIDON (ISP Inc.) and low substituted hydroxypropyl cellulose (L-HPC manufactured by Shin-Etsu Chemical Co., Ltd.) is primarily coated on a core particle, and then the resulting coated particle is secondarily coated with a diffusion-controlled layer which is prepared by mixing at a fixed ratio one or more kinds of polymers selected from ethyl acrylate-methyl methacrylate-trimethylammoniumethyl methacrylate chloride copolymer (Eudragit RS or Eudragit RL; manufactured by Rohm Co.), methyl methacrylate-ethyl acrylate copolymer (Eudragit NE30D manufactured by Rohm Co.), ethyl cellulose and the like; with hydrophilic pore forming substances such as HPMC, HPC, carboxyvinyl polymer, polyethylene glycol 6000, lactose, mannitol and an organic acid. The secondary coating material may be enteric polymers which release pH-dependently an active ingredient, such as hydroxypropyl methylcellulose phthalate (HP-55, HP-50; manufactured by Shin-Etsu Chemical Co., Ltd.), cellulose acetate phthalate, carboxymethyl ethylcellulose (CMEC; manufactured by Freund Industrial Co., Ltd.), methyl methacrylate-methacrylic acid copolymer (Eudragit L100 (methacrylic acid copolymer L) or Eudragit S100 (methacrylic acid copolymer S); manufactured by Rohm Co.), methacrylic acid-ethyl acrylate copolymer (Eudragit L100-55 (dried methacrylic acid copolymer LD) or Eudragit L30D-55 (methacrylic acid copolymer LD); manufactured by Rohm Co.), methacrylic acid-methyl acrylate-methyl methacrylate copolymer (Eudragit FS30D; manufactured by Rohm Co.), hydroxypropyl cellulose acetate succinate (HPMCAS; manufactured by Shin-Etsu Chemical Co., Ltd.), polyvinyl acetate and shellac. The amount of coating material is 1% to 200% based on the core particle, preferably 20% to 100% and more preferably 30% to 60%.

Plasticizers such as polyethylene glycol, dibutyl sebacate, diethyl phthalate, triacetin and triethyl citrate, stabilizers and the like may be used for coating, if necessary. The controlled release tablet, granule or fine granule may be a tablet, granule or fine granule wherein a material which becomes viscous by contact with water, such as polyethylene oxide (PEO, for example, Polyox WSR 303 (molecular weight: 7000000), Polyox WSR Coagulant (molecular weight: 5000000), Polyox WSR 301 (molecular weight: 4000000), Polyox WSR N-60K (molecular weight: 2000000), and Polyox WSR 205 (molecular weight: 600000); manufactured by Dow Chemical Co., Ltd.), hydroxypropyl methylcellulose (HPMC, Metlose 90SH10000, Metlose 90SH50000, Metlose 90SH30000; manufactured by Shin-Etsu Chemical Co., Ltd.), carboxymethyl cellulose (CMC-Na, Sanlose F-1000MC), hydroxypropyl cellulose (HPC, for example, HPC-H manufactured by Nippon Soda Co., Ltd.), hydroxyethyl cellulose (HEC), carboxyvinyl polymer (HIVISWAKO (R) 103, 104, 105: manufactured by Wako Pure Chemical Industries Ltd.; CARBOPOL 943 manufactured by Goodrich Co., Ltd.), chitosan, sodium alginate and pectin, is coated on the active ingredient release-controlled tablet, granule or fine granule thus obtained.

In the tablet, granule or fine granule having 2 or more kinds of release-controlled coating-layers having different release properties of active ingredient, a layer containing an active ingredient may be set up between said release-controlled coating-layers. A form of these multi-layer structure containing an active ingredient between release-controlled coating-layers includes a tablet, granule or fine granule which is prepared by coating an active ingredient on the tablet, granule or fine granule wherein the release of active ingredient is controlled by the release-controlled coating-layer of the present invention, followed by further coating with the release-controlled coating-layer of the present invention.

Another form of the tablet, granule or fine granule wherein the release of at least one of the active ingredients is controlled may be a tablet, granule or fine granule in which the active ingredients are dispersed in a release-controlled matrix. These controlled release tablet, granule or fine granule can be produced by homogeneously dispersing the active ingredients into hydrophobic carriers such as waxes such as hardened castor oil, hardened rape seed oil, stearic acid and stearyl alcohol, and polyglycerin fatty acid ester. The matrix is a composition in which the active ingredients are homogeneously dispersed in a carrier. If necessary, excipients such as lactose, mannitol, corn starch and crystalline cellulose which are usually used for preparation of a drug may be dispersed with the active ingredients. Further, powders of polyoxyethylene oxide, cross-linked acrylic acid polymer (HIVISWAKO (R) 103, 104 and 105, CARBOPOL), HPMC, HPC, chitosan and the like which form viscous gels by contact with water may be dispersed into the matrix together with the active ingredients and excipients.

As the preparation method, they can be prepared by methods such as spray dry, spray chilling and melt granulation.

The controlled release tablet, granule or fine granule may be a tablet, granule or fine granule wherein a material which becomes viscous by contact with water, such as polyethylene oxide (PEO, for example, Polyox WSR 303 (molecular weight: 7000000), Polyox WSR Coagulant (molecular weight: 5000000), Polyox WSR 301 (molecular weight: 4000000), Polyox WSR N-60K (molecular weight: 2000000), and Polyox WSR 205 (molecular weight: 600000); manufactured by Dow Chemical Co., Ltd.), hydroxypropyl methylcellulose (HPMC, Metlose 90SH10000, Metlose 90SH50000, Metlose 90SH30000; manufactured by Shin-Etsu Chemical Co., Ltd.), carboxymethyl cellulose (CMC-Na, Sanlose F-1000MC), hydroxypropyl cellulose (HPC, for example, HPC-H manufactured by Nippon Soda Co., Ltd.), hydroxyethyl cellulose (HEC), carboxyvinyl polymer (HIVISWAKO (R) 103, 104, 105: manufactured by Wako Pure Chemical Industries Ltd.; CARBOPOL 943 manufactured by Goodrich Co., Ltd.), chitosan, sodium alginate and pectin, is coated on the active ingredient release-controlled tablet, granule or fine granule thus obtained. These materials which become viscous by contact with water may be coexisted in one preparation such as a capsule and the like as well as using for coat.

The tablet, granule or fine granule of the present invention wherein the release of active ingredient is controlled may be a form having the above-mentioned various kinds of release-controlled coating-layers, release-controlled matrixes and the like in combination.

As the size of tablet, granule or fine granule wherein the release of active ingredient is controlled, particles having a particle size of 50 μm to 5 mm, preferably 100 μm to 3 mm and more preferably 100 μm to 2 mm are used. Granules or fine granules having a particle size of about 100 μm to 1500 μm are most preferred.

Further, additives such as excipients for providing preparations (for example, glucose, fructose, lactose, sucrose, D-mannitol, erythritol, multitol, trehalose, sorbitol, corn starch, potato starch, wheat starch, rice starch, crystalline cellulose, silicic acid anhydride, calcium metaphosphorate, sedimented calcium carbonate, calcium silicate, and the like), binders (for example, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinyl pyrrolidone, methyl cellulose, polyvinyl alcohol, carboxymethyl cellulose sodium, partial α starch, α starch, sodium alginate, pullulan, gum arabic powder, gelatin and the like), disintegrants (for example, low substituted hydroxypropyl cellulose, carmelose, carmelose calcium, carboxymethylstarch sodium, cross carmelose sodium, crosspovidon, hydroxypropylstarch and the like), flavoring agents (for example, citric acid, ascorbic acid, tartaric acid, malic acid, aspartame, acesulfam potassium, thaumatin, saccharin sodium, glycylrrhizin dipotassium, sodium glutamate, sodium 5'-inosinate, sodium 5'-guanylate and the like), surfactants (for example, polysolvate (polysolvate 80 and the like), polyoxyethylene-polyoxypropylene copolymer, sodium laurylsulfate and the like), perfumes (for example, lemon oil, orange oil, menthol, peppermint oil and the like), lubricants (for example, magnesium stearate, sucrose fatty acid eater, sodium stearylfumarate, stearic acid, talc, polyethylene glycol and the like), colorants (for example, titanium oxide, edible Yellow No.5, edible Blue No.2, iron (III) oxide, yellow iron (III) oxide, and the like), antioxidants (for example, sodium ascorbate, L-cysteine, sodium bisulfate, and the like), masking agents (for example, titanium oxide and the like), and antistatic agents (for example, talc, titanium oxide and the like) can be used.

The particle diameter of raw materials used here are not particularly limited, and particles having a diameter of about 500 μm or less are preferred from the viewpoint of productivity and dosing.

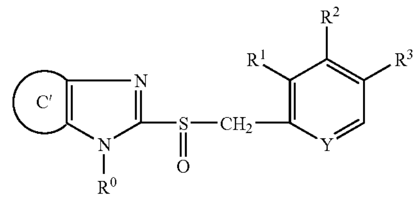
The tablet, granule or fine granule thus obtained may be administrated as it is by mixing with a digestive tract retentive gel-forming polymer, or can be formulated as a capsule by filling in capsules. The amount of the gel-forming polymer being retentive in the digestive tract is 0.1% to 100% relative to the controlled release tablet, granule or fine granule, preferably 2% to 50%, more preferably 10% to 40%, and further more preferably 10% to 35%.

The pharmaceutical composition of the present invention thus obtained is a composition having a extended activity of drug by a release-controlled system wherein therapeutic effect is revealed for at least 6 hours, preferably 8 hours, more preferably 12 hours and further preferably 16 hours.

The active ingredients are not particularly limited, and can be applied irrespective of the region of drug efficacy. Exemplified are anti-inflammatory drugs such as indomethacin and acetaminophen, analgesics such as morphine, cardiovascular agonists such as diazepam and diltiazepam, antihistamines such as chlorophenylamine maleate, antitumors such as fluorouracil and aclarubicin, narcotics such as midazolam, anti-hemostasis agents such as ephedrine, diuretics such as hydrochlorothiazide and furosemide, bronchodilators such as theophyline, antitussives such as codeine, antiarrythmic agents such as quinidine and dizoxin, antidiabetics such as tolbutamide, pioglitazone and troglitazone, vitamins such as ascorbic acid, anticonvulsants such as phenitoin, local anesthetics such as lidocaine, adrenocortical hormones such as hydrocortisone, drugs effective for central nerve such as eisai, hypolipidemic drugs such as pravastatin, antibiotics such as amoxicillin and cephalexin, digestive tract exitomotory agents such as mosapride and cisapride, H2 blockers such as famotidine, ranitidine and cimetidine which are the remedies of gastritis, symptomatic gastroesophageal reflux disease, and gastric and duodenal ulcers, and benzimidazole proton pump inhibitors (PPI) represented by lansoprazole and optically active isomers thereof (R-isomer and S-isomer, preferably R-isomer (hereinafter, occasionally referred to as Compound A)), omeprazole and optically active isomers thereof (S-isomer: S omeprazole), rabeprazole and optically active isomers thereof, pantoprazole and optically active isomers thereof and the like, and imidazopyridine PPI represented by tenatoprazole and the like.

According to the present invention, the preparations which contain, as an active ingredient, a PPI such as acid-labile imidazole compounds represented by the following general formula (I') such as lansoprazole and optically active isomers thereof, in particular, acid-labile benzimidazole compounds represented by the following formula (I), and relatively acid-stable imidazole compound derivatives (prodrug type PPI) represented by the following general formula (II) or (III) or salts thereof or optically active isomers thereof have an excellent sustainability of drug efficacy. As a result, dosing compliance is also improved and therapeutic effect is increased.

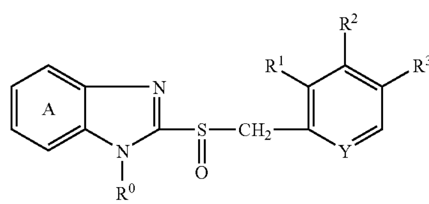
(I')



Wherein ring C' indicates a benzene ring optionally having a substituent group or an aromatic monocyclic heterocyclic ring optionally having a substituent group; R^0 indicates a hydrogen atom, an aralkyl group optionally having a substituent group, an acyl group or an acyloxy group; R^1, R^2 and R^3 are the same or different and indicate a hydrogen atom, an alkyl group optionally having a substituent group, an alkoxy group optionally having a substituent group or an amino group optionally having a substituent group, respectively; and Y indicates a nitrogen atom or CH.

Among the compounds represented by the above-mentioned formula (I'), the compound in which the ring C' is a benzene ring optionally having a substituent group is particularly represented by the following formula (I).

(I)

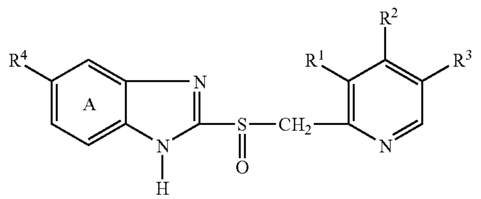


Namely, in the formula (I), ring A indicates a benzene ring optionally having a substituent group, and R^0, R^1, R^2R^3 and Y have the same meaning as in the above-mentioned formula (I').

In the above-mentioned formula (I), the preferable compound is a compound wherein ring A is a benzene ring which may have a substituent group selected from a halogen atom, an optionally halogenated C_{1-4} alkyl group, an optionally halogenated C_{1-4} alkoxy group and a 5- or 6-membered heterocyclic group; R^0 is a hydrogen atom, an optionally substituted aralkyl group, an acyl group or an acyloxy group; R^1 is a C_{1-6} alkyl group, a C_{1-6} alkoxy group, a C_{1-6} alkoxy-C_{1-6} alkoxy group or a di-C_{1-6} alkylamino group; R^2 is a hydrogen atom, a C_{1-6} alkoxy-C_{1-6} alkoxy group, or an optionally halogenated C_{1-6} alkoxy group; R^3 is a hydrogen atom or a C_{1-6} alkyl group, and Y is a nitrogen atom.

In particular, the preferable compound is a compound represented by the formula (Ia);

(Ia)



wherein R^1 indicates a C_{1-3} alkyl group or a C_{1-3} alkoxy group; R^2 indicates a C_{1-3} alkoxy group which may be halogenated or may be substituted with a C_{1-3} alkoxy group; R^3 indicates a hydrogen atom or a C_{1-3} alkyl group, and R^4 indicates a hydrogen atom, an optionally halogenated C_{1-3} alkoxy group or a pyrrolyl group (for example, 1-, 2- or 3-pyrrolyl group).

In the formula (Ia), the compound wherein R^1 is a C_{1-3} alkyl group; R^2 is an optionally halogenated C_{1-3} alkoxy group; R^3 is a hydrogen atom and R^4 is a hydrogen atom or an optionally halogenated C_{1-3} alkoxy group is particularly preferred.

In the compound represented by the above-mentioned formula (I) (hereinafter, referred to as Compound (I)), the "substituent group" of the "benzene ring optionally having a substituent group" represented by ring A includes, for example, a halogen atom, a nitro group, an alkyl group optionally having a substituent group, a hydroxy group, an alkoxy group optionally having a substituent group, an aryl group, an aryloxy group, a carboxy group, an acyl group, an acyloxy group, a 5- to 10-membered heterocyclic group and the like. The benzene ring may be substituted with about 1 to 3 of these substituent groups. When the number of substituents is 2 or more, each substituent groups may be the same or different. Among these substituent groups, a halogen atom, an alkyl group optionally having a substituent group, an alkoxy group optionally having a substituent group and the like are preferred.

The halogen atom includes fluorine, chlorine, bromine atom and the like. Among these, fluorine is preferred.

As the "alkyl group" of the "alkyl group optionally having a substituent group", for example, a C_{1-7} alkyl group (for example, a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, heptyl group and the like) is exemplified. As the "substituent group" of the "alkyl group optionally having a substituent group", for example, a halogen atom, a hydroxy group, a C_{1-6} alkoxy group (for example, methoxy, ethoxy, propoxy, butoxy and the like), a C_{1-6} alkoxy-carbonyl group (for example, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and the like), a carbamoyl group and the like can be exemplified, and the number of these substituent groups may be about 1 to 3. When the number of substituent group is 2 or more, each substituent groups may be the same or different.

The "alkoxy group" of the "alkoxy group optionally having a substituent group" includes, for example, a C_{1-6} alkoxy group (for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentoxy and the like) and the like. The "substituent group" of the "alkoxy group optionally having a substituent group" are exemplified by those for the above-mentioned "substituent group" of the "alkyl group optionally having a substituent group", and the number of the substituent group is the same.

The "aryl group" include, for example, a C_{6-14} aryl group (for example, a phenyl, 1-naphthyl, 2-naphthyl, biphenyl, 2-anthryl group and the like) and the like.

The "aryloxy group" includes, for example, a C_{6-14} aryloxy group (for example, a phenyloxy, 1-naphthyloxy, 2-naphthyloxy and the like) and the like.

The "acyl group" includes, for example, a formyl, alkylcarbonyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, alkylsulfinyl, alkylsulfonyl group and the like.

The "alkylcarbonyl group" includes, a C_{1-6} alkyl-carbonyl group (for example, acetyl, propionyl group and the like) and the like.

The "alkoxycarbonyl group" includes, for example, a C_{1-6} alkoxy-carbonyl group (for example, a methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl group and the like) and the like.

The "alkylcarbamoyl group" include, a N—C_{1-6} alkyl-carbamoyl group (for example, methylcarbamoyl, ethylcarbamoyl group and the like), a N,N-diC_{1-6} alkyl-carbamoyl group (for example, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl group and the like), and the like.

The "alkylsulfinyl group" includes, for example, a C_{1-7} alkylsulfinyl group (for example, a methylsulfinyl, ethylsulfinyl, propylsulfinyl, isopropylsulfinyl group and the like) and the like.

The "alkylsulfonyl group" includes, for example, a C_{1-7} alkylsulfonyl group (for example, a methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl group and the like) and the like.

The "acyloxy group" includes, for example, an alkylcarbonyloxy group, an alkoxycarbonyloxy group, a carbamoyloxy group, an alkylcarbamoyloxy group, an alkylsulfinyloxy group, an alkylsulfonyloxy group and the like.

The "alkylcarbonyloxy group" includes, a C_{1-6} alkyl-carbonyloxy group (for example, acetyloxy, propionyloxy group and the like) and the like.

The "alkoxycarbonyloxy group" includes, for example, a C_{1-6} alkoxy-carbonyloxy group (for example, methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, butoxycarbonyloxy group and the like) and the like.

The "alkylcarbamoyloxy group" includes, a C_{1-6} alkylcarbamoyloxy group (for example, methylcarbamoyloxy, ethylcarbamoyloxy group and the like) and the like.

The "alkylsulfinyloxy group" includes, for example, a C_{1-7} alkylsulfinyloxy group (for example, methylsulfinyloxy, ethylsulfinyloxy, propylsulfinyloxy, isopropylsulfinyloxy group and the like) and the like.

The "alkylsulfonyloxy group" includes, for example, a C_{1-7} alkylsulfonyloxy group (for example, methylsulfonyloxy, ethylsulfonyloxy, propylsulfonyloxy, isopropylsulfonyloxy group and the like) and the like.

The 5- to 10-membered heterocyclic group include, for example, a 5- to 10-membered (preferably 5- or 6-membered) heterocyclic group which contains one or more (for example, one to three) hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom in addition to a carbon atom. Specific example includes 2- or 3-thienyl group, 2-, 3- or 4-pyridyl group, 2- or 3-furyl group, 1-, 2- or 3-pyrrolyl group, 2-, 3-, 4-, 5- or 8-quinolyl group, 1-, 3-, 4- or 5-isoquinolyl group, 1-, 2- or 3-indolyl group; Among these, 5- or 6-membered heterocyclic groups such as 1-, 2- or 3-pyrrolyl groups are preferred.

Ring A is preferably a benzene ring which may have 1 or 2 substituent groups selected from a halogen atom, an optionally halogenated C_{1-4} alkyl group, an optionally halogenated C_{1-4} alkoxy group and 5- or 6-membered heterocyclic group.

In the above-mentioned formula (I'), the "aromatic monocyclic heterocyclic ring" of the "optionally substituted aromatic monocyclic heterocyclic ring" represented by ring C' includes, for example, 5- to 6-membered aromatic monocyclic heterocyclic rings such as furan, thiophene, pyrrole, oxazole, isoxazole, thiazole, isothiazole, imidazole, pyrazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole, furazane, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,3,4-thiadiazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, pyridine, pyridazine, pyrimidine, pyrazine and triazine. As the "aromatic monocyclic heterocyclic ring" represented by ring C', "a benzene ring which may have a substituent group" represented by the above-mentioned ring A and "a pyridine ring optionally having a substituent group" are particularly preferred. The "pyridine ring optionally having a substituent group" represented by ring C' may have 1 to 4 of the same substituent groups as those exemplified with respect to the "benzene ring which may have a substituent group" represented by the above-mentioned ring A at substitutable positions.

The position wherein "aromatic monocyclic heterocyclic ring" of the "aromatic monocyclic heterocyclic ring optionally having a substituent group" is condensed with an imidazole moiety is not specifically limited.

In the above-mentioned formula (I') or (I), the "aralkyl group" of the "aralkyl group optionally having a substituent group" represented by R^0 includes, for example, a C_{7-16} aralkyl group (for example, C_{6-10} arylC_{1-6} alkyl group such as benzyl and phenethyl and the like) and the like. Examples of the "substituent group" of the "aralkyl group optionally having a substituent group" include the same groups as those exemplified with respect to the "substituent group" of the above-mentioned "alkyl group optionally having a substituent group", and the number of the substituent groups is 1 to about 4. When the number of the substituent group is 2 or more, each substituent groups may be the same or different.

The "acyl group" represented by R^0 includes, for example, the "acyl group" described as the substituent group of the above-mentioned ring A.

The "acyloxy group" represented by R^0 includes, for example, the "acyloxy group" described as the substituent group of the above-mentioned ring A.

The preferable R^0 is a hydrogen atom.

In the above-mentioned formula (I') or (I), the "alkyl group optionally having a substituent group" represented by R^1, R^2 or R^3 includes the "alkyl group optionally having a substituent group" described as the substituent group of the above-mentioned ring A.

The "alkoxy group optionally having a substituent group" represented by R^1, R^2 or R^3 includes the "alkoxy group optionally having a substituent group" described as the substituent group of the above-mentioned ring A.

The "amino group optionally having a substituent group" represented by R^1, R^2 or R^3 includes, for example, an amino group, a mono-C_{1-6} alkylamino group (for example, methylamino, ethylamino and the like), a mono-C_{6-14} arylamino group (for example, phenylamino, 1-naphthylamino, 2-naphthylamino and the like), a di-C_{1-6} alkylamino group (for example, dimethylamino, diethylamino and the like), a di-C_{6-14} arylamino group (for example, diphenylamino and the like) and the like.

The preferable R^1 is a C_{1-6} alkyl group, a C_{1-6} alkoxy group, a C_{1-6} alkoxy-C_{1-6} alkoxy group and a di-C_{1-6} alkylamino group. Further preferable R^2 is a C_{1-3} alkyl group or a C_{1-3} alkoxy group.

The preferable R^2 is a hydrogen atom, a C_{1-6} alkoxy-C_{1-6} alkoxy group or an optionally halogenated C_{1-6} alkoxy group. Further preferable R^3 is a C_{1-3} alkoxy group which may be optionally halogenated or may be optionally substituted with a C_{1-3} alkoxy group.

The preferable R^3 is a hydrogen atom or a C_{1-6} alkyl group. Further preferable R^3 is a hydrogen atom or a C_{1-3} alkyl group (in particular, a hydrogen atom).

The preferable Y is a nitrogen atom.

As the specific example of the compound (I), the following compounds are exemplified.

2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (lansoprazole),

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

2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole sodium salt,

5-difluoromethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and the like.

Among these compounds, lansoprazole, namely 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole is preferable in particular.

The present invention is preferably applied to the PPI of imidazopyridine compound in addition to the PPI of the above-mentioned benzimidazole compound. As the PPI of the imidazopyridine compound, for example, tenatoprazole is exemplified.

Further, the above-mentioned compound (I) and compound (I') including the imidazopyridine compound may be racemic, and optically active compounds such as R-isomer and S-isomer. For example, the optically active compounds such as optically active compound of lansoprazole, that is, (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole and (S)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole are preferable for the present invention in particular. Further, for lansoprazole, lansoprazole R-isomer and lansoprazole S-isomer, crystals are usually preferred, but since they are stabilized by preparation itself as described later and stabilized by compounding a basic inorganic salt and further providing an intermediate layer, those being amorphous as well as crystalline can be also used.

The salt of compound (I') and compound (I) is preferably a pharmacologically acceptable salt, and for example, a salt with an inorganic base, a salt with an organic base, a salt with a basic amino acid and the like are mentioned.

The preferable salt with an inorganic base includes, for example, alkali metal salts such as sodium salt and potassium salt; alkali earth metal salts such as calcium salt and magnesium salt; ammonium salt and the like.

The preferable example of the salt with an organic base includes, for example, salts with an alkylamine (trimethylamine, triethylamine and the like), a heterocyclic amine (pyridine, picoline and the like), an alkanolamine (ethanolamine, diethanolamine, triethanolamine and the like), dicyclohexylamine, N,N'-dibenzylethylenediamine and the like.

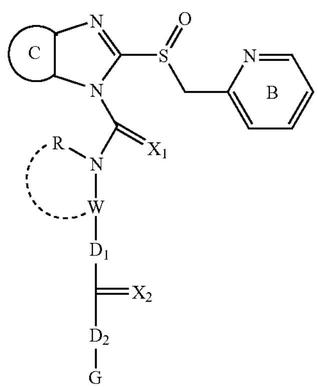
The preferable example of the salt with a basic amino acid includes, for example, salts with arginine, lysine, ornithine and the like.

Among these salts, an alkali metal salt and an alkali earth metal salt are preferred. A sodium salt is preferred particularly.

The compound (I') or (I) can be produced by known methods, and are produced by methods disclosed in, for example, JP-A 61-50978, U.S. Pat. No. 4,628,098, JP-A 10-195068, WO 98/21201, JP-A 52-62275, JP-A 54-141783 and the like, or analogous methods thereto. Further, the optically active compound (I) can be obtained by optical resolution methods (a fractional recrystallization method, a chiral column method, a diastereomer method, a method using microorganism or enzyme, and the like) and an asymmetric oxidation method, etc. Further, lansoprazole R-isomer can be produced according to production methods described in, for example, WO 00-78745, WO 01/83473 and the like.

The benzimidazole compound having antitumor activity used in the present invention is preferably lansoprazole, omeprazole, rabeprazole, pantoprazole, leminoprazole, tenatoprazole (TU-199) and the like, or optically active compounds thereof and pharmacologically acceptable salts thereof. Lansoprazole or an optically active compound thereof, in particular R-isomer is preferred. Lansoprazole or an optically active compound thereof, in particular R-isomer is preferably in a form of crystal, but may be an amorphous form. Further, they are also suitably applied to the prodrug of these PPIs.

Examples of these preferable prodrugs include the compound represented by the following general formula (II) and (III) in addition to the prodrug which is included in compound (I) or (I').



(II)

In the compound represented by the above formula (II) (hereinafter, referred to as compound (II)), ring B designates a "pyridine ring optionally having substituents".

The pyridine ring of the "pyridine ring optionally having substituents" represented by ring B may have 1 to 4 substituents at substitutable positions thereof. As the substituent, for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine etc.), a hydrocarbon group optionally having substituents (e.g., alkyl group having 1 to 6 carbon atoms such as methyl group, ethyl group, n-propyl group etc., and the like), an amino group optionally having substituents (e.g., amino; amino group mono- or di-substituted by alkyl group having 1 to 6 carbon atoms, such as methylamino, dimethylamino, ethylamino, diethylamino group etc., and the like), an amide group (e.g., C_{1-3} acylamino group such as formamide, acetamide etc., and the like), a lower alkoxy group optionally having substituents (e.g., alkoxy group having 1 to 6 carbon atoms such as methoxy, ethoxy, 2,2,2-trifluoroethoxy, 3-methoxypropoxy group and the like), a lower alkylenedioxy group (e.g., C_{1-3} alkylenedioxy group such as methylenedioxy, ethylenedioxy etc., and the like) and the like can be mentioned.

As the substituent, which is the substituent of the "pyridine ring optionally having substituents" represented by ring B can have, for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine etc.), a lower alkyl group (e.g., alkyl group having 1 to 6 carbon atoms such as methyl, ethyl, propyl group and the like), a lower alkenyl group (e.g., alkenyl group having 2 to 6 carbon atoms such as vinyl, allyl group and the like), a lower alkynyl group (e.g., alkynyl group having 2 to 6 carbon atoms such as ethynyl, propargyl group and the like), a cycloalkyl group (e.g., cycloalkyl group having 3 to 8 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl group and the like), a lower alkoxy group (e.g., alkoxy group having 1 to 6 carbon atoms such as methoxy, ethoxy group and the like), a nitro group, a cyano group, a hydroxy group, a thiol group, a carboxyl group, a lower alkanoyl group (e.g., formyl; C_1-C_6 alkyl-carbonyl group, such as acetyl, propionyl, butyryl group and the like), a lower alkanoyloxy group (e.g., formyloxy; C_1-C_6 alkyl-carbonyloxy group, such as acetyloxy, propionyloxy group and the like), a lower alkoxycarbonyl group (e.g., C_1-C_6 alkoxy-carbonyl group, such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl group and the like), an aralkyloxycarbonyl group (e.g., C_7-C_{11} aralkyloxy-carbonyl group, such as benzyloxycarbonyl group and the like), an aryl group (e.g., aryl group having 6 to 14 carbon atoms such as phenyl, naphthyl group and the like), an aryloxy group (e.g., aryloxy group having 6 to 14 carbon atoms such as phenyloxy, naphthyloxy group and the like), an arylcarbonyl group (e.g., C_6-C_{14} aryl-carbonyl group, such as benzoyl, naphthoyl group and the like), an arylcarbonyloxy group (e.g., C_6-C_{14} aryl-carbonyloxy group, such as benzoyloxy, naphthoyloxy group and the like), a carbamoyl group optionally having substituents (e.g., carbamoyl; carbamoyl group mono- or di-substituted by alkyl group having 1 to 6 carbon atoms, such as methylcarbamoyl, dimethylcarbamoyl group etc., and the like), an amino group optionally having substituents (e.g., amino; amino group mono- or di-substituted by alkyl group having 1 to 6 carbon atoms, such as methylamino, dimethylamino, ethylamino, diethylamino group etc., and the like) and the like, can be mentioned, wherein the number of substituents and the position of the substitution are not particularly limited.

While the number of substituents and the position of substitution of the "pyridine ring optionally having substituents" represented by ring B are not particularly limited, 1 to 3 substituents mentioned above preferably substitute any of the 3-, 4- and 5-positions of the pyridine ring.

As the "pyridine ring optionally having substituents" represented by ring B, 3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl is preferable.

In the present invention, ring C represents a "benzene ring optionally having substituents" or an "aromatic monocyclic heterocycle optionally having substituents", which is condensed with an imidazole part. Of these, the former is preferable.

The benzene ring of the "benzene ring optionally having substituents" represented by ring C may have 1 to 4 substituents at substitutable positions thereof. As the substituent, for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine etc.), a hydrocarbon group optionally having substituents (e.g., alkyl group having 1 to 6 carbon atoms selected from methyl group, ethyl group, n-propyl group etc., and the like), an amino group optionally having substituents (e.g., amino; amino group mono- or di-substituted by alkyl group having 1 to 6 carbon atoms, such as methylamino, dimethylamino, ethylamino, diethylamino group etc., and the like), an amide group (e.g., C_{1-3} acylamino group such as formamide, acetamide etc., and the like), a lower alkoxy group optionally having substituents (e.g., alkoxy group having 1 to 6 carbon atoms, such as methoxy, ethoxy, difluoromethoxy group etc., and the like), a lower alkylenedioxy group (e.g., C_{1-3} alkylenedioxy group such as methylenedioxy, ethylenedioxy etc., and the like), and the like can be mentioned.

As the substituent, which is the substituent of the "benzene ring optionally having substituents" represented by ring C can have, for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine etc.), a lower alkyl group (e.g., alkyl group having 1 to 6 carbon atoms such as methyl, ethyl, propyl group and the like), a lower alkenyl group (e.g., alkenyl group having 2 to 6 carbon atoms such as vinyl, allyl group and the like), a lower alkynyl group (e.g., alkynyl group having 2 to 6 carbon atoms such as ethynyl, propargyl group and the like), a cycloalkyl group (e.g., cycloalkyl group having 3 to 8 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl group and the like), a lower alkoxy group (e.g., alkoxy group having 1 to 6 carbon atoms such as methoxy, ethoxy group and the like), a nitro group, a cyano group, a hydroxy group, a thiol group, a carboxyl group, a lower alkanoyl group (e.g., formyl; C_{1-6} alkyl-carbonyl group, such as acetyl, propionyl, butyryl group and the like), a lower alkanoyloxy group (e.g., formyloxy; C_{1-6} alkyl-carbonyloxy group, such as acetyloxy, propionyloxy group and the like), a lower alkoxycarbonyl group (e.g., C_{1-6} alkoxy-carbonyl group, such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl group and the like), an aralkyloxycarbonyl group (e.g., C_{7-17} aralkyloxy-carbonyl group, such as benzyloxycarbonyl group and the like), an aryl group (e.g., aryl group having 6 to 14 carbon atoms such as phenyl, naphthyl group and the like), an aryloxy group (e.g., aryloxy group having 6 to 14 carbon atoms such as phenyloxy, naphthyloxy group and the like), an arylcarbonyl group (e.g., C_{6-14} aryl-carbonyl group, such as benzoyl, naphthoyl group and the like), an arylcarbonyloxy group (e.g., C_{6-14} aryl-carbonyloxy group, such as benzoyloxy, naphthoyloxy group and the like), a carbamoyl group optionally having substituents (e.g., carbamoyl; carbamoyl group mono- or di-substituted by alkyl group having 1 to 6 carbon atoms such as methylcarbamoyl, dimethylcarbamoyl group etc., and the like), an amino group optionally having substituents (e.g., amino; amino group mono- or di-substituted by alkyl group having 1 to 6 carbon atoms such as methylamino, dimethylamino, ethylamino, diethylamino group etc., and the like) and the like can be mentioned, wherein the number of substituents and the position of the substitution are not particularly limited.

As the "benzene ring optionally having substituents" represented by ring C, a benzene ring is preferable.

As the "aromatic monocyclic heterocycle" of the "aromatic monocyclic heterocycle optionally having substituents" represented by ring C, for example, a 5- or 6-membered aromatic monocyclic heterocycle such as furan, thiophene, pyrrole, oxazole, isoxazole, thiazole, isothiazole, imidazole, pyrazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole, furazan, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,3,4-thiadiazole, 1,2,3-triazole, 1,2,4-triazole, tetraxole, pyridine, pyridazine, pyrimidine, pyrazine, triazine etc., and the like can be mentioned. As the "aromatic monocyclic heterocycle" represented by ring C, a pyridine ring is particularly preferable. It may have, at substitutable positions thereof, 1 to 4 substituents similar to those for the "benzene ring optionally having substituents" represented by ring C.

The position where the "aromatic monocyclic heterocycle" of the "aromatic monocyclic heterocycle optionally having substituents" is condensed with the imidazole part is not particularly limited.

In the present invention, X_1, and X_2 represent an oxygen atom and a sulfur atom, respectively. Both X_1, and X_2 preferably represent an oxygen atom.

In the present invention, W represents a "divalent chain hydrocarbon group optionally having substituents", or the formula:

$$—W_1\text{-}Z\text{-}W_2—$$

wherein W_1 and W_2 are each a "divalent chain hydrocarbon group" or a bond, and Z is a divalent group such as a "divalent hydrocarbon ring group optionally having substituents", a "divalent heterocyclic group optionally having substituents", an oxygen atom, SO_n wherein n is 0, 1 or 2 or >N-E wherein E is a hydrogen atom, a hydrocarbon group optionally having substituents, a heterocyclic group optionally having substituents, a lower alkanoyl group, a lower alkoxycarbonyl group, an aralkyloxycarbonyl group, a thiocarbamoyl group, a lower alkylsulfinyl group, a lower alkylsulfonyl group, a sulfamoyl group, a mono-lower alkylsulfamoyl group, a di-lower alkylsulfamoyl group, an arylsulfamoyl group, an arylsulfinyl group, an arylsulfonyl group, an arylcarbonyl group, or a carbamoyl group optionally having substituents, when Z is an oxygen atom, SO_n or >N-E, W_1 and W_2 are each a "divalent chain hydrocarbon group". Particularly, W is preferably a "divalent chain hydrocarbon group optionally having substituents".

As the "divalent chain hydrocarbon group" of the "divalent chain hydrocarbon group optionally having substituents" represented by W and "divalent chain hydrocarbon group" represented by W_1 and W_2, for example, a C_{1-6} alkylene group (e.g., methylene, ethylene, trimethylene etc.), a C_{2-6} alkenylene group (e.g., ethenylene etc.), a C_{2-6} alkynylene group (e.g., ethynylene etc.) and the like can be mentioned. The divalent chain hydrocarbon group for W may have 1 to 6 substituents similar to those for the "benzene ring optionally having substituents" represented by ring C at substitutable positions thereof.

As the "divalent chain hydrocarbon group" of the "divalent chain hydrocarbon group optionally having substituents" represented by W and "divalent chain hydrocarbon group" represented by W_1 and W_2, a methylene group and an ethylene group are preferable. As W, an ethylene group is particularly preferable. When Z is an oxygen atom, SO_n or >N-E (n and E are as defined above), the "divalent chain hydrocarbon group" represented by W_1 is preferably a hydrocarbon group having 2 or more carbon atoms.

As the "hydrocarbon ring" of the "divalent hydrocarbon ring group optionally having substituents" represented by Z, for example, an alicyclic hydrocarbon ring, an aromatic hydrocarbon ring and the like can be mentioned, with preference given to one having 3 to 16 carbon atoms, which may have 1 to 4 substituents similar to those for the "benzene ring optionally having substituents" represented by ring C at substitutable positions thereof. As the hydrocarbon ring, for example, cycloalkane, cycloalkene, arene and the like are used.

As a cycloalkane in the "divalent hydrocarbon ring group optionally having substituents" represented by Z, for example, a lower cycloalkane and the like are preferable, and, for example, C_{3-10} cycloalkane such as cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, bicyclo[2.2.1]heptane, adamantane etc., and the like are generally used.

As a cycloalkene in the "divalent hydrocarbon ring group optionally having substituents" represented by Z, for example, a lower cycloalkene is preferable, and, for example, C_{4-9} cycloalkene such as cyclopropene, cyclobutene, cyclopentene, cyclohexene, cycloheptene, cyclooctene etc., and the like are generally used.

As an arene in the "divalent hydrocarbon ring group optionally having substituents" represented by Z, for example, a C_{6-14} arene such as benzene, naphthalene, phenan-