IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

TAKEDA PHARMACEUTICAL COMPANY LIMITED, a Japanese Corporation, TAP PHARMACEUTICAL PRODUCTS INC., a Delaware Corporation, and ETHYPHARM, S.A., a French Corporation, Plaintiffs, v. TEVA PHARMACEUTICALS USA, INC., a Delaware Corporation, and TEVA PHARMACEUTICAL INDUSTRIES LTD., an Israeli Corporation, Defendants.	)	C.A. No. _____

COMPLAINT

Plaintiffs Takeda Pharmaceutical Company Limited, TAP Pharmaceutical Products Inc., and Ethypharm, S.A. (collectively, "Plaintiffs"), as and for their Complaint against defendants Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd. (collectively "Defendants"), allege as follows:

THE PARTIES

1. Plaintiff Takeda Pharmaceutical Company Limited ("Takeda") is a Japanese corporation, having a principal place of business at 1-1, Doshomachi 4-chome, Chuo-ku, Osaka, Japan. As part of its business, Takeda is involved in the research, development, and marketing of pharmaceutical products.

2. Plaintiff TAP Pharmaceutical Products Inc. ("TAP") is a Delaware corporation, having a principal place of business at 675 North Field Drive, Lake Forest, Illinois

60045. As part of its business, TAP is involved in the research, development, and marketing of pharmaceutical products.

3. Plaintiff Ethypharm, S.A. ("Ethypharm") is a French corporation, having a principal place of business at 21 rue Saint Matthieu 78550, Houdan, France. As part of its business, Ethypharm is involved in the research, development, manufacturing, and licensing of pharmaceutical products. Ethypharm appears as a plaintiff in this action solely by virtue of being the record owner of U.S. Patent No. 5,464,632 ("the '632 Patent"). Ethypharm seeks relief in this action solely in respect to the '632 Patent.

4. On information and belief, defendant Teva Pharmaceuticals USA, Inc. ("Teva USA") is a Delaware corporation, having a principal place of business located at 1090 Horsham Road, North Wales, Pennsylvania 19454 and is engaged in the manufacture and sale of pharmaceutical products.

5. On information and belief, defendant Teva Pharmaceuticals Industries, Ltd. ("Teva Industries") is an Israeli corporation, having a principal place of business located at 5 Basel St., Petach Tikva 49131, Israel. On information and belief, Teva Industries manufactures bulk pharmaceutical products.

6. On information and belief, Teva Industries owns 100% of the ownership and voting interest in Teva USA.

7. On information and belief, Teva USA is controlled and/or dominated by Teva Industries.

8. On information and belief, Teva Industries conducts its North American operations, in part, through Teva USA.

JURISDICTION AND VENUE

9. This action arises under the patent laws of the United States of America, Title 35, United States Code. This Court has subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338(a).

10. Teva USA is subject to personal jurisdiction in this District by virtue of, *inter alia*, its incorporation in Delaware, its conduct of business in this District, its purposeful availment of the rights and benefits of Delaware law, and its substantial and continuing contacts with the State.

11. On information and belief, Teva Industries regularly transacts business within this District, including but not limited to directing the operations and management of Teva USA, as well as shipping pharmaceuticals to Teva USA from locations outside the United States for distribution by Teva USA within the United States generally, and within this District specifically.

12. On information and belief, Teva USA acts as an agent of Teva Industries with respect to the acts complained of herein.

13. On information and belief, the acts of Teva USA complained of herein were done at the direction of, with the authorization of, with the cooperation, participation, and assistance of, and, in part, for the benefit of Teva Industries.

14. On information and belief, Teva Industries directed Teva USA to perform the acts complained of herein to, in whole or in part, shield itself from liability for patent infringement based upon those acts.

15. Teva USA's acts and contacts with this District, as an agent of Teva Industries, are attributable to Teva Industries for jurisdictional purposes.

16. Teva Industries is subject to the personal jurisdiction in this District by virtue of, *inter alia*, its incorporation of Teva USA in Delaware, its conduct of business in this District, its purposeful availment of the rights and benefits of Delaware law, and its substantial and continuing contacts with the State.

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

FACTS PERTINENT TO ALL CLAIMS FOR RELIEF

18. On December 9, 1986, the United States Patent and Trademark Office ("the PTO") issued U.S. Patent No. 4,628,098 ("the '098 Patent"), entitled "2-[2-Pyridylmethylthio-(Sulfinyl)-]Benzimidazoles," to Takeda Chemical Industries, Ltd., the assignee of the named inventors Akira Nohara and Yoshitaka Maki. Plaintiff Takeda is the record owner of the '098 Patent, and Plaintiff TAP is the exclusive licensee. A copy of the '098 Patent is attached hereto as Exhibit A.

19. The original expiration date of the '098 Patent was July 29, 2005.

20. On January 6, 1997, the PTO granted the '098 Patent a term extension of 1381 days pursuant to 35 U.S.C. § 156, extending the expiration date of the '098 Patent to May 10, 2009.

21. On September 3, 1991, the PTO issued U.S. Patent No. 5,045,321 ("the '321 Patent"), entitled "Stabilized Pharmaceutical Composition and Its Production," to Takeda Chemical Industries, Ltd., the assignee of the named inventors Tadashi Makino, Tetsuro Tabata, and Shin-ichiro Hirai. Plaintiff Takeda is the record owner of the '321 Patent, and Plaintiff TAP is the exclusive licensee. A copy of the '321 Patent is attached hereto as Exhibit B.

22. On November 7, 1995, the PTO issued U.S. Patent No. 5,464,632, entitled "Rapidly Disintegratable Multiparticular Tablet," to Laboratoires Prographarm, the assignee of the named inventors Gerard Cousin, Etienne Bruna, and Edouard Gendrot. Laboratoires Prographarm granted Plaintiff Takeda an exclusive license to the '632 Patent with the right to sublicense. Plaintiff Ethypharm subsequently acquired Laboratoires Prographarm and is the record owner of the '632 Patent. Plaintiff TAP is the exclusive sublicensee to the '632 Patent. On February 20, 2001, the PTO issued a Reexamination Certificate for the '632 Patent. A copy of the '632 Patent and its Reexamination Certificate is attached hereto as Exhibit C.

23. On December 11, 2001, the PTO issued U.S. Patent No. 6,328,994 ("the '994 Patent"), entitled "Orally Disintegrating Tablets," to Takeda Chemical Industries, Ltd., the assignee of the named inventors Toshihiro Shimizu, Shuji Morimoto, and Tetsuro Tabata. Plaintiff Takeda is the record owner of the '994 Patent, and Plaintiff TAP is the exclusive licensee. A copy of the '994 Patent is attached hereto as Exhibit D.

24. On August 30, 2002, the United States Food and Drug Administration ("FDA") approved New Drug Application ("NDA") No. 21-428 for lansoprazole delayed release orally disintegrating tablets, 15 and 30 mg. TAP is the holder of NDA No. 21-428 for lansoprazole delayed release orally disintegrating tablets, which it sells under the name Prevacid® SoluTab™.

25. The '098, '321, '632 and '994 Patents (collectively, "the patents-in-suit") are listed in a publication entitled *Approved Drug Products with Therapeutic Equivalence Evaluations* (known as the "Orange Book") as covering Prevacid® SoluTab™, delayed release orally disintegrating tablets, 15 and 30 mg.

26. On information and belief, through the coordinated efforts of research and development staff in Israel, Europe and North America, Teva Industries seeks constantly to expand the range of generic products it sells.

27. On information and belief, Teva USA and Teva Industries collaborate in the manufacture, marketing and sale of many pharmaceutical products (including generic drug products manufactured and sold pursuant to an approved abbreviated new drug application) within the United States generally and the State of Delaware specifically.

28. On information and belief, Teva Industries actively reviews pharmaceutical patents and seeks opportunities to challenge those patents.

29. On information and belief, Teva Industries reviewed the patents-in-suit and certain commercial and economic information relating to Prevacid® SoluTab™, including estimates of the revenues generated by the sale of Prevacid® SoluTab™, and decided to file an Abbreviated New Drug Application ("ANDA"), seeking approval to market lansoprazole delayed release orally disintegrating tablets.

30. On information and belief, Teva USA and Teva Industries collaborated in the research, development, preparation and filing of Abbreviated New Drug Application ("ANDA") No. 78-730 for lansoprazole delayed release orally disintegrating tablets.

31. On information and belief, Teva USA submitted to FDA ANDA No. 78-730 seeking approval to engage in the commercial manufacture, use and sale of lansoprazole delayed release orally disintegrating tablets, 15 and 30 mg, prior to the expiration of the patents-in-suit.

32. Plaintiffs have received a letter dated April 12, 2007 from Teva USA notifying them that Teva USA's ANDA No. 78-730 includes a certification under 21 U.S.C.

§ 355(j)(2)(A)(vii)(IV) (a "Paragraph IV certification") that, in Teva USA's opinion, the patents-in-suit are invalid, unenforceable or will not be infringed by the commercial manufacture, use or sale of the lansoprazole delayed release orally disintegrating tablet products described in ANDA No. 78-730.

33. On information and belief, Teva Industries made the ultimate decision to file ANDA No. 78-730 with the FDA, and encouraged and directed Teva USA to file ANDA No. 78-730 and the Paragraph IV certification, and Teva USA did so at Teva Industries' direction.

34. On information and belief, Teva Industries was necessarily aware of the patents-in-suit when it directed Teva USA to file ANDA No. 78-730 and the Paragraph IV certification.

35. Plaintiffs commenced this action within 45 days of the date they received Teva USA's notice of ANDA No. 78-730 containing the Paragraph IV certification.

36. On information and belief, Teva USA and Teva Industries continue to collaborate in seeking approval of ANDA No. 78-730 from the FDA and intend to collaborate in the commercial manufacture, marketing, and sale of lansoprazole delayed release orally disintegrating tablets (including commercial marketing and sale of such products in the State of Delaware) in the event that FDA approves ANDA No. 78-730.

FIRST CLAIM FOR RELIEF
DIRECT INFRINGEMENT OF THE '098 PATENT BY TEVA USA AND TEVA INDUSTRIES

37. Plaintiffs Takeda and TAP repeat and reallege each and every allegation contained in paragraphs 1 through 36 hereof, as if fully set forth herein.

38. Through the conduct alleged above, Teva USA and Teva Industries (collectively "Teva") have directly infringed, and continue to directly infringe, one or more claims of the '098 Patent.

39. By filing ANDA No. 78-730 with a Paragraph IV certification seeking FDA approval to engage in the commercial manufacture, use and sale of the lansoprazole delayed release orally disintegrating tablet products described therein, prior to the expiration of the '098 Patent, Teva has infringed the '098 Patent under 35 U.S.C. § 271(e)(2).

40. Teva was aware of the existence of the '098 Patent prior to filing ANDA No. 78-730, but took such action knowing that it would constitute an infringement of the '098 Patent.

41. On information and belief, Teva acted without a reasonable basis for a good faith belief that it would not be liable for infringing the '098 Patent.

42. Teva does not dispute that the lansoprazole delayed release orally disintegrating tablet products described in ANDA No. 78-730 infringe claims 1, 2, 5, 6, 8, and 10 of the '098 Patent. Instead, Teva's Paragraph IV certification is premised upon a baseless assertion that claims 1, 2, 5, 6, 8, and 10 of the '098 Patent are invalid as obvious under 35 U.S.C. § 103 or unenforceable for inequitable conduct.

43. Teva disregarded its duty to exercise due care by making these baseless assertions of invalidity and unenforceability, and therefore, this case is "exceptional" as described in 35 U.S.C. § 285.

44. Plaintiffs Takeda and TAP will be irreparably harmed if Teva is not enjoined from infringing the '098 Patent.

SECOND CLAIM FOR RELIEF
INDUCEMENT OF INFRINGEMENT OF THE '098 PATENT BY TEVA INDUSTRIES

45. Plaintiffs Takeda and TAP repeat and reallege each and every allegation contained in paragraphs 1 through 44 hereof, as if fully set forth herein.

46. Through the conduct alleged above, Teva Industries has knowingly and actively induced Teva USA to infringe, and continue to infringe, one or more claims of the '098 Patent.

47. By reason of Teva Industries' inducement of Teva USA's direct infringement of the '098 Patent, Teva Industries has caused and continues to cause irreparable harm to Plaintiffs Takeda and TAP.

48. On information and belief, Teva Industries' inducement of Teva USA's direct infringement of the '098 Patent will continue unless enjoined by this Court.

49. Plaintiffs Takeda and TAP have no adequate remedy at law for Teva Industries' inducement of Teva USA's direct infringement of the '098 Patent.

50. This is an exceptional case within the meaning of 35 U.S.C. § 285, which warrants reimbursement of Plaintiffs' reasonable attorneys' fees.

THIRD CLAIM FOR RELIEF
DIRECT INFRINGEMENT OF THE '321 PATENT BY TEVA USA AND TEVA INDUSTRIES

51. Plaintiffs Takeda and TAP repeat and reallege each and every allegation contained in paragraphs 1 through 50 hereof, as if fully set forth herein.

52. Through the conduct alleged above, Teva has directly infringed, and continues to directly infringe, one or more claims of the '321 Patent.

53. By filing ANDA No. 78-730 with a Paragraph IV certification seeking FDA approval to engage in the commercial manufacture, use and sale of lansoprazole delayed

release orally disintegrating tablets, 15 and 30 mg, prior to the expiration of the '321 Patent, Teva has infringed the '321 Patent under 35 U.S.C. § 271(e)(2).

54. Teva was aware of the existence of the '321 Patent prior to filing ANDA No. 78-730, but took such action knowing that it would constitute an infringement of the '321 Patent.

55. On information and belief, Teva acted without a reasonable basis for a good faith belief that it would not be liable for infringing the '321 Patent.

56. Teva's conduct renders this case "exceptional" as described in 35 U.S.C. § 285.

57. Plaintiffs Takeda and TAP will be irreparably harmed if Teva is not enjoined from infringing the '321 Patent.

FOURTH CLAIM FOR RELIEF
INDUCEMENT OF INFRINGEMENT OF THE '321 PATENT BY TEVA INDUSTRIES

58. Plaintiffs Takeda and TAP repeat and reallege each and every allegation contained in paragraphs 1 through 57 hereof, as if fully set forth herein.

59. Through the conduct alleged above, Teva Industries has knowingly and actively induced Teva USA to infringe, and continue to infringe, one or more claims of the '321 Patent.

60. By reason of Teva Industries' inducement of Teva USA's direct infringement of the '321 Patent, Teva Industries has caused and continues to cause irreparable harm to Plaintiffs Takeda and TAP.

61. On information and belief, Teva Industries' inducement of Teva USA's direct infringement of the '321 Patent will continue unless enjoined by this Court.

62. Plaintiffs Takeda and TAP have no adequate remedy at law for Teva Industries' inducement of Teva USA's direct infringement of the '321 Patent.

63. This is an exceptional case within the meaning of 35 U.S.C. § 285, which warrants reimbursement of Plaintiffs' reasonable attorneys' fees.

FIFTH CLAIM FOR RELIEF
DIRECT INFRINGEMENT OF THE '632 PATENT BY TEVA USA AND TEVA INDUSTRIES

64. Plaintiffs repeat and reallege each and every allegation contained in paragraphs 1 through 63 hereof, as if fully set forth herein.

65. Through the conduct alleged above, Teva has directly infringed, and continues to directly infringe, one or more claims of the '632 Patent.

66. By filing ANDA No. 78-730 with a Paragraph IV certification seeking FDA approval to engage in the commercial manufacture, use and sale of lansoprazole delayed release orally disintegrating tablets, 15 and 30 mg, prior to the expiration of the '632 Patent, Teva has infringed the '632 Patent under 35 U.S.C. § 271(e)(2).

67. Teva was aware of the existence of the '632 Patent prior to filing ANDA No. 78-730, but took such action knowing that it would constitute an infringement of the '632 Patent.

68. On information and belief, Teva acted without a reasonable basis for a good faith belief that it would not be liable for infringing the '632 Patent.

69. Teva's conduct renders this case "exceptional" as described in 35 U.S.C. § 285.

70. Plaintiffs will be irreparably harmed if Teva is not enjoined from infringing the '632 Patent.

SIXTH CLAIM FOR RELIEF
INDUCEMENT OF INFRINGEMENT OF THE '632 PATENT BY TEVA INDUSTRIES

71. Plaintiffs repeat and reallege each and every allegation contained in paragraphs 1 through 70 hereof, as if fully set forth herein.

72. Through the conduct alleged above, Teva Industries has knowingly and actively induced Teva USA to infringe, and continue to infringe, one or more claims of the '632 Patent.

73. By reason of Teva Industries' inducement of Teva USA's direct infringement of the '632 Patent, Teva Industries has caused and continues to cause irreparable harm to Plaintiffs.

74. On information and belief, Teva Industries' inducement of Teva USA's direct infringement of the '632 Patent will continue unless enjoined by this Court.

75. Plaintiffs have no adequate remedy at law for Teva Industries' inducement of Teva USA's direct infringement of the '632 Patent.

76. This is an exceptional case within the meaning of 35 U.S.C. § 285, which warrants reimbursement of Plaintiffs' reasonable attorneys' fees.

SEVENTH CLAIM FOR RELIEF
DIRECT INFRINGEMENT OF THE '994 PATENT BY TEVA USA AND TEVA INDUSTRIES

77. Plaintiffs Takeda and TAP repeat and reallege each and every allegation contained in paragraphs 1 through 76 hereof, as if fully set forth herein.

78. Through the conduct alleged above, Teva has directly infringed, and continues to directly infringe, one or more claims of the '994 Patent.

79. By filing ANDA No. 78-730 with a Paragraph IV certification seeking FDA approval to engage in the commercial manufacture, use and sale of lansoprazole delayed

release orally disintegrating tablets, 15 and 30 mg, prior to the expiration of the '994 Patent, Teva has infringed the '994 Patent under 35 U.S.C. § 271(e)(2).

80. Teva was aware of the existence of the '994 Patent prior to filing ANDA No. 78-730, but took such action knowing that it would constitute an infringement of the '994 Patent.

81. On information and belief, Teva acted without a reasonable basis for a good faith belief that it would not be liable for infringing the '994 Patent.

82. Teva's conduct renders this case "exceptional" as described in 35 U.S.C. § 285.

83. Plaintiffs Takeda and TAP will be irreparably harmed if Teva is not enjoined from infringing the '994 Patent.

EIGHTH CLAIM FOR RELIEF
INDUCEMENT OF INFRINGEMENT OF THE '994 PATENT BY TEVA INDUSTRIES

84. Plaintiffs Takeda and TAP repeat and reallege each and every allegation contained in paragraphs 1 through 83 hereof, as if fully set forth herein.

85. Through the conduct alleged above, Teva Industries has knowingly and actively induced Teva USA to infringe, and continue to infringe, one or more claims of the '994 Patent.

86. By reason of Teva Industries' inducement of Teva USA's direct infringement of the '994 Patent, Teva Industries has caused and continues to cause irreparable harm to Plaintiffs Takeda and TAP.

87. On information and belief, Teva Industries' inducement of Teva USA's direct infringement of the '994 Patent will continue unless enjoined by this Court.

88. Plaintiffs Takeda and TAP have no adequate remedy at law for Teva Industries' inducement of Teva USA's direct infringement of the '994 Patent.

89. This is an exceptional case within the meaning of 35 U.S.C. § 285, which warrants reimbursement of Plaintiffs' reasonable attorneys' fees.

WHEREFORE, Plaintiffs respectfully request the following relief:

A. An order adjudging and decreeing that Teva USA and Teva Industries have infringed the patents-in-suit;

B. An order adjudging and decreeing that Teva Industries has induced infringement of the patents-in-suit;

C. An order pursuant to 35 U.S.C. § 271(e)(4)(A) decreeing that the effective date of any approval of ANDA No. 78-730 be no earlier than the expiration date of the last of the patents-in-suit, including any extensions;

D. A preliminary and permanent injunction pursuant to 35 U.S.C. § 271(e)(4)(B) restraining and enjoining Teva USA and Teva Industries, their officers, agents, attorneys, and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of the lansoprazole products described in ANDA No. 78-730 or any other ANDA not colorably different from ANDA No. 78-730 until the expiration date of the last of the patents-in-suit, including any extensions;

E. A declaration that this case is exceptional and an award of attorneys' fees under 35 U.S.C. § 285 and costs and expenses in this action; and

F. Such other and further relief as the Court may deem just and proper.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP

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Dated: May 25, 2007
841122

EXHIBIT A

United States Patent [19]

Nohara et al.

[11] **Patent Number: 4,628,098**

[45] **Date of Patent: Dec. 9, 1986**

[54] **2-[2-PYRIDYLMETHYLTHIO-(SULFINYL)-]BENZIMIDAZOLES**

[75] Inventors: **Akira Nohara; Yoshitaka Maki,** both of Kyoto, Japan

[73] Assignee: **Takeda Chemical Industries, Ltd.,** Osaka, Japan

[21] Appl. No.: **760,568**

[22] Filed: **Jul. 29, 1985**

[30] **Foreign Application Priority Data**

Aug. 16, 1984 [JP] Japan 59-171069

[51] **Int. Cl.**[4] **C07D 401/12**

[52] **U.S. Cl.** **546/271**

[58] **Field of Search** 546/271

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,045,563	8/1977	Berntsson et al.	546/271
4,255,431	3/1981	Junggren et al.	546/271
4,472,409	9/1984	Jenn-Bilfinger	546/271
4,575,554	3/1986	Sih	546/271

FOREIGN PATENT DOCUMENTS

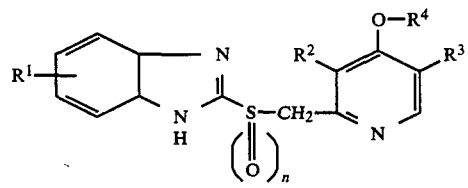
5129	10/1979	European Pat. Off. .
45200	2/1982	European Pat. Off. .
74341	3/1983	European Pat. Off. .
2134523A	8/1984	United Kingdom .

Primary Examiner—Jane T. Fan

Attorney, Agent, or Firm—Wegner & Bretschneider

[57] **ABSTRACT**

The compound of the formula



wherein R^1 is hydrogen, methoxy or trifluoromethyl, R^2 and R^3 are independently hydrogen or methyl, R^4 is a C_{2-5} fluorinated alkyl and n denotes 0 or 1, or a pharmacologically acceptable salt thereof is novel, and useful for prophylaxis and therapy of digestive ulcers (e.g. gastric ulcer, duodenal ulcer) and gastritis.

36 Claims, No Drawings

2-[2-PYRIDYLMETHYLTHIO-(SULFINYL)]BENZIMIDAZOLES

This invention relates to pyridine derivatives useful as e.g. anti-ulcer agents and to a method of preparing them.

As the pyridine derivatives having anti-ulcer activity, those disclosed in U.S. Pat. No. 4,255,431 (Japanese Unexamined Patent Laid-open No. 141783/79) and U.S. Pat. No. 4,472,409 (Japanese Unexamined Patent Laid-open No. 135881/83) etc. have been known.

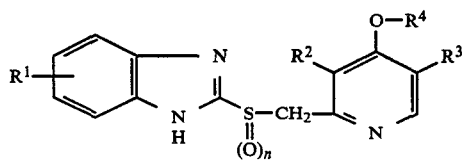
However, while these known compounds have an acid-secretion-inhibiting action, their gastric mucous membrane protecting action is insufficient, thus being hardly considered satisfactory as anti-ulcer agents. Besides, these compounds are possessed of such drawbacks in the physico-chemical properties as being unstable and readily decomposed.

It is considered that gastrointestinal ulcer is induced by unbalance between aggressive factors, e.g. hydrochloric acid, pepsin, and defensive factors, e.g. mucus secretion and mucosal blood flow. Therefore, a medicine having both an action of inhibiting gastric acid secretion and an action of enhancing protection of gastric mucosa has been desired.

The present inventors diligently studied with the purpose of preparing an anti-ulcer agent having excellent actions of inhibiting gastric acid secretion, of protecting gastric mucosa and of antagonizing ulceration. They found that a certain type of pyridine derivatives meets the said purpose, and they conducted further study to accomplish the present invention.

The present invention relates to

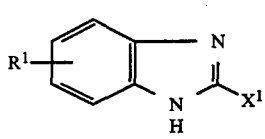
(1) pyridine derivatives of the formula (I)



(I)

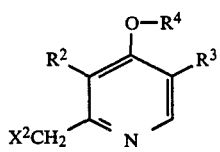
wherein R^1 is hydrogen, methoxy or trifluoromethyl, R^2 and R^3 are independently hydrogen or methyl, R^4 is a C_{2-5} fluorinated alkyl, and n denotes 0 or 1, or their pharmacologically acceptable salts and

(2) a method for preparing a compound (I) or its pharmacologically acceptable salt, which comprises allowing a compound of the formula (II)



(II)

wherein R^1 is of the same meaning as defined above, to react with a compound of the formula (III)



(III)

wherein R^2, R^3 and R^4 are of the same meaning as defined above, one of X^1 and X^2 is SH and the other is a leaving group and, when necessary, by subjecting the reaction product to oxidation.

In the above formulae, C_{2-5} fluorinated alkyl groups shown by R^4 are exemplified by 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, 2,2,3,3-tetrafluoropropyl 1-(trifluoromethyl)-2,2,2-trifluoroethyl, 2,2,3,3,4,4,4-heptafluorobutyl and 2,2,3,3,4,4,5,5-octafluoropentyl.

Examples of the leaving groups X^1 and X^2 in the above formulae are halogen, preferably chlorine, bromine or iodine, or a reactive esterified hydroxy group, e.g. an arylsulfonyloxy, for example, phenylsulfonyloxy or tosyloxy, or C_{1-4} alkylsulfonyloxy, for example, methanesulfonyloxy, or an organic phosphoryloxy, for example, diphenylphosphoryloxy, dibenzylphosphoryloxy or di-C_{1-4}alkylphosphoryloxy and the like.

R^1 may be located at 4- or 5-position, and preferably at 5-position.

A sulfide derivative (I) (n=0), among the object compounds of this invention, can be prepared by allowing a compound (II) to react with a compound (III). It is convenient to conduct this reaction in the presence of a base. The base is exemplified by alkali metal hydride e.g. sodium hydride and potassium hydride; alkali metal e.g. metallic sodium; sodium alcoholate e.g. sodium methoxide and sodium ethoxide; alkali metal carbonate e.g. potassium carbonate and sodium carbonate; and organic amines e.g. triethylamine. The solvent used for the reaction is exemplified by alcohols e.g. methanol and ethanol, as well as dimethylformamide. The amount of a base used for the reaction is usually in a little excess to the equivalent, but it may be in a large excess. Specifically, it is about 1–10 equivalents, more preferably about 1–equivalents. The reaction temperature ranges usually from about 0° C. to about the boiling point of the solvent then used, more preferably from about 20° C. to about 80° C. The reaction time ranges from about 0.2 to about 24 hours, more preferably from about 0.5 to about 2 hours.

A sulfinyl derivative (I) (n=1), which is also among the object compounds of this invention, can be prepared by subjecting a compound (I) (n=0) to oxidation. The oxidizing agent to be employed here is exemplified by peracid e.g. m-chloroperbenzoic acid, peracetic acid, trifluoroperacetic acid and permaleic acid, or sodium bromite or sodium hypochlorite or hydrogen peroxide. The solvent used for the reaction is exemplified by halogenated hydrocarbon e.g. chloroform and dichloromethane, ethers e.g. tetrahydrofuran and dioxane, amides e.g. dimethylformamide, alcohols, e.g. methanol, ethanol, propanol, and t-butanol or water, and these solvents may used singly or in admixture. The oxidizing agent is used preferably in approximately equivalent or a little excess amount relative to the compound (I) (n=0). Specifically, it is about 1 to about 3 equivalents, more preferably about 1–1.5 equivalent. The reaction temperature ranges from that under ice-cooling to about the boiling point of the solvent then employed, usually from that under ice-cooling to room temperature, more preferably from about 0° C. to about 10° C. The reaction time usually ranges from about 0.1 to about 24 hours, more preferably from about 0.1 to about 4 hours.

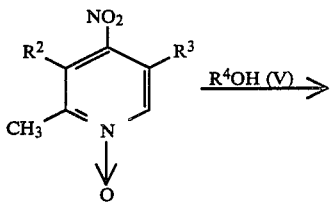
The object compound (I) produced by the above reaction can be isolated and purified by conventional means e.g. recrystallization and chromatography.

The compound (I) of this invention may be led to pharmacologically acceptable salts thereof by per se conventional means, the salts being exemplified by hydrochloride, hydrobromide, hydroiodide, phosphate, nitrate, sulfate, acetate and citrate.

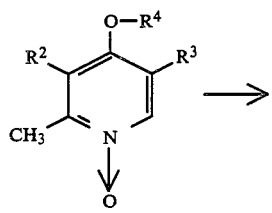
Among the compounds (I), those of n=0 give stable salts, while those of n=1 may exist as an aqueous solution though unstable.

The process of preparing the starting material (III) is described as follows.

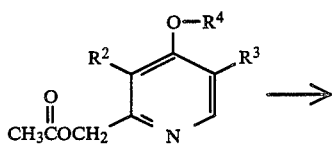
(Process 1)



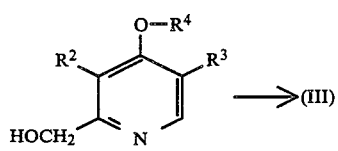
(IV)



(VI)



(VII)



(VIII)

A nitro compound of the formula (IV) [wherein R^2 and R^3 are of the same meaning as defined above] is allowed to react with an alcohol derivative R^4OH (V) [wherein R^4 is of the same meaning as defined above] in the presence of a base to give an alkoxy derivative of the formula (VI) [wherein R^2, R^3 and R^4 are of the same meaning as defined above]. The base is exemplified by alkali metal e.g. lithium, sodium and potassium; alkali metal hydride e.g. sodium hydride and potassium hydride; alcoholate e.g. potassium t-butoxide and sodium propoxide; alkali metal carbonate or hydrogen carbonate e.g. potassium carbonate, lithium carbonate, sodium carbonate, potassium hydrogen carbonate and sodium hydrogen carbonate; or alkali hydroxide e.g. sodium hydroxide and potassium hydroxide. The solvent used for the reaction is exemplified by, besides R^4OH itself, ethers such as tetrahydrofuran and dioxane as well as ketones such as acetone and methyl ethyl ketone, acetonitrile, dimethylformamide and hexamethylphosphoric acid triamide. The reaction temperature is suitably selected within the range from those under ice-cooling to those near the boiling point of the solvent used. The reaction time ranges usually from about 1 to about 48 hours.

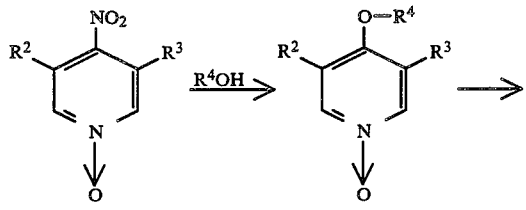
The thus-obtained compound (VI) is subjected to heating (about 80° to about 120° C.) in the presence of acetic anhydride singly or together with a mineral acid e.g. sulfuric acid and perchloric acid to give a 2-acetoxymethylpyridine derivative of the formula (VII) [wherein R^2, R^3 and R^4 are of the same meaning as defined above]. The reaction time ranges usually from about 0.1 to about 10 hours.

Then, the compound (VII) is subjected to alkali-hydrolysis to give a 2-hydroxymethyl pyridine derivative of the formula (VIII) [wherein R^2, R^3 and R^4 are of the same meaning as defined above]. The alkali is exemplified by sodium hydroxide, potassium hydroxide, potassium carbonate and sodium carbonate. The solvent used for the reaction is exemplified by methanol, ethanol and water. The reaction temperature ranges usually from about 20° C. to about 60° C. The reaction time is within the range of from about 0.1 to about 2 hours.

The compound (VIII) is further subjected to reaction with a chlorinating agent such as thionyl chloride, or an esterifying agent, e.g. an organic sulfonic acid chloride such as methanesulfonyl chloride or p-toluenesulfonyl chloride, or an organic phosphoric acid chloride such as diphenylphosphoryl chloride to give the compound (III). The amount of the chlorinating agent used for the reaction is usually in equivalent to a large excess relative to the compound (VIII). The solvent used for the reaction is exemplified by chloroform, dichloromethane and tetrachloroethane. The reaction temperature is usually within the range of from about 20° C. to about 80° C., and the reaction time is about 0.1 to about 2 hours.

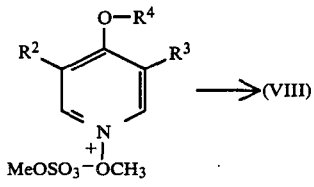
The amount of the organic sulfonic acid chloride or organic phosphoric acid chloride used for the reaction is usually in equivalent to a little excess, and the reaction is usually conducted in the presence of a base. The base is exemplified by organic base e.g. triethylamine and tributylamine, or inorganic base e.g. sodium carbonate, potassium carbonate and sodium hydrogen carbonate. The amount of a base used for the reaction is usually in equivalent to a little excess. The solvent used for the reaction is exemplified by chloroform, dichloromethane, carbon tetrachloride or acetonitrile. The reaction temperature ranges usually from that under ice-cooling to about the boiling point of the solvent then used. The raction time ranges usually from a few minutes to a few hours. It is usually preferable to use the thus-produced compound (III) immediately for the reaction with a compound (II).

(Process 2)



(IX) (X)

-continued



(XI)

By a reaction similar to the above-described process (1), a compound of the formula (IX) [wherein R^2 and R^3 are of the same meaning as defined above] is led to a compound of the formula (X) [wherein R^2, R^3 and R^4 are of the same meaning as defined above].

Then, the compound (X) is subjected to methylation with dimethyl sulfate to give a compound of the formula (XI) [wherein R^2, R^3 and R^4 are of the same meaning as defined above]. The reaction can be conducted usually without solvent. The reaction temperature ranges from about 100° C. to about 120° C., and the reaction time is within the range of from about 0.1 to about 4 hours.

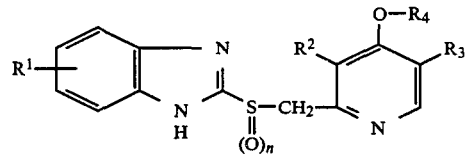
Further, the compound (XI) is allowed to react with a radical source such as ammonium persulfate or any other persulfate in methanol to give the above-mentioned compound (VIII). The reaction temperature is within the range of from about 20° C. to about 80° C., and the reaction time ranges from about 0.5 to about 4 hours.

Pharmacological actions of the compounds of the present invention are described as follows.

As the models of gastrointestinal ulcers, restraint and water-immersion stress-induced ulcer, indomethacin-induced ulcer and ethanol-induced gastric mucosal lesions have been used. However, as a model mimicking human gastric ulcer, indomethacin-induced gastric antral ulcer was reported in "Gastroenterology" (Satoh et al. 81, p. 719, 1981), which is considered to be of value as an experimental model. Therefore, the following are data of anti-ulcer actions of the object compounds (I) and of some representable known compounds, on the ulcer model in the above-mentioned literature reference. Experimental Method:

Male Sprague-Dawley rats of 7-weeks old were fasted for 24 hours. These animals were administered test compounds into stomach by using a gastric tube. After 30 minutes, indomethacin, 30 mg/kg subcutaneously, was administered. During 30–90 minutes after the administration of indomethacin, these animals had free access to chow pellets (Japan Clea, CE-2). At 5 hours after the administration of indomethacin, 1 ml of 1% Evans blue was injected to the animals via the tail vein, followed by sacrificing these animals with carbon dioxide gas. The stomach was removed together with the lower part of esophagus and the duodenum. The esophagus was clipped, 10 ml of 1% formalin solution was instilled into the stomach from the duodenum, and then the duodenum was clipped. The whole stomach waa immersed in 1% formalin solution. About 15 minutes later, the stomachs were opened along the greater curvature. The area of the lesions which occurred in the gastric antral mucosa was measured under a dissecting microscope with a square-grid eye piece (x10). The sum total of the individual lesions in each animal was measured, and the average value per group was calculated. Based on the difference between the average value of each group and that of the control group, the inhibition rate was determined. The test compound and indomethacin were suspended in a 5% gum arabic solution, respectively and administered in a volume of 2 ml/kg.

Experimental Results:



R^1	R^2	R^3	R^4	n	Anti-ulcer action[a] ID_{50} (mg/kg, p.o.)
H	H	H	CH_2CF_3	1	2.4
H	CH_3	H	CH_2CF_3	1	<1.0
H	H	H	$CH_2CF_2CF_3$	1	1.3
H	CH_3	H	$CH_2CF_2CF_3$	1	<1.0
H	H	H	$CH_2CF_2CF_2H$	1	1.3
H	CH_3	H	$CH_2CF_2CF_2H$	1	<1.0
H	CH_3	H	$CH_2CF_2CF_3$	0	3.7
5-OCH_3	CH_3	CH_3	CH_3*1		21.0
5-CF_3	CH_3	H	CH_3*2		5.5

*1The compound disclosed in Example 23 of USP. 4,255,431 (Japanese Unexamined Patent Laid-open No. 141783/1979)

*2The compound disclosed in Example 3 of USP. 4,472,409 (Japanese Unexamined Patent Laid-open No. 135881/1983)

[a]Using 6 rats per group, each of the test compounds was administered in a dose of 1, 3, 10 and 30 mg/kg to determine ID_{50}.

As shown by the above data, the compounds of this invention have superior anti-ulcer action as compared with known compounds by about 1.5–20 times or more. Besides, the compound (I) of this invention shows excellent actions of inhibiting gastric acid secretion, protecting gastric mucous membrane and preventing ulceration.

Regarding about the toxicity of the compound (I) of this invention, oral administration of the compound employed for the experiment of anti-ulceration (compound of R^1=H, R^2=CH_3, R^3=H, R^4=$CH_2CF_2CF_3$, n=1) to mice even in a dose of 2000 mg/kg caused no fatal effect; thus the compound (I) is low in toxicity.

As described in the foregoing, the compound (I) of this invention has an anti-ulcer action, a gastric acid secretion controlling action and a mucous membrane protecting action, furthermore is of low toxicity and is relatively stable as a chemical substance. The compound (I) of this invention can thus be used for prophylaxis and therapy of digestive ulcers (e.g. gastric ulcer, duodenal ulcer) and gastritis in mammalian animals (e.g. mouse, rat, rabbit, dog, cat and man).

When the compound (I) of this invention is used as an anti-ulcer agent for the therapy of digestive ulcers in mammalian animals, it can be administered orally in a dosage form of capsules, tablets, granules, etc. by formulating with a pharmacologically acceptable carrier, excipient, diluent, etc. The daily dose is about 0.01–30 mg/kg, more preferably about 0.1–3 mg/kg.

Incidentally, the compound of this invention (I) (n=0) is useful as a starting material for preparing the compound (I) (n=1).

The processes of producing the starting compounds to be employed in the method of this invention as well as those of producing the compound (I) of this invention are specifically explained by the following Reference Examples and Working Examples.

REFERENCE EXAMPLE 1

In 2,2,3,3-tetrafluoropropanol (10 ml) was dissolved 2,3-dimethyl-4-nitropyridine-1-oxide (2 g). To the solution was added potassium t-butoxide (1.6 g) little by little at room temperature. The mixture was then heated at 80°–90° C. for 22 hours. The reaction solution was diluted with water, which was subjected to extraction with chloroform. The extract was dried on magnesium sulfate, and then concentrated. The concentrate was chromatographed on a column of silica gel (70 g). Elution was conducted with methanol-chloroform (1:10), and then subjected to recrystallization from ethyl acetate-hexane to yield 2.6 g of 2,3-dimethyl-4-(2,2,3,3-tetrafluoropropoxy)pyridine-1-oxide as colorless needles, m.p. 138°–139° C.

After the manner above, compounds (VI) were prepared from compounds (IV).

		Compound (VI)	
R^2	R^3	R^4	Melting point (°C.)
H	H	CH_2CF_3	148–150
CH_3	CH_3	CH_2CF_3	138–139

REFERENCE EXAMPLE 2

A mixture of 2,3-dimethyl-4-nitropyridine-1-oxide (2.0 g), methyl ethyl ketone (30 ml), 2,2,3,3,3-pentafluoropropanol (3.05 ml), anhydrous potassium carbonate (3.29 g) and hexamethyl phosphoric acid triamide (2.07 g) was heated at 70°–80° C. for 4.5 days under stirring, then insolubles were filtered off. The filtrate was concentrated, to which was added water. The mixture was subjected to extraction with ethyl acetate. The extract solution was dried on magnesium sulfate, followed by removing the solvent by evaporation. The residue was chromatographed on a column of silica gel (50 g), eluted with chloroform-methanol (10:1), and recrystallized from ethyl acetate-hexane to yield 2.4 g of 2,3-dimethyl-4-(2,2,3,3,3-pentafluoropropoxy)pyridine-1-oxide as colorless needles, m.p. 148°–149° C.

By this process, compounds (VI) were prepared from starting compounds (IV).

		Compound (VI)	
R^2	R^3	R^4	Melting point (°C.)
CH_3	H	CH_2CF_3	131.0–131.5
H	CH_3	CH_2CF_3	153–154
H	H	$CH_2CF_2CF_3$	79–81
H	CH_3	$CH_2CF_2CF_3$	140–142
H	H	$CH_2CF_2CF_2H$	Oily
H	CH_3	$CH_2CF_2CF_2H$	143.5–144.5
CH_3	H	$CH_2CF_2CF_2H$	138–139

REFERENCE EXAMPLE 3

Concentrated sulfuric acid (two drops) was added to a solution of 2,3-dimethyl-4-(2,2,3,3-tetrafluoropropoxy)pyridine-1-oxide (2.6 g) in acetic anhydride (8 ml). The mixture was stirred at 110° C. for 4 hours, which was then concentrated. The residue was dissolved in methanol (20 ml), to which was added sodium hydroxide (1.2 g) dissolved in water (5 ml). The mixture was stirred at room temperature for 30 minutes, which was concentrated. To the residue was added water, and the mixture was subjected to extraction with ethyl acetate. The extract was dried on magnesium sulfate, followed by removal of the solvent by evaporation. The residue was chromatographed on a column of silica gel (50 g), eluted with chloroform-methanol (10:1), and recrystallized from isopropyl ether to yield 1.6 g of 2-hydroxymethyl-3-methyl-4-(2,2,3,3-tetrafluoropropoxy)pyridine as yellow crystals, m.p. 67°–68° C.

By this process, compounds (VIII) were prepared from compounds (VI).

		Compound (VIII)	
R^2	R^3	R^4	Melting point (°C.)
H	H	CH_2CF_3	Oily
CH_3	H	CH_2CF_3	93.5–94.0
H	H	$CH_2CF_2CF_3$	Oily
CH_3	H	$CH_2CF_2CF_3$	Oily
H	CH_3	$CH_2CF_2CF_3$	87–89
H	H	$CH_2CF_2CF_2H$	88–89
H	CH_3	$CH_2CF_2CF_2H$	98–99
CH_3	H	$CH_2CF_2CF_2H$	67–68

REFERENCE EXAMPLE 4

To a solution of 3,5-dimethyl-4-nitropyridine-1-oxide (2.0 g) in 2,2,3,3,3-pentafluoropropanol (10 g) was added at 0° C. little by little potassium t-butoxide (2 g) over 15 minutes. The mixture was stirred at 60° C. for 18 hours. To the reaction mixture was added chloroform, which was subjected to filtration with celite. The filtrate was chromatographed on a column of silica gel (80 g), eluted with ethyl acetate-hexane (1:1), then with 20% methanol-ethyl acetate, and recrystallized from ether-hexane to yield 2.6 g of 3,5-dimethyl-4-(2,2,3,3,3-pentafluoropropoxy)pyridine-1-oxide as crystals, m.p. 89°–91° C.

By this process, compounds (X) were prepared from compounds (IX).

		Compound (X)	
R^2	R^3	R^4	Melting point (°C.)
CH_3	H	CH_2CF_3	82–94
CH_3	CH_3	CH_2CF_3	138–139

REFERENCE EXAMPLE 5

A mixture of 3,5-dimethyl-4-(2,2,3,3,3-pentafluoropropoxy)pyridine-1-oxide (2.5 g) and dimethyl sulfate (1 ml) was heated at 120° C. for 30 minutes, to which was then added methanol (12.5 ml). To the mixture was added dropwise at 80° C. ammonium persulfate (4.3 g) dissolved in water (20 ml)-methanol (10 ml) over 30 minutes, which was stirred for further 30 minutes. The resultant solution was concentrated. To the residue was added ice, which was neutralized with sodium carbonate, followed by extraction with chloroform. The extract was dried on sodium sulfate, followed by removing the solvent by evaporation to give 2.2 g of 3,5-dimethyl-2-hydroxymethyl-4-(2,2,3,3,3-pentafluoropropoxy)pyridine as an oily substance.

By this process, compounds (VIII) were prepared from compounds (X).

		Compound (VIII)	
R^2	R^3	R^4	Melting point (°C.)
H	CH_3	CH_2CF_3	116–119
CH_3	CH_3	CH_2CF_3	62–63

EXAMPLE 1

To a solution of 2-hydroxymethyl-3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)pyridine (350 mg) in chloroform (10 ml) was added thionyl chloride (0.2 ml). The mixture was refluxed for 30 minutes, which was then concentrated. The residue was dissolved in methanol (5 ml). The solution was added to a mixture of 2-mercaptobenzimidazole (200 mg), 28% sodium methoxide solution (1 ml) and methanol (6 ml), which was refluxed for 30 minutes. From the resultant was removed methanol by evaporation. To the residue was added water, which was subjected to extraction with ethyl acetate. The extract was washed with a dilute sodium hydroxide solution, followed by drying on magnesium sulfate. From the resultant was removed the solvent by evaporation. The residue was then chromatographed on a column of silica gel (20 g), eluted with ethyl acetate-hexane (2:1), and then recrystallized from ethyl acetate-hexane to yield 370 mg of 2-[3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)-pyrid-2-yl]methylthiobenzimidazole.½ hydrate as colorless plates, m.p. 145°–146° C.

By this process, compounds (I) (n=0) were prepared by allowing compounds (II) to react with compounds (III).

Compound (I) (n = 0)				
R^1	R^2	R^3	R^4	Melting point (°C.)
H	H	H	CH_2CF_3	138–139
H	CH_3	H	CH_2CF_3	149–150
H	H	CH_3	CH_2CF_3	168–170
H	CH_3	CH_3	CH_2CF_3	151.5–152.0
H	H	H	$CH_2CF_2CF_3$	125–126
H	H	CH_3	$CH_2CF_2CF_3$	151–152
H	H	H	$CH_2CF_2CF_2H$	Oily*3
H	CH_3	H	$CH_2CF_2CF_2H$	134–135
H	H	CH_3	$CH_2CF_2CF_2H$	148–149
H	CH_3	CH_3	$CH_2CF_2CF_3$	158–160
*4 5-CF_3	CH_3	H	CH_2CF_3	92–93
5-OCH_3	CH_3	H	CH_2CF_3	159–160
5-OCH_3	H	H	CH_2CF_3	152–153

*3NMR spectrum ($CDCl_3$)δ: 4.35(S), 4.39 (t,t,J=1.5 and 12 Hz), 5.98 (1H,t,t,J=52.5 and 4 Hz), 6.81 (1H,d,d,J=2 and 6 Hz) 6.95 (1H,d,J=2Hz), 7.1–7.3 (2H,m), 7.4–7.7 (2H,m), 8.50 (1H,d,J=6 Hz)
*4 ½H_2O (crystal water)

EXAMPLE 2

To a solution of 2-[3-methyl-4-(2,2,3,3,3,-pentafluoropropoxy)pyrid-2-yl-methylthiobenzimidazole (2.2 g) in chloroform (20 ml) was added dropwise under ice-cooling over a period of 30 minutes m-chloroperbenzoic acid (1.3 g) dissolved in chloroform (15 ml). The solution was washed with a saturated aqueous solution of sodium hydrogen carbonate, then dried on magnesium sulfate, and concentrated. The residue was chromatographed on a column of silica gel (50 g), eluted with ethyl acetate, and then recrystallized from aceton-isopropyl ether to give 1.78 g of 2-[3-methyl-4-(2,2,3,3,3-pentafluoropropxy)pyrid-2-yl]methylsulfinylbenzimidazole as pale yellow prisms, m.p. 161°–163° C. (decomp.).

By this process, compounds (I) (n=1) were prepared from compounds (I) (n=0).

Compound (I) (n = 1)				
R^1	R^2	R^3	R^4	Melting point (°C.)
H	H	H	CH_2CF_3	176–177

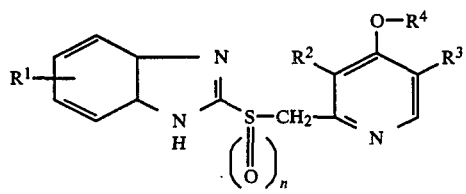
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Compound (I) (n = 1)				
R^1	R^2	R^3	R^4	Melting point (°C.)
H	CH_3	H	CH_2CF_3	178–182(d)
H	H	CH_3	CH_2CF_3	175–177(d)
H	CH_3	CH_3	CH_2CF_3	177–178(d)
H	H	H	$CH_2CF_2CF_3$	148–150(d)
H	H	CH_3	$CH_2CF_2CF_3$	145–148(d)
H	H	H	$CH_2CF_2CF_2H$	132–133
H	CH_3	H	$CH_2CF_2CF_2H$	147–148(d)
H	H	CH_3	$CH_2CF_2CF_2H$	136–139(d)
H	CH_3	CH_3	$CH_2CF_2CF_3$	157–159
5-CF_3	CH_3	H	CH_2CF_3	161–162(d)
5-OCH_3	CH_3	H	CH_2CF_3	140.5–142(d)
5-OCH_3	H	H	CH_2CF_3	162–163(d)

(Note) (d): decomposition

What we claim is:

1. A compound of the formula



wherein R^1 is hydrogen, methoxy or trifluoromethyl, R^2 and R^3 are independently hydrogen or methyl, R^4 is a C_{2-5} fluorinated alkyl and n denotes 0 or 1, and a pharmacologically acceptable salt thereof.

2. A compound according to claim 1, wherein R^1 is hydrogen.

3. A compound according to claim 1, wherein R^1 is methoxy.

4. A compound according to claim 1, wherein R^2 is hydrogen.

5. A compound according to claim 1, wherein R^2 is methyl.

6. A compound according to claim 1, wherein R^3 is hydrogen.

7. A compound according to claim 1, wherein R^3 is methyl.

8. A compound according to claim 1, wherein R^4 is a C_{2-3} fluorinated alkyl.

9. A compound according to claim 1, wherein the compound is 2-[4-(2,2,2-trifluoroethoxy)-pyrid-2-yl]methylsulfinylbenzimidazole.

10. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-pyrid-2-yl]methylsulfinylbenzimidazole.

11. A compound according to claim 1, wherein the compound is 2-[4-(2,2,2-trifluoroethoxy)-5-methyl-pyrid-2-yl]methylsulfinylbenzimidazole.

12. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-5-methyl-pyrid-2-yl]methylsulfinylbenzimidazole.

13. A compound according to claim 1, wherein the compound is 2-[4-(2,2,3,3,3-pentafluoropropoxy)-pyrid-2-yl]methylsulfinylbenzimidazole.

14. A compound according to claim 1, wherein the compound is 2-[4-(2,2,3,3,3-pentafluoropropoxy)-5-methyl-pyrid-2-yl]methylsulfinylbenzimidazole.

15. A compound according to claim 1, wherein the compound is 2-[4-(2,2,3,3-tetrafluoropropoxy)-pyrid-2-yl]methylsulfinylbenzimidazole.

16. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)-pyrid-2-yl]methylsulfinylbenzimidazole.

17. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,3,3-tetrafluoropropoxy)-pyrid-2-yl]methylsulfinylbenzimidazole.

18. A compound according to claim 1, wherein the compound is 2-[5-methyl-4-(2,2,3,3-tetrafluoropropoxy)-pyrid-2-yl]methylsulfinylbenzimidazole.

19. A compound according to claim 1, wherein the compound is 2-[3,5-dimethyl-4-(2,2,3,3,3-pentafluoropropoxy)-pyrid-2-yl]methylsulfinylbenzimidazole.

20. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-pyrid-2-yl]methylsulfinyl-5-trifluoromethylbenzimidazole.

21. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-pyrid-2-yl]methylsulfinyl-5-methoxybenzimidazole.

22. A compound according to claim 1, wherein the compound is 2-[4-(2,2,2-trifluoroethoxy)-pyrid-2-yl]-methylsulfinyl-5-methoxybenzimidazole.

23. A compound according to claim 1, wherein the compound is 2-[4-(2,2,2-trifluoroethoxy)-pyrid-2-yl]-methylthiobenzimidazole.

24. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-pyrid-2-yl]methylthiobenzimidazole.

25. A compound according to claim 1, wherein the compound is 2-[5-methyl-4-(2,2,2-trifluoroethoxy)-pyrid-2-yl]methylthiobenzimidazole.

26. A compound according to claim 1, wherein the compound is 2-[3,5-dimethyl-4-(2,2,2-trifluoroethoxy)-pyrid-2-yl]methylthiobenzimidazole.

27. A compound according to claim 1, wherein the compound is 2-[4-(2,2,3,3,3-pentafluoropropoxy)-pyrid-2-yl]methylthiobenzimidazole.

28. A compound according to claim 1, wherein the compound is 2-[5-methyl-4-(2,2,3,3,3-pentafluoropropoxy)-pyrid-2-yl]methylthiobenzimidazole.

29. A compound according to claim 1, wherein the compound is 2-[4-(2,2,3,3-tetrafluoropropoxy)-pyrid-2-yl]methylthiobenzimidazole.

30. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,3,3-tetrafluoropropoxy)-pyrid-2-yl]methylthiobenzimidazole.

31. A compound according to claim 1, wherein the compound is 2-[5-methyl-4-(2,2,3,3-tetrafluoropropoxy)-pyrid-2-yl]methylthiobenzimidazole.

32. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)-pyrid-2-yl]methylthiobenzimidazole.

33. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)-5-methyl-pyrid-2-yl]methylthiobenzimidazole.

34. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-pyrid-2-yl-methylthio-5-trifluoromethylbenzimidazole.

35. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-pyrid-2-yl-methylthio-5-methoxybenzimidazole.

36. A compound according to claim 1, wherein the compound is 2-[4-(2,2,2-trifluoroethoxy)-pyrid-2-yl]methylthio-5-methoxybenzimidazole.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

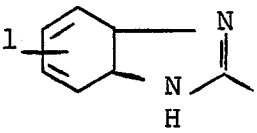
CERTIFICATE OF CORRECTION

PATENT NO. : 4,628,098

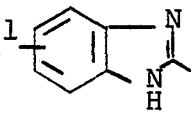
DATED : December 9, 1986 Page 1 of 2

INVENTOR(S) : Akira NOHARA et al

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

In the Abstract delete "

"

and insert --

--.

In column 1, line 40, delete " (O)n" and insert --(O) n--.

In column 4, line 52, delete "raction" and insert --reaction--.

In column 6, line 10, delete " (O)n and insert --(O)n--.

In column 9, line 49, delete "pyrid-2-yl-methyl" and insert --pyrid-2-yl]methyl--.

UNITED STATES PATENT AND TRADEMARK OFFICE

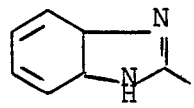
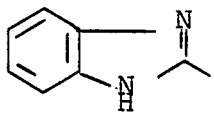
CERTIFICATE OF CORRECTION

PATENT NO. : 4,628,098

DATED : December 9, 1986

INVENTOR(S) : Akira NOHARA et al

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

In column 10, line 23, claim 1, delete "R^1  " and insert --R^1  --.

Signed and Sealed this

Twelfth Day of April, 1988

Attest:

DONALD J. QUIGG

Attesting Officer

Commissioner of Patents and Trademarks

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE EXTENDING PATENT TERM UNDER 35 U.S.C. § 156

PATENT NO.	:	4,628,098
ISSUED	:	December 9, 1986
INVENTOR(S)	:	Akira Nohara et al.
PATENT OWNER	:	Takeda Chemical Industries Ltd.

This is to certify that there has been presented to the

COMMISSIONER OF PATENTS AND TRADEMARKS

an application under 35 U.S.C. § 156 for an extension of the patent term. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

1381 days

from the original expiration date of the patent, July 29, 2005, with all rights pertaining thereto as provided by 35 U.S.C. § 156(b).

I have caused the seal of the Patent and Trademark Office to be affixed this 6th day of January 1997.

Bruce A. Lehman
Assistant Secretary of Commerce and
Commissioner of Patents and Trademarks

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE EXTENDING PATENT TERM UNDER 35 U.S.C. § 156

PATENT NO.	:	4,628,098
ISSUED	:	December 9, 1986
INVENTOR(S)	:	Akira Nohara et al.
PATENT OWNER	:	Takeda Chemical Industries Ltd.

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COMMISSIONER OF PATENTS AND TRADEMARKS

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I have caused the seal of the Patent and Trademark Office to be affixed this 6th day of January 1997.

Bruce A. Lehman
Assistant Secretary of Commerce and
Commissioner of Patents and Trademarks

EXHIBIT B

United States Patent [19]

Makino et al.

[11] **Patent Number: 5,045,321**

[45] **Date of Patent: Sep. 3, 1991**

[54] **STABILIZED PHARMACEUTICAL COMPOSITION AND ITS PRODUCTION**

[75] Inventors: **Tadashi Makino; Tetsuro Tabata,** both of Osaka; **Shin-ichiro Hirai,** Kyoto, all of Japan

[73] Assignee: **Takeda Chemical Industries, Ltd.,** Osaka, Japan

[21] Appl. No.: **14,303**

[22] Filed: **Feb. 13, 1987**

[30] **Foreign Application Priority Data**

Feb. 13, 1986 [JP] Japan 61-29567
Feb. 21, 1986 [JP] Japan 61-38059

[51] **Int. Cl.**[5] **A61K 9/30;** A61K 9/16; A61K 33/12; A61K 33/10

[52] **U.S. Cl.** **424/475;** 424/495; 424/683; 424/686; 424/692; 514/394; 514/395; 514/925; 514/927

[58] **Field of Search** 514/970, 338, 155, 156, 514/157, 394, 395, 925, 927; 424/475, 495, 683, 686, 692

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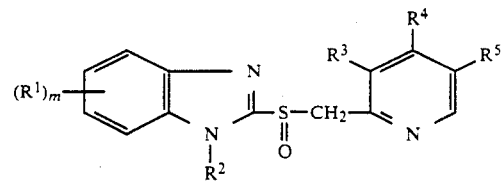
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Primary Examiner—Frederick E. Waddell
Assistant Examiner—Kevin E. Weddington
Attorney, Agent, or Firm—Wegner, Cantor, Mueller & Player

[57] **ABSTRACT**

The pharmaceutical composition of the invention, which comprises a benzimidazole compound of the formula



wherein R^1 is hydrogen, alkyl, halogen, cyano, carboxy, carboalkoxy, carboalkoxyalkyl, carbamoyl, carbamoylaklyl, hydroxy, alkoxy, hydroxyalkyl, trifluoromethyl, acyl, carbamoyloxy, nitro, acyloxy, aryl, aryloxy, alkylthio or alkylsulfinyl, R^2 is hydrogen, alkyl, acyl, carboalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, alkylcarbonylmethyl, alkoxycarbonylmethyl or alkylsulfonyl, R^3 and R^5 are the same or different and each is hydrogen, alkyl, alkoxy or alkoxyalkoxy, R^4 is hydrogen, alkyl, alkoxy which may optionally be fluorinated, or alkoxyalkoxy, and m is an integer of 0 through 4, and a basic inorganic salt of magnesium and/or a basic inorganic salt of calcium, is physically stable.

3 Claims, No Drawings

STABILIZED PHARMACEUTICAL COMPOSITION AND ITS PRODUCTION

This invention relates to a pharmaceutical composition which comprises 2-[(2-pyridyl)methylsulphinyl]-benzimidazole or a derivative thereof (hereinafter sometimes referred to collectively as "benzimidazole compounds"), which is useful as an antiulcer agent, as stabilized by incorporation of a basic inorganic salt of magnesium and/or a basic inorganic salt of calcium and its production.

Certain benzimidazole compounds are recently under clinical study as gastric acid secretion inhibitors. They serve as therapeutic agents for digestive ulcer. Their principal pharmacological effect consists in gastric acid secretion suppression based on $(H^+ + K^+)$-ATPase inhibition and is more potent and durable as compared with histamine H_2 receptor antagonists such as cimetidine and ranitidine. They also have gastric mucosa protecting activity. Therefore, they have attracted attention as next-generation potent therapeutic agents for digestive ulcer.

Those benzimidazole compounds which are described in Japanese Unexamined Patent laid open Nos. 62275/77, 141783/79, 53406/82, 135881/83, 192880/83 and 181277/84, corresponding to U.S. Pat. No. 4,045,563, U.S. Pat. No. 4,255,431, European Patent Publication No. 45,200, U.S. Pat. No. 4,472,409, European Patent Publication No. 5,129 and G.B. Patent Publication No. 2,134,523A, respectively, among others are known to have antiulcer activity.

These compounds, however, are poor in stability. In solid state, they are susceptible to heat, moisture and light and, in aqueous solution or suspension, their stability decreases with decreasing pH. In dosage forms, i.e. tablets, powders, fine granules, granules and capsules, said compounds are apt to interact with other components contained in said dosage forms and accordingly are in less stable state as compared with the case where they occur alone. Thus, the content decreases and the color changes significantly in the manufacturing process of dosage form and with the lapse of time. Microcrystalline cellulose, polyvinylpyrrolidone (PVP), carboxymethylcellulose calcium, polyethylene glycol 6000 and Pluronic F68 (polyoxyethylenepolyoxypropylene copolymer), for instance are dosage form components adversely affecting the stability of said compounds. Furthermore, in the case of coated tablets and coated granules among the above dosage forms, enteric coating bases such as cellulose acetate phthalate, hydroxypropylmethylcellulose acetate succinate and Eudragit (methacrylic acid-acrylic acid copolymer) have poor compatibility with said compounds and cause content decrease and color change. Nevertheless, one or more of these components or ingredients, which, as mentioned above, can produce adverse effects on the stability of said compounds, are essential in the manufacture of oral preparations and therefore difficulties are inevitably encountered in dosage form manufacture.

The prior art avoids the above-mentioned stability problem by using said benzimidazole compounds in a salt form, say in the form of a lithium, sodium, potassium, magnesium, calcium or titanium salt [Japanese Unexamined Patent laid open No. 167587/84 (European Patent Publication No. 124,495A)]

However, the above prior art method requires, for the stabilization of the benzimidazole compounds, a step

of converting said compounds to such a salt form as mentioned above in advance.

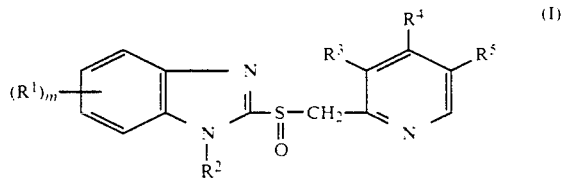
In view of the above, the present inventors made investigations in an attempt to stabilize pharmaceutical preparations containing benzimidazole compounds and, as a result, have completed the present invention.

Thus, this invention relates to

(1) A pharmaceutical composition which comprises 2-[(2-pyridyl)methylsulfinyl]benzimidazole or a derivative thereof, which has an antiulcer activity, and a basic inorganic salt of magnesium and/or a basic inorganic salt of calcium, and

(2) A method of producing a stabilized pharmaceutical composition which comprises incorporating a basic inorganic salt of magnesium and/or a basic inorganic salt of calcium in a pharmaceutical composition containing 2-[(2-pyridylmethylsulfinyl]benzimidazole or a derivative thereof, which has an antiulcer activity.

The benzimidazole compounds having an antiulcer activity which are to be used in the practice of the invention are those compounds which are described in the above-cited laid-open patent specifications, for instance and are represented by the formula



wherein R^1 is hydrogen, alkyl, halogen, cyano, carboxy, carboalkoxy, carboalkoxyalkyl, carbamoyl, carbamoylalkyl, hydroxy, alkoxy, hydroxyalkyl, trifluoromethyl, acyl, carbamoyloxy, nitro, acyloxy, aryl, aryloxy, alkylthio or alkylsulfinyl, R^2 is hydrogen, alkyl, acyl, carboalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, alkylcarbonylmethyl, alkoxycarbonylmethyl or alkylsulfonyl, R^3 and R^5 are the same or different and each is hydrogen, alkyl, alkoxy or alkoxyalkoxy, R^4 is hydrogen, alkyl, alkoxy which may optionally be fluorinated, or alkoxyalkoxy, and m is an integer of 0 through 4.

The compounds of the formula(I) can be produced by the methods described in the above-cited laid-open patent specifications or modifications thereof.

In the following, brief mention is made of the substituents in those compounds which have the formula (I) and are already known.

Referring to R^1 in the above formula, C_{1-7} alkyls may be mentioned as the alkyl represented by R^1; C_{1-4} alkoxys as the alkoxy moiety of the carboalkoxy; C_{1-4} alkoxys as the alkoxy moiety of the carboalkoxyalkyl and C_{1-4} alkyls as the alkyl moiety; C_{1-4} alkyls as the alkyl moiety of the carbamoylalkyl; C_{1-5} alkoxys as the alkoxy; C_{1-7} alkyls as the alkyl moiety of the hydroxyalkyl; C_{1-4}alkanoyls as the acyl; phenyl as the aryl; phenyl as the aryl moiety of the aryloxy; C_{1-6} alkyls as the alkyl moiety of the alkylthio; and C_{1-6} alkyls as the alkyl moiety of the alkylsulfinyl.

Referring to R^2, C_{1-5} alkyls may be mentioned as the alkyl represented by R^2; C_{1-4} alkanoyls as the acyl; C_{1-4} alkoxys as the alkoxy moiety of the carboalkoxy; C_{1-4} alkyls as the alkyl moiety of the alkylcarbamoyl; C_{1-4} alkyls as each of the alkyl moieties of the dialkylcarbamoyl; C_{1-4} alkyls as the alkyl moiety of the alkylcarbonyl-

methyl; C_{1-4} alkoxys as the alkoxy moiety of the alkoxycarbonylmethyl; and C_{1-4} alkyls as the alkyl moiety of the alkylsulfonyl.

Referrring to R^3, R^4 and R^5, C_{1-4} alkyls may be mentioned as the alkyl represented by any of them; C_{1-8} alkoxys as the alkoxy; and C_{1-4} alkoxys as each of the alkoxy moieties of the alkoxyalkoxy.

Referring to R^4, C_{1-8} alkoxys may be mentioned as the alkoxy, which may optionally be fluorinated.

Among those compounds of the above forumula (I), (1) the compounds of which R^1 is hydrogen, methoxy or trifluoromethyl, R^2 is hydrogen, R^3 and R^5 are the same or different and each is hydrogen or methyl, R^4 is fluorinated C_{2-5} alkoxy and m is 1, (2) the compounds of which R^1 is hydrogen, fluorine, methoxy or trifluoromethyl, R^2 is hydrogen, R^3 is hydrogen or methyl, R^4 is C_{3-8} alkoxy, R^5 is hydrogen and m is 1, and (3) the compounds of which R^1 is hydrogen, fluorine, methoxy or trifluoromethyl, R^2 is hydrogen, R^3 is C_{1-8} alkoxy, R^4 is C_{1-8} alkoxy which may be fluorinated, R^5 is hydrogen and m is 1.

Detailed mention is now made of the substituents in such novel compounds.

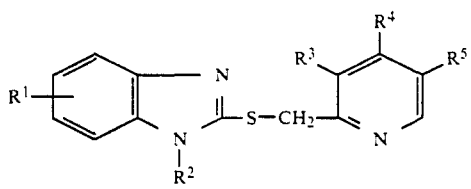
Referring to R^3, the lower alkyl represented thereby is preferably C_{1-8} lower alkoxy such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentyloxy, hexyloxy, heptyloxy or octyloxy and more preferably C_{1-4} lower alkoxy.

Referring to R^4, C_{1-8} lower alkoxys may be mentioned as the lower alkoxy, which may optionally be fluorinated, and preferred examples are as mentioned above for R^3. As the fluorinated lower alkoxy, there may be mentioned, for example, 2,2,2-trifluoroethoxy, 2,2,3,3,3-pentafluoropropoxy, 1-(trifluoromethyl)-2,2,2-trifluoroethoxy, 2,2,3,3-tetrafluoropropoxy, 2,2,3,3,4,4,4-heptafluorobutoxy and 2,2,3,3,4,4,5,5-octafluoropentoxy, and fluorinated C_{2-4} lower alkoxys are preferred.

The position of R^1 is position 4 or position 5, preferably position 5.

Some methods of producing the above novel compounds [hereinafter referred to as "compounds of formula (I')"] are described below.

Said compounds can be produced by subjecting a compound of the formula



(II)

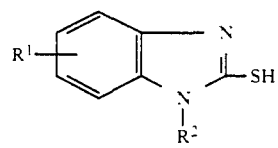
wherein R^1–R^5 are as defined above, to oxidation.

The oxidizing agent to be used is, for example, metachloroperbenzoic acid, peracetic acid, trifluoroperacetic acid, permaleic acid or the like peracid, sodium bromite or sodium hypochlorite. Examples of the solvent to be used in carrying out the reaction are halogenated hydrocarbons such as chloroform and dichloromethane, ethers such as tetrahydrofuran and dioxane, amides such as dimethylformamide, and water. These solvents may be used either singly or in admixture. Said oxidizing agent is used preferably in an amount approximately equivalent or slightly excessive relative to the compound (II). Thus, said agent is used in an amount of about 1–3 equivalents, more preferably about 1 to 1.5 equivalents. The reaction is carried out at a temperature from about 0° C. (ice cooling) to around the boiling point of the solvent used, generally at a temperature from about 0° C. (ice cooling) to room temperature, preferably at a temperature of about 0° C. to 10° C. The reaction time is generally about 0.1 to 24 hours, preferably about 0.1 to 4 hours.

The desired novel compounds (I') produced by the above reaction can be isolated and purified by conventional means such as recrystallization, chromatography and so on.

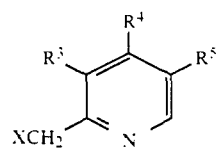
Said compounds may be converted to pharmacologically acceptable salts by conventional means. As such salts, there may be mentioned hydrochloride, hydrobromide, hydroiodide, phosphate, nitrate, sulfate, acetate and citrate, among others.

The novel compounds (II) can be produced by reacting a starting compound of the formula



(III)

wherein R^1 and R^2 are as defined above, with a starting compound of the formula



(IV)

wherein R^3–R^5 are as defined above and X is a halogen atom.

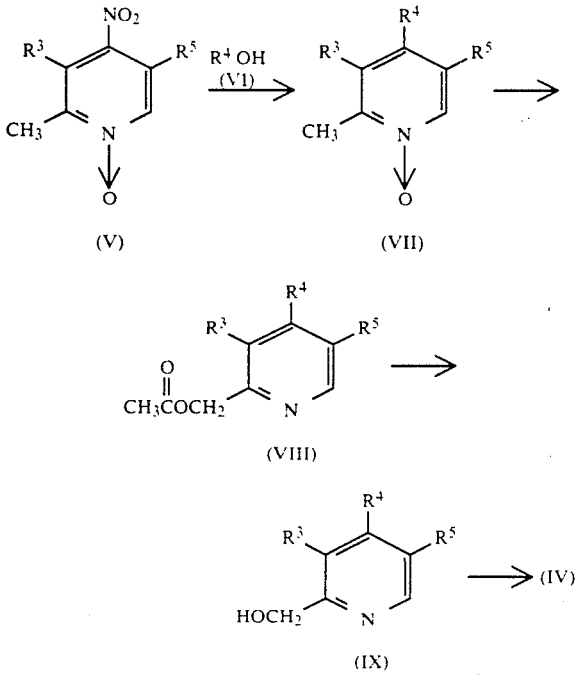
The halogen atom represented by X is, for example, chlorine, bromine or iodine.

The reaction is carried out advantageously in the presence of a base. As said base, there may be mentioned alkali metal hydrides such as sodium hydride and potassium hydride, alkali metals such as metallic sodium, sodium alcoholates such as sodium methoxide and sodium ethoxide, alkali metal carbonates such as potassium carbonate and sodium carbonate, and organic amines such as triethylamine, among others. As the solvent to be used in carrying out the reaction, there may be mentioned, for example, alcohols such as methanol and ethanol, and dimethylformamide. The base is used generally in an amount slightly excessive relative to the equivalent amount but may also be used in large excess. Thus, it is used in an amount of about 2–10 equivalents, preferably about 2–4 equivalents. The above reaction is carried out generally at a temperature of about 0° C. to around the boiling point of the solvent used, preferably at about 20° C. to 80° C., for a period of about 0.2–24 hours, preferably about 0.5–2 hours.

Some methods of producing the starting compounds (IV) are described below.

Among the compounds (IV), those compounds wherein R^3 and R^5 are the same or different and each is hydrogen or methyl and R^4 is fluorinated C_{2-5} alkoxy or C_{3-8} alkoxy can be produced by the following process:

Process (1)



A nitro compound of the formula (V), wherein R^3 and R^5 are as defined above, is reacted with an alcohol derivative of the formula $R^{4'}OH$ (VI) wherein $R^{4'}$ is fluorinated C_{2-5} alkyl or C_{3-8} alkyl, in the presence of a base to give an alkoxy derivative of the formula (VII) wherein R^3, R^4 and R^5 are as defined above. The base to be used in carrying out the reaction includes, among others, alkali metals such as lithium, sodium and potassium, alkali metal hydrides such as sodium hydride and potassium hydride, alcoholates such as potassium t-butoxide and sodium propoxide, alkali metal carbonates and hydrogen carbonates such as potassium carbonate, lithium carbonate, sodium carbonate, potassium hydrogen carbonate and sodium hydrogen carbonate, and alkali metal hydroxides such as sodium hydroxide and potassium hydroxide. The alcohol derivative to be submitted to the reaction includes, among others, propanol, isopropanol, butanol, pentanol, hexanol, 2,2,2-trifluoroethanol, 2,2,3,3,3-pentafluoropropanol, 2,2,3,3-tetrafluoropropanol, 1-(trifluoromethyl)-2,2,2-trifluoroethanol, 2,2,3,3,4,4,4-heptafluorobutanol and 2,2,3,3,4,4,5,5-octafluoropentanol. While $R^{4'}OH$ itself may be used as a solvent in carrying out the reaction, ethers such as tetrahydrofuran and dioxane, ketones such as acetone and methyl ethyl ketone, acetonitrile, dimethylformamide and hexamethylphosphoric acid triamide, for instance, may also be used as solvents. An appropriate reaction temperature may be selected within the range of about 0° C. (ice cooling) to around the boiling point of the solvent used. The reaction time is about 1–48 hours.

Heating (about 80°–120° C.) of the thus-obtained compound (VII) with acetic anhydride alone or in the presence of an inorganic acid such as sulfuric acid or perchloric acid gives an 2-acetoxymethylpyridine derivative of the formula (VIII) wherein R^3, R^4 and R^5 are as defined above. The reaction period is generally about 0.1–10 hours.

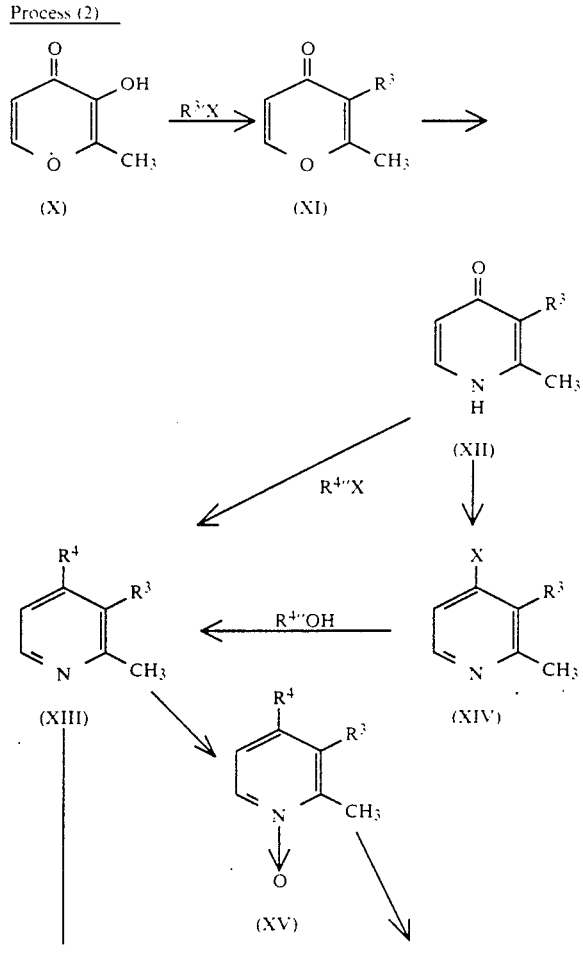
The subsequent alkaline hydrolysis of the compound (VIII) gives a 2-hydroxymethylpyridine derivative of the formula (IX). Sodium hydroxide, potassium hydroxide, potassium carbonate and sodium carbonate, for instance, are usable as alkalis, and methanol, ethanol and water, among others, are usable as solvents. The reaction is generally conducted at about 20°–60° C. for about 0.1–2 hours.

The compound (IX) is further halogenated with a chlorinating agent such as thionyl chloride to give a 2-halomethylpyridine derivative of the formula (IV) wherein R^3, R^4 and R^5 are as defined above and X is chlorine, bromine or iodine. Usable as solvents are, for example, chloroform, dichloromethane and tetrachloroethane. The reaction is generally carried out at about 20–80° C. for about 0.1–2 hours.

The compound (IV) thus produced occurs in the form of a salt of hydrohalogenic acid corresponding to the halogenating agent used and it is generally preferable to subject said compound to reaction with the compound (III) immediately.

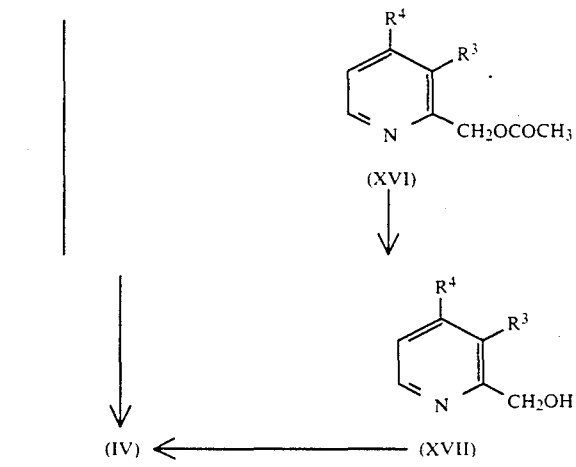
Among the compounds (V), those compounds wherein R^3 is C_{1-8} lower alkoxy, R^4 is alkoxy which may optionally be fluorinated, and R^5 is hydrogen can be produced by the following process:

Process (2)



-continued

Process (2)



Thus, maltol (X) is reacted with a alkyl halide of the formula R^3X in the presence of silver oxide, for instance, to give a compound of the formula (XI). Reaction of (XI) with aqueous ammonia gives a pyridone derivative of the formula (XII). Direct alkylation of the compound (XII) with an alkyl halide, or halogenation of (XII) with a halogenating agent such as phosphorus oxychloride followed by reaction of the resultant halo derivative (XIV) with a lower alcohol of the formula R^4OH in the presence of a base gives a compound of the formula (XIII). The compound (XIII) can be converted to the compound (IV) by direct halogenation with N-bromosuccinimide or chlorine, for instance. The compound (XIII) may also be converted to the compound (IV) by oxidizing the same with an oxidizing agent such as m-chloroperbenzoic acid, reacting the resulting compound (XV) with acetic anhydride, hydrolyzing the resulting comppund (XVI) and halogenating the resulting compound (XVII) with a halogenating agent such as thionyl chloride.

The alkyl halide to be used in the production of the compound (XI) includes, among others, methyl iodide, ethyl iodide, propyl iodide, isopropyl iodide, butyl iodide, pentyl iodide and hexyl iodide, and the alkyl halide to be used in the production of the compound (XIII) further includes, in addition to those mentioned above for use in the production of the compounds (XI), 2,2,2-trifluoroethyl iodide, 2,2,3,3,3-pentafluoropropyl iodide, 2,2,3,3-tetrafluoropropyl iodide, 1-(trifluoromethyl)-2,2,2-trifluoroethyl iodide, 2,2,3,3,4,4,4-heptafluorobutyl iodide and 2.2,3,3,4,4,5,5-octafluoropentyl iodide, for instance. Such alkyl iodides are used in an amount of about 1–10 equivalents. Silver oxide, potassium carbonate, sodium carbonate or the like is used as a deacidifying agent and dimethylformamide, dimethylacetamide or the like is used as a solvent. The reaction is generally carried out at room temperature.

The halogenating agent to be used in the production of the compound (XIV) includes, among others, phosphorus oxychloride, phosphorus pentoxide and phosphorus tribromide and is used in an amount of 1 equivalent to a large excess. The reaction is carried out at a temperature of about 50°–150° C. The alcohol to be used for the conversion of compound (XIV) to compound (XIII) includes methanol and ethanol and further those alcohol derivaitves mentioned for use in process 1) and is used in an amount of 1 equivalent to a large excess, and the base includes those sodium alcoholates and potassium alcoholates which correspong to the respective alcohols as well as potassium t-butoxide, sodium hydride and so forth. An appropriate reaction temperature may be selected within the range of room temperature to the boiling point of the solvent used.

For direct bromination of the compound (XIII) with N-bromosuccinimide, the reaction is preferably carried out under light irradiation, and carbon tetrachloride, chloroform, tetrachloroethane or the like is used as a solvent.

The oxidizing agent to be used for the conversion of compound (XIII) to compound (XV) includes, among others, peracids such as meta-chloroperbenzoic acid, peracetic acid, trifluoroperacetic acid and permaleic acid as well as hydrogen peroxide. Usable as solvents for the reaction are halogenated hydrocarbons such as chloroform and dichloromethane, ethers such as tetrahydrofuran and dioxane, amides such as dimethylformamide, acetic acid and water, for instance, and these can be used either singly or in admixture. Said oxidizing agent is preferably used in an amount of about 1 equivalent to an excess relative to the compound (XIII), more preferably about 1–10 equivalents. The reaction is carried out at a temperature of about 0° C. (ice cooling) to around the boiling point of the solvent used generally for a period of about 0.1–24 hours, preferably for about 0.1–4 hours.

The conversion of compound (XV) to compound (XVI) is effected by heating (at about 80°–120° C.) the compound (XV) with acetic anhydride alone or in the presence of an inorganic acid such as sulfuric acid or perchloric acid and so on. The reaction period is generally 0.1–10 hours.

The alkali to be used in the alkaline hydrolysis of compound (XVI) to compound (XVII) includes, among others, sodium hydroxide, potassium hydroxide, potassium carbonate and sodium carbonate. Methanol, ethanol and water, for instance, may be mentioned as usable solvents. The reaction is generally carried out at a temperature of about 20°–60° C. for a period of about 0.1–2 hours.

For the production of compound (IV) from compound (XVII), a chlorinating agent such as thionyl chloride or an organic sulfonic or organic phosphoric acid chloride such as methanesulfonyl chloride, p-toluenesulfonyl chloride or diphenylphosphoryl chloride is used. When a chlorinating agent such as thionyl chloride is used, it is used in an amount of 1 equivalent to a large excess relative to the compound (XVII) and a solvent such as chloroform, dichloromethane or tetrachloroethane is used, and the reaction is generally carried out at a temperature of about 20°–80° C. for a period of about 0.1–2 hours. When an organic sulfonic or organic phosphoric acid chloride is used, it is used in an amount of 1 equivalent to a slight excess relative to the compound (XVII) and the reaction is generally carried out in the presence of a base. As usable bases, there may be mentioned organic bases such as triethylamine and tributylamine and inorganic bases such as sodium carbonate, potassium carbonate and sodium hydrogen carbonate. The base is used in an amount of 1 equivalent to a slight excess. As usable solvents, there may be mentioned, for example, chloroform, dichloromethane, carbon tetrachloride and acetonitrile. An appropriate reaction temperature and an appropriate reaction can be selected within the ranges of about 0° C. (ice cooling) to

around the boiling point and several minutes to several hours, respectively.

The above-mentioned novel benzimidazole compounds have excellent gastric antisecretory activity, gastric mucosa-protecting activity and antiulcer activity but have low toxicity, so that they can be used in the treatment of digestive ulcers in mammals (e.g. mouse, rat, rabbit, dog, cat, human).

The basic inorganic salt of magnesium and that of calcium, which are to be used in accordance with the invention, are now described.

Said basic inorganic salt of magnesium includes, among others, heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metasilicate aluminate, magnesium silicate aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite [$Mg_6Al_2(OH)_{16}.CO_3.4H_2$)] and aluminum magnesium hydroxide [$2.5MgO.Al_2O_3.xH_2O$] and said basic inorganic salt of calcium includes, among others, precipitated calcium carbonate and calcium hydroxide. It is only required of such basic inorganic magnesium and calcium salts to show basicity (pH of not less than 7) when they are in the form of a 1% aqueous solution or suspension.

Said basic inorganic magnesium and calcium salts may be used either singly or in combination of two or more species in an amount which may vary depending on the kinds thereof but generally lies within the range of about 0.3–20 parts by weight, preferably about 0.6–7 parts by weight, per part by weight of the benzimidazole compounds.

The composition of the invention may further contain such additives as vehicles (e.g. lactose, corn starch, light silicic anhydride, microcrystalline cellulose, sucrose), binders (e.g. α-form starch, methylcellulose, carboxymethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone), disintegrating agents (e.g. carboxymethylcellulose calcium, starch, low substituted hydroxypropylcellulose), surfactants [e.g. Tween 80 (Kao-Atlas), Pluronic F68 (Asahi Denka; polyoxyethylene-polyoxypropylene copolymer], antioxidants (e.g. L-cysteine, sodium sulfite, sodium ascorbate), lubricants (e.g. magnesium stearate, talc), etc.

The composition of the invention is prepared by homogeneously admixing the above benzimidazole compound, the basic inorganic salt of magnesium and/or basic inorganic salt of calcium, and the above additives.

The particle sizes of said benzimidazole compound and said inorganic salt are not especially critical in a condition that they can be homogeneously admixed. For example, preferable perticle size is about less than 100 μm, more preferable one is about less than 20 μm.

The moisture amount in the composition is preferably about 6–60%, more preferably about 20–40% as equibrium relative humidity (E.R.H). The method of admixing is optional if the benzimidazole compound can finally be in contact with the basic inorganic salt of magnesium and/or of calcium evenly. Thus, for example, the additives may be admixed with a mixture of the benzimidazole compound and the basic inorganic salt of magnesium and/or calcium as prepared by preliminary admixing, or the basic inorganic salt of magnesium and/or of calcium may be added to a mixture of the benzimidazole compound and the additives as prepared by preliminary admixing.

Said mixture can be made up into dosage forms suited for oral administration, such as tablets, capsules, powders, granules and fine granules, by per se known means.

Tablets, granules and fine granules may be coated by a per se known method for the purpose of masking of the taste or providing them with enteric or sustained release property. Usable as coating agents are, for example, hydroxypropylmethylcellulose, ethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, polyoxyethylene glycol, Tween 80, Pluornic F68, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, Eudragit (Röhm, West Germany; methacrylic acid-acrylic acid copolymer) and pigments such as titanium oxide and ferric oxide.

Tablets, granules, powders, fine granules and capsules can be produced by a conventional method (e.g. the method described in the 10th edition of the Japanese Pharmacopeia under General Rules for Preparations). Thus, for example, tablets are produced by adding the basic inorganic salt of magnesium and/or of calcium to a mixture of the benzimidazole compound, vehicle and disintegrant, mixing, adding a binder, granulating the mixture, adding a lubricant etc. and tableting the resultant granular composition. Granules are produced by extrusion in approximately the same manner as in the production of tablets or by coating nonpareils, which contain sucrose and corn starch, with a mixture of benzimidazole compound, a basic inorganic salt of magnesium and/or a basic inorganic salt of calcium, and additives (e.g. sucrose, corn starch, crystalline cellulose, hydroxypropylcellulose, methylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone) Capsules are produced by mere mixing and filling. The dosage forms thus obtained show excellent stability with slight changes in appearance and little decreases in content even after storage for a long period of time.

The pharmaceutical composition of the present invention as obtained in the above manner exhibits excellent gastric antisecretory, gastric mucosa-protecting and antiulcer activities and has low toxicity and therefore can be used in the treatment of digestive ulcers in mammals (e.g. mouse, rat, rabbit, dog, cat, pig, human).

The pharmaceutical composition of the invention can be orally administered for the treatment of digestive ulcers in mammals in admixture with pharmacologically acceptable carriers, vehicles, diluents and so forth and in the form of capsules, tablets, granules and some other dosage forms, as mentioned hereinabove. The dose as the benzimidazole compound lies within the range of about 0.01 mg to 30 mg/kg/day, preferably about 0.1 mg to 3 mg/kg/day.

The following reference examples and working examples as well as the experimental examples described later herein illustrate the present invention in more detail but are by no means limitative of the present invention.

REFERENCE EXAMPLE 1

A mixture of 2,3-dimethyl-4-nitropyridine-1-oxide (2.0 g), methyl ethyl ketone (30 ml), 2,2,3,3,3-pentafluoropropanol (3.05 ml), anhydrous potassium carbonate (3.29 g) and hexamethylphosphoric acid triamide (2.07 g) was heated at 70°–80° C. with stirring for 4.5 days. Then, the insoluble matter was filtered off and the filtrate was concentrated. Water was added to the residue and the mixture was extracted with ethyl acetate. The extract layer was dried over magnesium sulfate, then the solvent was distilled off, and the residue was

applied to a silica gel column (50 g). Elution with chloroform-methanol (10:1) and recrystallization from ethyl acetate-hexane gave 2.4 g of 2,3-dimethyl-4-(2,2,3,3,3-pentafluoropropoxy)pyridine-1-oxide as colorless needles. Melting point 148°–149° C.

The following compounds (VII) were produced from the corresponding compounds (V) in the same manner as above.

	Compounds (VII)			
	R^3	R^5	R^4	Melting point (°C.)
	CH_3	H	OCH_2CF_3	131.0–131.5
Note 1	H	H	$OCH_2CH_2CH_3$	Oil
Note 2	CH_3	H	$OCH_2CH_2CH_3$	Oil

Note 1:
NMR spectrum ($CDCl_3$) δ: 1.01 (3H, t, J = 7 Hz), 1.81 (2H, m), 2.50 (3H, s), 3.93 (2H, t, J = 7 Hz), 6.50–6.80 (2H, m), 8.10 (1H, d, J = 7 Hz)
Note 2:
NMR spectrum ($CDCl_3$) δ: 1.07 (3H, t, J = 7.5 Hz), 1.65–2.02 (2H, m), 2.21 (3H, s), 2.52 (3H, s), 3.99 (2H, t, J = 6 Hz), 6.68 (1H, d, J = 6 Hz), 8.15 (1H, d, J = 6 Hz)

REFERENCE EXAMPLE 2

Concentrated sulfuric acid (2 drops) was added to a solution of 2,3-dimethyl-4-(2,2,3,3,3-pentafluoropropoxy)-pyridine-1-oxide (2.5 g) in acetic anhydride (8 ml) and the mixture was stirred at 110° C. for 2 hours and then concentrated. The residue was dissolved in methanol (30 ml), 2 N aqueous sodium hydroxide (20 ml) was added, and the mixture was stirred at room temperature for 2 hours. After concentration, water was added to the residue and the mixture was extracted with ethyl acetate. The extract was dried over magnesium sulfate, the solvent was then distilled off, and the residue was applied to a silica gel (50 g) column. Elution with chloroform-methanol (10:1) and recrystallization from isopropyl ether gave 1.6 g of 2-hydroxymethyl-3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)-pyridine as a brown oil.

NMR spectrum ($CDCl_3$) δ: 2.07 (3H, s), 4.28 (1H, brs), 4.49 (2H, t, J=12 Hz), 4.67 (2H, s), 6.69 (1H, d, J=5 Hz), 8.34 (1H, d, J=5 Hz)

The following compounds (IX) were produced from the corresponding compounds (VII) in the same manner as mentioned above.

	Compounds (IX)			
	R^3	R^5	R^4	Melting point (°C.)
	CH_3	H	OCH_2CF_3	93.5–94.0
Note 1	H	H	$OCH_2CH_2CH_3$	Oil
Note 2	CH_3	H	$OCH_2CH_2CH_3$	Oil

Note 1
NMR spectrum ($CDCl_3$) δ: 1.0 (3H, t, J = 7.5 Hz), 1.79 (2H, m), 3.92 (2H, t, J = 6 Hz), 4.51–4.90 (1H, br), 4.68 (2H, s), 6.68 (1H, dd, J = 2 and 6 Hz), 6.80 (1H, d, J = 2 Hz), 8.28 (1H, d, J = 6 Hz)
Note 2
NMR spectrum ($CDCl_3$) δ: 1.03 (3H, t, J = 7.5 Hz), 1.82 (2H, m), 2.02 (3H, s), 3.95 (2H, t, J = 6 Hz), 4.62 (2H, s), 5.20 (1H, brd, s), 6.68 (1H, d, J = 6 Hz), 8.25 (1H, d, J = 6 Hz)

REFERENCE EXAMPLE 3

Thionyl chloride (0.2 ml) was added to a solution of 2-hydroxymethyl-3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)-pyridine (350 mg) in chloroform (10 ml) and the mixture was refluxed for 30 minutes and then concentrated. The residue was dissolved in methanol (5 ml) and the solution was added to a mixture of 2-mercaptobenzimidazole (200 mg), 28% sodium methoxide solution (1 ml) and methanol (6 ml). The resultant mixture was refluxed for 30 minutes. The methanol was distilled off, water was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with dilute sodium hydroxide solution and dried over magnesium sulfate. The solvent was then distilled off, and the residue was applied to a silica gel (20 g) column. Elution with ethyl acetate-hexane (2:1) and recrystallization from ethyl acetate-hexane gave 370 mg of 2-[[3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)-2-pyridyl]-methylthio]benzimidazole hemihydrate as colorless plates. Melting point 145°–146° C.

The following compounds (II) were produced by reacting the compound (III) with the corresponding compound (IV) in the same manner as mentioned above.

	Compounds (II)					
	R^1	R^2	R^3	R^5	R^4	Melting point (°C.)
	H	H	CH_3	H	OCH_2CF_3	149–150
	H	H	H	H	$OCH_2CH_2CH_3$	84–86
Note	H	H	CH_3	H	$OCH_2CH_2CH_3$	Oil

Note
NMR spectrum ($CDCl_3$) δ: 0.98 (3H, t, J = 7.5 Hz), 1.54–1.92 (2H, m), 2.15 (3H, s), 3.80 (2H, t, J = 6 Hz), 4.43 (2H, s), 6.55 (1H, d, J = 6 Hz), 7.09 (2H, m), 7.50 (2H, m), 8.21 (1H, d, J = 6 Hz)

REFERENCE EXAMPLE 4

A solution of m-chloroperbenzoic acid (1.3 g) in chloroform (15 ml) was added dropwise to a solution of 2-[[3-methyl-4-(2,2,3,3,3-pentafuloropropoxy)-2-pyridyl]methylthio]-methylthio]benzimidazole 2.2 g) in chloroform (20 ml) with ice cooling over 30 minutes and, then, the reaction mixture was washed with saturated aqueous sodium hydrogen carbonate solution, dried over magnesium sulfate and concentrated. The concentrate was applied to a silica gel (50 g) column. Elution with ethyl acetate and recrystallization from acetone-isopropyl ether gave 1.78 g of 2-[[3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)-2-pyridyl]methyl-sulfinyl]benzimidazole [hereinafter sometimes referred to as compound (A)] as pale yellow prisms. Melting point 161°–163° C. (decomposition).

The following compounds (I) [hereinafter sometimes referred to as compound (B), compound (C) and compound (D), respectively] were produced in the same manner from the corresponding compounds (II).

	Compounds (I)					
	R^1	R^2	R^3	R^5	R^4	Melting point (°C.)
(B)	H	H	CH_3	H	OCH_2CF_3	178–182 (decomp.)
(C)	H	H	H	H	$OCH_2CH_2CH_3$	123–125 (decomp.)
(D)	H	H	CH_3	H	$OCH_2CH_2CH_3$	81–83

EXAMPLE 1

Of the components given below, the compound (A), magnesium hydroxide, L-cysteine, corn starch and lactose were mixed together, then microcrystalline cellulose, light silicic anhydride and magnesium stearate, each in half the intended amount, were added. After sufficient admixing, the mixture was compression-molded on a dry granulator (roller compactor; Freund, Japan. The compressed mass was ground in a mortar, the resultant granular mass was passed through a round sieve (16 mesh). The remaining portions of microcrystalline cellulose, light silicic anhydride and magnesium stearate were added to the sieved mass and, after admix-

ing, the whole mixture was made up into tablets each weighing 250 mg on a rotary tableting machine (Kikusui Seisakusho, Japan).

Composition per tablet:	
Compound (A)	50 mg
Magnesium hydroxide	30 mg
L-Cysteine	20 mg
Corn starch	20 mg
Lactose	65.2 mg
Microcrystalline cellulose	60 mg
Light silicic anhydride	1.8 mg
Magnesium stearate	3.0 mg
Total	250.0 mg

EXAMPLE 2

Tablets were produced in the same manner as in Example 1 except that omeprazole (Note) was used instead of the compound (A).

Note: 5-Methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methylsulfinyl]benzimidazole.

EXAMPLE 3

Of the components given below, the compound (B), precipitated calcium carbonate, corn starch, lactose and hydroxypropylcellulose were mixed together, water was added, and the mixture was kneaded, then dried in vacuum at 40° C. for 16 hours, ground in a mortar and passed through a 16-mesh sieve to give granules. To this was added magnesium stearate and the resultant mixture was made up into tablets each weighing 200 mg on a rotary tableting machine (Kikusui Seisakusho, Japan).

Composition per tablet:	
Compound (B)	30 mg
Precipitated calcium carbonate	50 mg
Corn starch	40 mg
Lactose	73.4 mg
Hydroxypropylcellulose	6 mg
Magnesium stearate	0.6 mg
Water	(0.05 ml)
Total	200.0 mg

EXAMPLE 4

Tablets were produced in the same manner as in Example 3 except that timoprazole (Note) was used instead of the compound (B).

Note: 2-[(2-Pyridyl)methylsulfinyl]benzimidazole.

EXAMPLE 5

The ingredients given below were mixed well in the porportions given below, water was added, and the mixture was kneaded and granulated in an extruder granulator (Kikusui Seisakusho; screen size 1.0 mm ϕ). The granules were immediately converted to spherical form in a spheronizer (Fuji Powder's Marumerizer, Japan; 1,000 rpm). The spherical granules were then dried under vacuum at 40° C. for 16 hours and passed through round sieves to give 12- to 42-mesh granules.

Composition per 200 mg of granules	
Compound (B)	30 mg
Heavy magnesium carbonate	20 mg
Corn starch	80 mg
Microcrystalline cellulose	20 mg
Carboxymethylcellulose calcium	10 mg
Hydroxypropylcellulose	10 mg
Pluronic F68	4 mg
Lactose	26 mg
Water	(0.1 ml)
Total	200 mg

EXAMPLE 6

Granules were produced in the same manner as in Example 5 except that the compound (D) was used instead of the compound (B).

EXAMPLE 7

Enteric granules were produced by coating the granules obtained in Example 2 with an enteric coating composition specified below using a fluidized bed granulator (Okawara, Japan) under conditions such that the inlet air temperature was 50° C. and the granule temperature was 40°60 C. No. 1 hard capsules were filled with the enteric granules thus obtained in an amount of 260 mg per capsule using a capsule filling machine (Parke-Davis, U.S.A.).

Enteric coating composition:	
Eudragit L-30D	138 mg (solids 41.4 mg)
Talc	4.1 mg
Polyethylene glycol 6000	12.4 mg
Tween 80	2.1 mg
Water	276 µl
Composition of enteric granules:	
Granules of Example 5	200 mg
Enteric coat	60 mg
Total	260 mg
Composition per capsule:	
Enteric granules	260 mg
No. 1 hard capsule	76 mg
Total	336 mg

EXAMPLE 8

Of the components given below, the compound (B), magunesium carbonate, socrose, corn starch and crystalline cellulose were thoroughly mixed together to obtain dusting powder.

Nonpareils were put on a centrifugal fluidized coating-granulatar (CF-360 Freund, Japan) and then coated with the dusting powder as described above, while spraying hydroxypropylcellulose solution [4% (w/w)], to give spherical granules. The spherical granules were dried in vacuum at 40° C. for 16 hours and then passed through round sieves to give 12 to 32-mesh granules.

Composition per 190 mg of granules:	
Nonpareil	75 mg
Compound (B)	15 mg
Magnesium carbonate	15 mg
Sucrose	29 mg
Corn starch	27 mg
Crystalline cellulose	27 mg
Hydroxypropylcellulose [Hydroxypropoxy group content: 53.4–77.5%]	2 mg
Water	(0.05 ml)
Total	190 mg

EXAMPLE 9

Enteric granules were produced by coating the granules obtained in Example 8 with an enteric coatig composition specified below usig a fluidized bed granulator (Okawara, Japan) under conditions such that inlet air temperature was 50° C. and the granule temperature was 40° C. No. 2 hard capsules were filled with the enteric granules thus obtained in an amount of 240mg per capsule using a capsule filling machine (Parke-Davis, USA).

Enteric coating composition:	
Eudragit L-30D	104.7 mg (solids 31.4 mg)
Talc	9.6 mg
Polyethylene glycol 6000	3.2 mg
Tween 80	1.6 mg
Titanium oxide	4.2 mg
Water	(220 μl)
Composition of enteric granules:	
Granules of Example 8	190 mg
Enteric coat	50 mg
Total	240 mg
Composition per capsule:	
Enteric granules	240 mg
No. 2 hard capsule	65 mg
Total	305 mg

EXAMPLE 10

Composition 1:	
Compound (B)	450 g
Magnesium carbonate	450 g
Sucrose	450 g
Corn starch	450 g
Low substituted hydroxypropylcellulose [Hydroxypropoxy group content: 10.0–13.0% (w/w), average particle size: no more than 30 μm]	450 g
Composition 2:	
Sucrose	420 g
Corn starch	360 g
Low substituted hydroxypropylcellulose [Hydroxypropoxy group content: 10.0–13.0% (w/w), average particle size: no more than 30 μm]	360 g

Ingredients of the above composition 1 and composition 2 were thoroughly mixed together to obtain dusting powder 1 and dusting powder 2, respectively.

2250 g of nonpareils were put on a centrifugal fluidized coating granulatar (CF-360 Freund, Japan) and then coated with the dusting powder 1, then with the dusting powder 2, while spraying 60 g of hydroxypropylcellulose in water (2000 ml) to give spherical granules.

The spherical granules were dried in vacuum at 40° C. for 16 hours and then passed through round sieve to give 12 to 32 - mesh granules.

EXAMPLE 11

Enteric granules were produced by coating 3800 g of the granules obtained in Example 10 with an enteric coating composition specified below using a fluidized bed granulatar (Okawara, Japan) under conditions such that inlet air temperature was 50° C. and the granule temperature was 40° C. No. 2 hard capsules were filled with the enteric granules thus obtained in an amount of 240 mg per capsule using a filling machine (Parke-Davis), USA).

Enteric coating composition:	
Eudragit L30D-55	628 g
Talc	192 g
Polyethylene glycol 6000	64 g
Titanium oxide	64 g
Tween 80	32 g
Water	4400 ml
Composition per capsule:	
Enteric granules	240 mg
No. 2 hard capsule	65 mg

Experimental Example 1

Granules were produced by the method of Example 5 and, after storage at 50° C. and 75% RH for 1 week, were observed for changes in appearance. Granules were also produced in the same manner except that lactose was used instead of heavy magnesium carbonate or that one of other additives specified below in Table 1.

TABLE 1

Additive	Changes in apperance after 1 week at 50° C. and 75% RH
The invention:	
Heavy magnesium carbonate	–
Magnesium oxide	–
Magnesium metasilicate aluminate	–
Synthetic hydrotalcite	–
Aluminum magnesium hydroxide	–
Magnesium silicate	–
Precipitated calcium carbonate	–
Magnesium hydroxide	–
Controls:	
Sodium carbonate	– (to yellow)
Potassium carbonate	– (to yellow)
Sodium hydrogen carbonate	– (to yellow)
Magnesium chloride	– – (to violet)
Magnesium sulfate	– – (to violet)
Calcium chloride	– – (to violet)
Aluminum silicate	– (to violet)
No additive (lactose)	– – (to violet)

Notes:
–: No changes in
–: Moderately
– –: Severely

As a result, no substantial changes in appearance were noted for the compositions supplemented with the additives of the invention.

Experimental Example 2

Granules were produced in the same manner as in Example 5 except that the compound (A), the compound (C), the compound (D), omeprazole or timoprazole was used instead of the compound (B). After storage at 50° C. and 75% RH for 1 week, they were observed for changes in appearance. As a control to each composition, granules were also produced in the same manner except that lactose was used instead of heavy magnesium carbonate and stored under the same conditions.

Compound		Additive	Changes in appearance after 1 week at 50° C. and 75% RH
Compound (A)	Invention:	Heavy magnesium carbonate	−
	Control:	Lactose	++
Omeprazole	Invention:	Heavy magnesium carbonate	−
	Control:	Lactose	++
Timoprazole	Invention:	Heavy magnesium carbonate	−
	Control:	Lactose	++
Compound (C)	Invention:	Heavy magnesium carbonate	−
	Control:	Lactose	++
Compound (D)	Invention:	Heavy magnesium carbonate	−
	Control:	Lactose	++

Notes:
−: No changes
++: Severely

As is evident from the above results, the pharmaceutical compositions of the invention were all stable whether the active ingredient was the compound (A), omeprazole, timoprazole, the compound (C) or the compound (D).

Experimental Example 3

Pharmaceutical conditions were produced in the same manner as in Example 3 and 5 except that different basic inorganic Mg or Ca salts were used or that lactose was used as a control, and Example 6. After strage at 50° C. and 75% RH for 1 week or at 40° C. for 6 months, the compositions were observed for changes in appearance and for active ingredient content (residual percentage).

TABLE 2

	Additive		Initial	50° C., 75% RH, 1 week	40° C., 6 months
		Tablets made by the procedure of Example 3			
Invention	Heavy magnesium carbonate	Appearance	White	No change	No change
		Content	100%	98.0%	99.5%
	Precipitated calcium carbonate	Appearance	White	No change	No change
		Content	100%	97.4%	96.5%
	Magnesium silicate	Appearance	White	No change	No change
		Content	100%	94.5%	95.0%
Control	No addition (lactose)	Appearance	Pale violet	Dark violet	Dark violet
		Content	100%	73.5%	82.1%
		Granudles made by the procedure of Example 5			
Invention	Heavy magnesium carbonate	Appearance	White	No change	No change
		Content	100%	98.2%	99.1%
	Precipitate calcium carbonate	Appearance	White	No change	No change
		Content	100%	97.2%	98.6%
	Magnesium oxide	Appearance	White	No change	No change
		Content	100%	99.4%	99.0%
Control	No addition (lactose)	Appearance	Pale violet	Dark violet	Dark violet
		Content	100%	84.2%	89.4%
		Capsules of Example 7			
Invention	Heavy magnesium carbonate	Appearance	White	No change	No change
		Content	100%	98.4%	99.1%

The above results clearly indicate that the compositions of the invention show no changes in appearance at all and are stable in terms of the active ingredient content.

What we claim is:

1. A pharmaceutical composition, wherein the composition is made up into tablets or granules and then coated by a coating agent, which comprises an effective amount of the anti-ulcer compound 2-[[3-methyl-4-(2,2,2-trifluoroethoxy-2-pyridyl]methylsulfinyl] benzimidazole, and at least one of the basic inorganic salts of magnesium and calcium selected from heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metasilicate aluminate, magnesium silicate aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite, aluminum magnesium hydroxide, precipitated calcium carbonate and calcium hydroxide; the amount of the basic inorganic salt relative to parts by weight of the benzimidazole compound being about 0.3–20 parts by weight; the benzimidazole compound being in contact with the basic inorganic salt evenly.

2. A pharmaceutical composition as claimed in claim 1, wherein the basic inorganic salt of magnesium is magnesium carbonate.

3. A pharmaceutical composition, wherein the composition is made up into tablets or granules and then coated by a coating agent, which comprises an effective amount of the anti-ulcer compound 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methylsulfinyl] benzimidazole, and at least one of the basic inorganic salts of magnesium and calcium selected from heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metasilicate aluminate, magnesium silicate aluminate, magnesium

silicate, magnesium aluminate, synthetic hydrotalcite, aluminum magnesium hydroxide, precipitated calcium carbonate and calcium hydroxide; the amount of the basic inorganic salt relative to parts by weight of the benzimidazole compound being about 0.3–20 parts by weight; the benzimidazole compound being in contact with the basic inorganic salt evenly.

* * * * *

EXHIBIT C

US005464632A

United States Patent [19]

Cousin et al.

[11] Patent Number: 5,464,632

[45] Date of Patent: Nov. 7, 1995

[54] **RAPIDLY DISINTEGRATABLE MULTIPARTICULAR TABLET**

[75] Inventors: **Gérard Cousin**, Gallardon; **Etienne Bruna**, Chartres; **Edouard Gendrot**, Vernouillet, all of France

[73] Assignee: **Laboratoires Prographarm**, Chateauneuf, France

[21] Appl. No.: **346,324**

[22] Filed: **Nov. 29, 1994**

Related U.S. Application Data

[63] Continuation of Ser. No. 35,355, Mar. 22, 1993, abandoned.

[30] **Foreign Application Priority Data**

Jul. 22, 1991 [FR] France 91 09245

[51] **Int. Cl.**[6] **A61K 9/20**

[52] **U.S. Cl.** **424/465**; 424/458; 424/489

[58] **Field of Search** 424/458, 440, 424/465, 428, 441, 473, 489

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Assistant Examiner—William E. Benston, Jr.
Attorney, Agent, or Firm—Caesar, Rivise, Bernstein, Cohen & Pokotilow, Ltd.

[57] **ABSTRACT**

Rapidly disintegratable multiparticulate tablet the excipient mixture of which is suitable for imparting a disintegration rate such that the tablet disintegrates in the mouth in an extremely short time, notably in less than sixty seconds, characterized by the fact that the active substance is present in the form of coated microcrystals or coated or uncoated microgranules.

6 Claims, No Drawings

RAPIDLY DISINTEGRATABLE MULTIPARTICULAR TABLET

This application is a continuation of application Ser. No. 08/035,355, filed Mar. 22, 1993, abandoned.

The invention relates to a rapidly disintegratable multiparticulate tablet, i.e. a pharmaceutical presentation for oral administration whose disintegration rate is such that, when it is placed into the buccal cavity and particularly on the tongue, it disintegrates in less than sixty seconds providing with the saliva present a suspension easy to be swallowed.

The disintegration rate is obtained due to a mixture of excipients or vehicles which comprises generally a disintegrating agent which may consist of a carboxymethylcellulose and a swelling agent which may consist of modified starch.

The active substance or principle is mixed with the abovesaid vehicles, the mixture then being tabletted after addition of a lubricant such as, for example, magnesium stearate.

The Applicants have had the merit of having found that it was possible, unexpectedly and surprisingly, to introduce into a multiparticulate tablet with high disintegration rate such as hereabove defined, the active substance in the form of coated or non-coated microcrystals or microgranules; thus, the physician has at his disposal a rapidly disintegratable multiparticulate tablet proper to facilitate the taking by the patient of most diversified active substances and especially of those whose taste is particularly unpleasant, the said tablet permitting the taking of the said active substances with as diversified features as gastroresistance and controlled release due to the fact that the said coated or non-coated microcrystals and microgranules preserve, after having been shaped in the form of a multiparticulate tablet, their initial properties amongst which masking of taste, gastroresistance and controlled release of the active principle.

Consequently, the rapidly disintegratable multiparticulate tablet according to the invention, which can be used for human beings and for animals, the excipient mixture of which is such as to provide it with a disintegration rate so that its disintegration in the buccal cavity occurs in an extremely short time and especially shorter than sixty seconds, is characterized by the fact that the active substance is in the form of coated or non-coated microcrystals or microgranules with modified action or non-modified action.

According to an advantageous embodiment of the abovesaid tablet, the mixture of excipients comprises one or several disintegrating agents of the carboxymethylcellulose type or insoluble reticulated PVP type, one or several swelling agents which may consist of a carboxymethylcellulose, a starch, a modified starch, for instance a carboxymethylated starch, or a microcrystalline cellulose, and possibly a direct compression sugar consisting for example of 92% of dextrose.

According to an advantageous embodiment, the tablets according to the invention, wherein the active substance is in the form of coated microcrystals, comprise as active substance at least one of those of the group comprising the gastrointestinal sedatives, the antacids, the analgesics, the anti-inflammatory agents, the coronary vasodilators, the peripheral and brain-vasodilators, the anti-infectious agents, the antibiotics, the antiviral agents, the antiparasitic agents, the anticancerous drugs, the antianxiety agents, the neuroleptic drugs, the agents stimulating the central nervous system, the antidepressant drugs, the antihistaminic agents, the antidiarrheal agents, the laxatives, the nutritional supplements, the immunodepressant drugs, the cholesterol lowering agents, the hormones, the enzymes, the antispasmodic agents, the antiangorous agents, the drugs acting on the rhythm of the heart, the drugs used in the treatment of arterial hypertension, the anti-migraine agents, the drugs acting on blood coagulability, the antiepileptic agents, the myorelaxing agents, the drugs used in the treatment of diabetes, the drugs used in the treatment of thyroidal dysfunctions, the diuretical agents, the anorexigenic drugs, the antiasthmatic agents, the expectorants, the antitussive agents, the mucoregulators, the decongestants, the hypnotics, the antinauseous agents, the hematopoietical agents, the uricosuric agents, the plant extracts, the contrast mediums.

According to another advantageous embodiment, the tablets according to the invention, wherein the active substance is present in the form of coated or non-coated microgranules with modified action or non-modified action, comprise as active substance at least one of those of the group comprising the gastrointestinal sedatives, the antacids, the analgesics, the anti-inflammatory agents, the coronary vasodilators, the peripheral and brain-vasodilators, the anti-infectious agents, the antibiotics, the antiviral agents, the antiparasitic agents, the anticancerous drugs, the antianxiety agents, the neuroleptic drugs, the agents stimulating the central nervous system, the antidepressant drugs, the antihistaminic agents, the antidiarrheal agents, the laxatives, the nutritional supplements, the immunodepressant drugs, the cholesterol lowering agents, the hormones, the enzymes, the antispasmodic agents, the antiangorous agents, the drugs acting on the rhythm of the heart, the drugs used in the treatment of arterial hypertension, the anti-migraine agents, the drugs acting on blood coagulability, the antiepileptic agents, the myorelaxing agents, the drugs used in the treatment of diabetes, the drugs used in the treatment of thyroidal dysfunctions, the diuretical agents, the anorexigenic drugs, the antiasthmatic agents, the expectorants, the antitussive agents, the mucoregulators, the decongestants, the hypnotics, the antinauseous agents, the hematopoietical agents, the uricosuric agents, the plant extracts, the contrast mediums.

The use of the tablet according to the invention is especially advantageous due to the fact that it may be very easily used by any users. The said tablet can be taken in any condition (when working, when travelling and so on), without a glass and without water. It constitutes an "ambulatory" pharmaceutical presentation which can advantageously be used instead of numerous pharmaceutical presentations such as sachets, effervescent tablets, drinkable ampoules, capsules, traditional tablets and so on.

Its very easy facility of administration is especially interesting when it is necessary that young children or old people take therapeutical substances, i.e. populations which often have swallowing difficulties, i.e. populations which keep the drug in the mouth and which are unable to swallow it. Contrary to the traditional tablet or to the capsule, the tablet according to the invention offers in connection with such populations an advantage of security as, as soon as it is introduced in the mouth, it provides a therapeutical protection.

On the other hand, it is important to emphasize that, even directly swallowed with a little water for example, the said tablet preserves its rapid disintegration rate within the stomach. This type of administration will again raise no security problem.

Furthermore, the tablet according to the invention provides a further big advantage with respect to tablets or simple capsules. In fact until today, people who need to swallow a tablet or a capsule under the above-mentioned

conditions (during working, during travelling, without water and without a glass), swallowed the said tablet or capsule without water and that could be dangerous as the tablet or capsule can block in the esophagus and provide thus an important delay as far as absorption of the active principle is concerned or even an ulceration at the level of the esophagus. Similarly, the fact that, on the one hand, the active principle is coated and, on the other hand, that it is present in the form of a multiparticulate tablet, prevents agressive active principles causing ulcerations of the esophagial or gastric mucous membranes, phenomenon which is sometimes caused by certain pharmaceutical presentations which are monolithic, especially when the patient suceeeds in swallowing them with a little water or no water.

Another advantage of the tablet according to the invention is that the said tablet has not the well-known drawbacks of effervescent tablets as for instance the taste which is very unpleasant to the child, the high sodium content which is disturbing to people which must follow a diet without sodium and finally the necessity of having water and a glass for its administration.

Furthermore, it permits the formulation of certain active principles which are not adapted to a previous extracorporeal dissolution and which consequently can be contemplated only under a dry form, which prevents their use in effervescent tablets; consequently, the tablet according to the present invention has all the advantages of the dry forms, i.e. the stability as well as the facility of packaging and storage.

On the other hand, this new pharmaceutical form may contain if necessary two or several active principles which are usually incompatible with one another and this without alteration of their stability.

Another advantage of the tablet according to the invention consists in the possibility of taking by the patient of doses of active principle which are more important than in the past. As a matter of fact as the said tablet is not to be swallowed under its initial form but after disintegration within the buccal cavity, its size might be greater than that of a classical pharmaceutical form which must be adapted to be swallowed without disturbing the taking of the drug.

Finally, the tablet according to the invention has all the advantages of coated particles which permit to obtain especially a taste-masking, a gastroresistance, a delayed release as well as all the advantages of the multiparticulate forms with modified action or non-modified action, i.e. a great exchange surface, the dispersion, less inter- and intra-individual variations, a very reduced gastric empting influence, a very reduced intestinal transit time influence as well as reduced pH influence in the digestive tract, reduced influence of the viscosity and consequently of food and of the position of the body, without local toxic manifestation.

The preparation of the rapidly disintegratable multiparticulate tablets according to the invention is as follows or similar.

When the active principle is in the form of coated microcrystals, it is possible to proceed as follows.

The microcrystals are coated by way of a process known by itself such as, for example, the fluidized air bed, the coacervation and the microencapsulation.

The mixture of excipients is then prepared by the dry- or wet-granulation method.

Then, the coated microcrystals are mixed under dry conditions with the mixture of excipients before compression.

The preparation of the tablet according to the invention wherein the active principle is in the form of coated or non-coated microgranules, may be as follows.

The active principle is put in the form of microgranules by way of a method known by itself such as, for example, extrusion-spheronisation, manufacture in pan, fluidized air bed and so on.

Once obtained, these microgranules are coated if necessary in a pan or in a fluidized air bed.

The mixture of excipients is then prepared by the dry- or wet-granulation method.

Then, the coated or non-coated microgranules are mixed under dry conditions with the mixture of excipients before compression.

The invention may even be better understood by way of the following non-limitating examples which relate to advantageous embodiments of the invention.

EXAMPLE 1

Rapidly disintegratable multiparticulate tablet based on coated crystals of paracetamol.

Tablets according to the invention are prepared whose composition is as follows.

Formula:	
coated paracetamol (with 6% ethylcellulose)	530 mg
direct compression sugar	160 mg
microcrystalline cellulose	90 mg
reticulated polyvinylpyrrolidone	60 mg
sodic carboxymethylcellulose	50 mg
colloidal silica	6 mg
lubricant	4 mg
sweetener	25 mg
aroma	15 mg
magnesium trisilicate	50 mg
Total	990 mg

The said tablet is prepared as follows.

The paracetamol crystals are introduced in a fluidized air bed installation and a solution of ethylcellulose in an ethanol/acetone mixture is sprayed thereon.

The excipients are sieved and the coated paracetamol is homogeneized with the excipients inside a mixing device under dry conditions.

Distribution and tabletting are carried out on a compressing machine fitted with punches having a diameter equal to 15 mm and a radius of curvature equal to 20 mm.

The pressure is equal to 16 KNewtons ±1. The hardness of the thus obtained tablets is equal to 100 Newtons ±10. The time of disintegration in the mouth is from 35 to 45 seconds.

EXAMPLE 2

Rapidly disintegratable multiparticulate tablet based on coated cimetidine crystals.

Tablets according to the invention are prepared whose composition is as follows.

Formula:	
coated cimetidine (with 15.25% of Eudragit E)	944 mg
reticulated polyvinylpyrrolidone	89 mg
magnesium stearate	5 mg
sweetener	50 mg
aroma	12 mg
Total	1100 mg

The said tablet is prepared as follows.

The cimetidine crystals are introduced in a fluidized air bed installation and a solution of a copolymer of dimethylaminoethyl-methacrylate and of neutral esters of methacrylic acid known under the trademark "Eudragit E" in alcohol is sprayed thereon.

The excipients are sieved and the coated cimetidine is homogeneized with the excipients inside a mixing apparatus under dry conditions.

Distribution and tabletting are executed on a compressing machine equipped with punches having a diameter equal to 16 mm and a radius of curvature equal to 20 mm.

The pressure is 20 KNewtons ±1. The hardness of the thus obtained tablets is 95 Newtons ±10. The time of disintegration in the mouth is from 15 to 20 seconds.

EXAMPLE 3

Rapidly disintegratable multiparticulate tablet based on coated crystals of paracetamol.

Tablets according to the invention composed as follows are prepared.

Formula:	
complex of paracetamol-codeine (30 mg of codeine and 18.4% of Eudragit*)	627.5 mg
reticulated polyvinylpyrrolidone	90 mg
sodium carboxymethylcellulose	70 mg
starch commercialized under the trademark "STARCH 1500"	100 mg
sweetener	40 mg
aroma	22.5 mg
Total	950 mg

*Eudragit is a copolymer of methacrylic acid.

This tablet is prepared as follows.

The crystals of paracetamol are introduced in a fluidized air bed installation and the codeine dissolved in a solution of Eudragit E and Eudragit NE 30D (neutral polymer of esters of polymethacrylic acid) is sprayed thereon.

The excipients are sieved and the coated paracetamol is homogeneized with the excipients in a mixing apparatus under dry conditions.

Distribution and tabletting are carried out on a compressing machine equipped with punches having a diameter equal to 16 mm and a radius of curvature equal to 20 mm.

The pressure is 21 KNewtons ±1. The hardness of the thus obtained tablets is 35 Newtons ±5. The time of disintegration in the mouth is from 50 to 60 seconds.

EXAMPLE 4

Rapidly disintegratable multiparticulate tablet based on coated crystals of ibuprofen.

Tablets according to the invention and whose composition is as follows are prepared.

Formula:	
ibuprofen (with 10% of ethylcellulose)	440 mg
reticulated polyvinylpyrrolidone	120 mg
starch commercialized under the trademark "STARCH 1500"	235 mg
sweetener	48 mg
aroma	52 mg
magnesium stearate	5 mg
Total	900 mg

This tablet is prepared as follows.

The crystals of ibuprofen are introduced in a fluidized air bed installation and a solution of ethylcellulose in ethanol is sprayed thereon.

The excipients are sieved and the coated ibuprofen is homogeneized with the excipients in a mixing apparatus under dry conditions.

Distribution and tabletting are carried out on a compressing machine equipped with punches having a diameter equal to 16 mm and a radius of curvature equal to 20 mm.

The pressure is 15 KNewtons ±1. The hardness of the thus obtained tablets is 50 Newtons ±5. The time of disintegration in the mouth is from 15 to 20 seconds.

EXAMPLE 5

Rapidly disintegratable multiparticulate tablet based on microgranules.

Formula:	
microgranules with delayed release based on doxycycline monohydrate (with 100 mg of active principle)	225 mg
microcrystalline cellulose	142 mg
starch commercialized under the trademark "SEPPISTAB ST 500"	98 mg
aspartam	20 mg
aroma	15 mg
Total	500 mg

The microgranules are prepared in a pan by coating a neutral sugar sphere with doxycycline according to the classical technology, the microgranules being then coated with Eudragit E also in coating pan.

The tablet is prepared by sieving of the excipients, followed by homogeneization of the microgranules of doxycycline with the excipients in a mixing apparatus under dry conditions, followed by distribution and tabletting in a rotary compressing machine equipped with punches having a diameter equal to 12 mm and radius of curvature is equal to 11 mm.

The pressure is 20 KNewtons ±1. The hardness of the thus obtained tablets is 100 Newtons ±10. The time of disintegration in the mouth is from 10 to 20 seconds.

As a result of which we have a rapidly disintegratable multiparticulate tablet, the constitution and method of manufacture of which are sufficiently disclosed above, such that it would be useless to repeat this subject and about which it is recalled that

- it consists of a tablet which combines a high level technology (control of release, of gastroresistance, of taste-masking of the active principle) with a high security of use due to its multiparticulate form by way of the coating during the process of manufacture and to the fact that its disintegration occurs in the mouth,
- it constitutes an ambulatory form which can be adapted to a great number of active principles and to high dosages, which did not previously exist,
- it offers a high facility of use, as the same pharmaceutical form can be disintegrated within the mouth, in a glass of water or in liquid or semi-liquid food, as for example, in yoghourt for children or infants, or in food for animals in connection with its use in the veterinary field,
- it consists of a single and same pharmaceutical form which can be prescribed to people requiring different strengths; thus, it can be used in connection with an active principle given at its maximum dose and manufactured in a divisible shape at one or several scored places in such a manner that it can be administered in totality or according to the age or the symptoms of the patient, in the form of a divisible part depending upon the shape of the punch, it being emphasized that it was not obvious to obtain a divisible multiparticulate tablet,
- it consequently consists of a pharmaceutical form which is suitable to everybody because it offers a great variety of means for administration and of dosages, which represents a definite economical advantage.

The fact that a single product permits, on the one hand, ways of administration normally permitted by several pharmaceutical forms and that, on the other hand, it gives rise to several posologies normally obtained by the creation of various strengths (tablets or capsules of different concentrations for example) constitutes an economical advantage of primary importance.

In fact from the industrial point of view, this means a single line production instead of several lines production each corresponding to each strength selected and to each pharmaceutical form selected.

We claim:

1. A rapidly disintegratable tablet for oral administration with or without the use of water, said tablet comprising an active substance and a mixture of excipients, wherein said active substance is multiparticulate and in the form of coated microcrystals, coated microgranules or uncoated microgranules and wherein said mixture of excipients comprises excipients which are responsible for the disintegration, said tablet being intended to be swallowed said disintegration occurring in less than sixty seconds under the action of the excipients which are responsible for the disintegration and which are selected from the group consisting at least one disintegrating agent and at least one swelling agent.

2. The tablet of claim **1**, wherein the active substance is in the form of coated microcrystals and is selected from the group consisting of gastrointestinal sedatives, antacids, analgesics, anti-inflammatory agents, coronary vasodilators, peripheral and brain-vasodilators, anti-infectious agents, antibiotics, antiviral agents, antiparasitic agents, anticancerous drugs, antianxiety agents, neuroleptic drugs, agents stimulating the central nervous systems, antidepressant drugs, antihistaminic agents, antidiarrheal agents, laxatives, nutritional supplements, immunodepressant drugs, cholesterol lowering agents, hormones, enzymes, antispasmodic agents, antiangorous agents, drugs acting on the rhythm of the heart, drugs used in the treatment of arterial hypertension, anti-migraine agents, drugs acting on blood coagulability, anti-epileptic agents, myorelaxing agents, drugs used in the treatment diabetes, drugs used in the treatment of thyroidal dysfunctions, diuretical agents, anorexigenic drugs, anti-asthmatic agents, expectorants, antitussive agents, mucoregulators, decongestants, hypnotics, antinausea agents, hematopoietical agents, uricosuric agents, plant extracts and contrast mediums.

3. The tablet of claim **1**, wherein the active substance is in the form of coated microgranules and is selected from the group consisting of gastrointestinal sedatives, antacids, analgesics, anti-inflammatory agents, coronary vasodilators, peripheral and brain-vasodilators, anti-infectious agents, antibiotics, antiviral agents, antiparasitic agents, anticancerous drugs, antianxiety agents, neuroleptic drugs, agents stimulating the central nervous system, anti-depressant drugs, antihistaminic agents, antidiarrheal agents, laxatives, nutritional supplements, immunodepressant drugs, cholesterol lowering agents, hormones, enzymes, anti-spasmodic agents, antiangorous agents, drugs acting on the rhythm of the heart, drugs used in the treatment of arterial hypertension, anti-migraine agents, drugs acting on blood coagulability, anti-epileptic agents, myorelaxing agents, drugs used in the treatment of diabetes, drugs used in the treatment of thyroidal dysfunctions, diuretical agents, anorexigenic drugs, anti-asthmatic agents, expectorants, antitussive agents, mucoregulators, decongestants, hypnotics, antinausea agents, hematopoietical agents, uricosuric agents, plant extracts and contrast mediums.

4. The tablet of claim **1**, wherein the mixture of excipients comprises at least one disintegrating agent selected from the group consisting of carboxymethylcellulose, insoluble reticulated PVP type and at lest one swelling agent selected from the group consisting of starch, modified starch and microcrystalline cellulose.

5. The tablet of claim **1**, wherein the mixture of excipients comprises at least one disintegrating agent selected from the group consisting of carboxymethylcellulose and insoluble reticulated PVP, and at least one swelling agent selected from the group consisting of starch, modified starch and microcrystalline cellulose and a direct compression sugar.

6. The tablet of claim **1**, wherein the active substance is in the form of uncoated microgranules and is selected from the group consisting of gastrointestinal sedatives, antacids, analgesics, anti-inflammatory agents, coronary vasodilators, peripheral and brain-vasodilators, anti-infectious agents, antibiotics, antiviral agents, antiparasitic agents, anticancerous drugs, antianxiety agents neuroleptic drugs, agents stimulating the central nervous system anti-depressant drugs antihistaminic agents, antidiarrheal agents, laxatives, nutritional supplements, immunodepressant drugs, cholesterol lowering agents, hormones, enzymes, anti-spasmodic agents, antiangorous agents, drugs acting on the rhythm of the heart, drugs used in the treatment of arterial hypertension, anti-migraine agents, drugs acting on blood coagulability, anti-epileptic agents, myorelaxing agents, drugs used in the treatment of diabetes, drugs used in the treatment of thyroidal dysfunctions, diuretical agents, anorexigenic drugs, anti-asthmatic agents, expectorants, antitussive agents, mucoregulators, decongestants, hypnotics, anti-nausea agents, hematopoietical agents, uricosuric agents, plant extracts and contrast mediums.

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CO CTION

PATENT NO. : 5,464,632

DATED : November 7,1995

INVENTOR(S) : Gerard Cousin et al

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

Column 7, claim 1, line 61, add "of" after consisting.

Signed and Sealed this

Seventh Day of January, 1997

Attest:

BRUCE LEHMAN

Attesting Officer

Commissioner of Patents and Trademarks

US005464632C1

(12) **REEXAMINATION CERTIFICATE** (4273rd)

United States Patent
Cousin et al.

(10) **Number: US 5,464,632 C1**
(45) **Certificate Issued: Feb. 20, 2001**

(54) **RAPIDLY DISINTEGRATABLE MULTIPARTICULAR TABLET**

(75) Inventors: **Gérard Cousin**, Gallardon; **Etienne Bruna**, Chartres; **Edouard Gendrot**, Vernouillet, all of (FR)

(73) Assignee: **Laboratoires Prographarm**, Chateaueuf-en-Thymerals (FR)

Reexamination Request:
No. 90/005,207, Dec. 31, 1999

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Issued: **Nov. 7, 1995**
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Filed: **Nov. 29, 1994**

Certificate of Correction issued Dec. 12, 1996.

Related U.S. Application Data

(63) Continuation of application No. 08/035,355, filed on Mar. 22, 1993, now abandoned.

(30) **Foreign Application Priority Data**

Jul. 22, 1991 (FR) 91 09245

(51) **Int. Cl.**[7] **A61K 9/20**
(52) **U.S. Cl.** **424/465**; 424/489; 424/490; 424/495; 424/497
(58) **Field of Search** 424/465, 489, 424/490, 495, 497

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(57) **ABSTRACT**

Rapidly disintegratable multiparticulate tablet the excipient mixture of which is suitable for imparting a disintegration rate such that the tablet disintegrates in the mouth in an extremely short time, notably in less than sixty seconds, characterized by the fact that the active substance is present in the form of coated microcrystals or coated or uncoated microgranules.

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REEXAMINATION CERTIFICATE ISSUED UNDER 35 U.S.C. 307

THE PATENT IS HEREBY AMENDED AS INDICATED BELOW.

Matter enclosed in heavy brackets [ ] appeared in the patent, but has been deleted and is no longer a part of the patent; matter printed in italics indicates additions made to the patent.

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

Claim **6** is cancelled.

Claims **1** and **4** are determined to be patentable as amended.

Claims **2**, **3**, **5**, dependent on an amended claim, are determined to be patentable.

1. A rapidly disintegratable tablet for oral administration **[**with or**]** *and disintegration in the buccal cavity* without the use of water, *wherein* said tablet **[**comprising**]** *comprises* an active substance and a mixture of *non-effervescent* excipients **[**wherein said active substance is**]** *and permits to obtain reduced ph influence in the digestive tract and reduced influence of viscosity, said active substance being* multiparticulate and in the form of coated microcrystals, *or* coated microgranules **[**or uncoated microgranules**]** and wherein said mixture of excipients comprises **[**excipients which are responsible for the disintegration, said tablet being intended to be swallowed said disintegration occurring in less than sixty seconds under the action of the excipients which are responsible for the disintegration and which are selected from the group consisting at least one **]** *a* disintegrating agent and **[**at least one**]** swelling agent *which are responsible for the disintegration of the tablet with the saliva present in the mouth, to achieve in less than 60 seconds a suspension easy to swallow*.

4. The tablet of claim **1**, wherein the mixture of excipients comprises at least one disintegrating agent selected from the group consisting of carboxymethylcellulose, insoluble reticulated PVP **[**type**]** and at **[**lest**]** *least* one swelling agent selected from the group consisting of starch, modified starch and microcrystalline cellulose.

* * * * *

EXHIBIT D

US006328994B1

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

(10) **Patent No.: US 6,328,994 B1**
(45) **Date of Patent: Dec. 11, 2001**

(54) **ORALLY DISINTEGRABLE TABLETS**

(75) Inventors: **Toshihiro Shimizu**, Itami; **Shuji Morimoto**; **Tetsuro Tabata**, both of Suita, 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.

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(51) **Int. Cl.**[7] **A61K 9/14**; A61K 9/20; A61K 9/46; A61K 9/16

(52) **U.S. Cl.** **424/489**; 424/464; 424/465; 424/466; 424/490; 424/493

(58) **Field of Search** 424/464, 465, 424/466, 489, 490, 493

(56) **References Cited**

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(57) **ABSTRACT**

An orally disintegrable tablet, of the present invention, which comprises (i) fine granules having an average particle diameter of 400 μm or less, which fine granules comprise a composition coated by an enteric coating layer, said composition having 10 weight % or more of an acid-labile physiologically active substance and (ii) an additive, has superior disintegrability or dissolution in the oral cavity so that it can be used for treatment or prevention of various diseases, as an orally disintegrable tablet capable of being administered to the aged or children and easily administered without water. Also, because the tablet of the present invention contains fine granules having the average particle diameter such that it will not impart roughness in mouth, it can be administered easily without discomfort at the administration.

45 Claims, No Drawings

ORALLY DISINTEGRABLE TABLETS

This application is a 371 of PCT/JP99/02548 filed May 17, 1999.

This application is the National Stage of International Application Serial No. PCT/JP99/02548, filed May 17, 1999.

TECHNICAL FIELD

The present invention relates to an orally disintegrable tablet having a characteristic of fast disintegration in the oral cavity even without water.

BACKGROUND ART

Pharmaceutical solid preparations, for example, tablets, usually are prepared to make pharmaceutically active ingredients absorb in a digestive organ by disintegration or dissolution through oral administration, without fast disintegration or dissolution in the Qral cavityl

JP-A-6-502194 (U.S. Pat. No. 5,464,632) discloses a rapidly disintegrable multiparticulate tablet, the excipient mixture of which is suitable for imparting a disintegration rate such that the tablet disintegrates in the mouth in less than sixty seconds, characterized by the fact that the active substance is present in the form of coated microcrystals or coated or uncoated microgranules. However, there is no disclosure of an acid-labile physiologically active substance with a basic inorganic salt as the active substance, weight percentage of the active substance in the excipient mixture, or the size of the coated microgranule.

On the other hand, JP-A-5-92918 discloses a powder consisting of a fine-particle core coated with a water-soluble high molecular compound and at least one physiologically active substance, and having a granule size of practically up to 500 μm. However, there is no disclosure of an acid-labile physiologically active substance with a basic inorganic salt as the physiologically active substance, weight percentage of the active substance in the coated granule or the size of the coated granule.

JP-A-63-301816 and U.S. Pat. No. 5,026,560 disclose spherical granules having a core coated with spraying powder containing a drug and low substituted hydroxypropylcellulose. However, there is no disclosure of an orally disintegrable tablet.

EP-A-0452862 discloses a spherical granule obtained by coating a pharmacologically inactive spherical seed core having at least 50 weight % microcrystalline cellulose and an average particle size of 100–1000 μm, with a powder comprising an active ingredient, by using an aqueous binding solution, and spraying an aqueous solution or suspension of a coating agent thereon. However, most of the particle sizes of thus obtained granules are 500 μm or more.

JP-A-1-268627, JP-A-1-268628 and JP-A-8-27033 disclose pharmaceutical compositions using erythritol, respectively. However, there is no disclosure of a solid pharmaceutical composition characterized by fast disintegration in the oral cavity.

JP-A-9-48726 discloses a buccal formulation consisting of a drug and a substance wetting in a mouldable way on humidifying, and retaining a shape after moulding and drying. As such substance, sugars, sugar alcohols and water-soluble polymers are exemplified.

JP-A-5-271054 discloses production of fast dissolving tablets comprising an active ingredient and sugars.

JP-A-9-71523 discloses a tablet with rapid disintegration in the oral cavity comprising medicine, crystalline cellulose, low-substituted hydroxypropyl cellulose and lubricant.

However, these prior art references nowhere disclose an acid-labile physiologically active substance with a basic inorganic salt as an active substance, weight percentage of the active substance in the tablet or the size of the coated fine granule.

To accompany an aging population and their changes in life environment, it is desired to develop an orally disintegrable solid preparation capable of being administered without water, retaining the convenience for use which is a characteristic of a tablet, and being administered on demand easily, anytime and anywhere, without water.

Conventional granules have large particle diameters, which results in inferior workability when dispensing, and also results in difficulties in consistently adding a regular amount of the granules when they are combined into tablet or capsules. Granules having a large particle diameter (400 μm or more of average particle diameter) also produce a feeling of roughness in the mouth. Accordingly, especially when used in an orally disintegrable tablet, the average particle a diameter of the included granules must be about 400 μm or less, preferably about 350 μm.

For many reasons, such as, masking a bitter taste, or providing enteric abilities or release abilities, it is desirable to prepare the solid pharmaceutical preparations as granules (or fine granules), In particular, in case of granules or fine granules in which the active ingredient of the drug is enteric coated to impart enteric dissolution, there is a need for enteric coating to prevent dissolution by stomach acid (i.e., to make the preparation acid-resistance). It is necessary to coat the whole surface of the particle—before the enteric coating—(including a case of the crystal of physiologically active substance only, and a case of the granule produced by granulation), with the enteric coating. Namely, at least some uniform thickness (at least 20 μm or more) of the coating layer is needed. Even a portion of thin and weak coating, is undesirable because acid-resistance is lowered. Accordingly, before the enteric coating, it is necessary that the particle is as spherical with as smooth a surface as possible in form, as uniform as possible in size, and has less cavities.

It is very difficult to produce an enteric coated fine granule with an average particle diameter of 400 μm or less, when the coating is performed no that at least 20 μm thickness of coating layer may coat the whole particle, and the enteric coated particle contains a basic inorganic salt for stabilization of an acid-labile physiologically active substance, and where it contains binders for maintaining the strength of the particle and/or disintegrants for maintaining the disintegrability (dissolution) of the particles. Further, in the case where the content of the acid-labile physiologically active substance is increased, it is necessary to also increase the content of the excipients such as basic inorganic salt, binders and disintegrants. Furthermore, it is very difficult to produce a small enteric coated fine granule containing the physiologically active substance in high content.

Accordingly, it is desired to develop a fine granule which is coated with the enteric coating layer on the composition containing the physiologically active substance such as a physiologically active substance containing a basic inorganic salt and which has a particle diameter so that roughness or oral discomfort is not felt, to develop a fine granule containing the physiologically active substance, i.e., the active ingredients of drugs, and so forth, in high content, to develop a fine granule while maintaining enteric dissolution, a disintegrability and dissolution and suitable strength, and to develop an orally disintegrable preparation containing such a fine granule, being a fast disintegration type, showing

superior oral disintegrability and dissolution and having suitable strength (hardness) so that it will not be damaged through production processes or handling.

In particular, there is a need to combine an acid-labile physiologically active substance, with basic inorganic salts and so forth for stability, and further to coat with coating layers such as an enteric layer. In such cases, it is an important problem to produce an small enteric coated fine granule, even though it contains the acid-labile physiologically active substance in high concentration and in high content.

DISCLOSURE OF INVENTION

The present invention relates to:

[1] an orally disintegrable tablet which comprises (i) fine granules having an average particle diameter of 400 μm or less, which fine granules comprise a composition coated by an enteric coating layer, said composition having 10 weight % or more of an acid-labile physiologically active substance and (ii) an additive;

[2] an orally disintegrable tablet of the above [1], wherein the average particle diameter of the fine granules is 300 to 400 μm;

[3] an orally disintegrable tablet of the above [1], wherein the fine granules further comprise a basic inorganic salt;

[4] an orally disintegrable tablet of the above [1], wherein the additive comprises a water-soluble sugar alcohol;

[5] an orally disintegrable tablet of the above [1], wherein the composition coated by an enteric coating layer is further coated by a coating layer which comprises a water-soluble sugar alcohol;

[6] an orally disintegrable tablet of the above [4], wherein the additive comprises (i) crystalline cellulose and/or (ii) low-substituted hydroxypropyl cellulose;

[7] an orally disintegrable tablet of the above [1], wherein the particle diameter of the fine granules is practically 425 μm or less;

[8] an orally disintegrable tablet of the above [1], wherein the particle diameter of the fine granules is practically 400 μm or less;

[9] an orally disintegrable tablet of the above [1], wherein the acid-labile physiologically active substance is a benzimidazole compound or a salt thereof;

[10] an orally disintegrable tablet of the above [9], wherein the benzimidazole compound is lansoprazole;

[11] an orally disintegrable tablet of the above [3], wherein the basic inorganic salt is a salt of magnesium and/or a salt of calcium;

[12] an orally disintegrable tablet of the above [1], wherein the composition comprises a core being coated by a benzimidazole compound and a basic inorganic salt, said core comprising crystalline cellulose and lactose;

[13] an orally disintegrable tablet of the above [12], wherein the core comprises 50 weight % or more of lactose;

[14] an orally disintegrable tablet of the above [12], wherein the core comprises 40 to 50 weight % of crystalline cellulose and 50 to 60 weight % of lactose;

[15] an orally disintegrable tablet of the above [1], wherein the composition comprises 20 weight % or more of an acid-labile physiologically active substance;

[16] an orally disintegrable tablet of the above [1], wherein the composition comprises 20 to 50 weight % of an acid-labile physiologically active substance;

[17] an orally disintegrable tablet of the above [1], wherein the fine granules are produced by fluidized-bed granulation method;

[18] an orally disintegrable tablet of the above [1], wherein the enteric coating layer comprises an aqueous enteric polymer agent;

[19] an orally disintegrable tablet of the above [18], wherein the aqueous enteric polymer agent is a methacrylate copolymer;

[20] an orally disintegrable tablet of the above [18], wherein the enteric coating layer further comprises a sustained-release agent;

[21] an orally disintegrable tablet of the above [20], wherein the sustained-release agent is a methacrylate copolymer;

[22] an orally disintegrable tablet of the above [20], wherein the sustained-release agent is in an amount of 5 to 15 weight % relative to 100 weight % of the aqueous enteric polymer agent;

[23] an orally disintegrable tablet of the above [4], wherein the water-soluble sugar alcohol is erythritol;

[24] an orally disintegrable tablet of the above [4], wherein the water-soluble sugar alcohol is mannitol;

[25] an orally disintegrable tablet of the above [5], wherein the water-soluble sugar alcohol is in an amount of 5 to 97 weight % relative to 100 weight % of the orally disintegrable tablet apart from the fine granules;

[26] an orally disintegrable tablet of the above [4], wherein the crystalline cellulose is in an amount of 3 to 50 weight % relative to 100 weight % of the tablet apart from the fine granule;

[27] an orally disintegrable tablet of the above [6], wherein the content of hydroxypropoxyl group in the low-substituted hydroxypropyl cellulose is 7.0 to 9.9 weight %;

[28] an orally disintegrable tablet of the above [6], wherein the content of hydroxypropoxyl group in the low-substituted hydroxypropyl cellulose is 5.0 to 7.0 weight %;

[29] an orally disintegrable tablet of the above [1], which further comprises crospovidone;

[30] an orally disintegrable tablet of the above [1], wherein the oral disintegration time is one minute or less;

[31] an orally disintegrable tablet of the above [1], which comprises no lubricant inside the tablet;

[32] fine granules having an average particle diameter of 400 μm or less, which comprise a composition coated by an enteric coating layer, said composition having (i) 25 weight % or more of an acid-labile physiologically active substance and (ii) a basic inorganic salt;

[33] fine granules of the above [32], wherein the average particle diameter of the fine granules is 300 to 400 μm;

[34] fine granules of the above [32], wherein the particle diameter of the fine granules is practically 425 μm or less;

[35] fine granules of the above [32], wherein the particle diameter of the fine granules is practically 400 μm or less;

[36] fine granules of the above [32], wherein the acid-labile physiologically active substance is a benzimidazole compound or a salt thereof;

[37] fine granules of the above [36], wherein the benzimidazole compound is lansoprazole;

[38] fine granules of the above [32], wherein the basic inorganic salt is a salt of magnesium and/or a salt of calcium;

[39] fine granules of the above [32], wherein the composition comprises a core being coated by a benzimidazole compound and a basic inorganic salt, said core comprising crystalline cellulose and lactose;

[40] fine granules of the above [39], wherein the core comprises 50 weight % or more of lactose;

[41] fine granules of the above [32], wherein the composition comprises 25 to 40 weight % of an acid-labile physiologically active substance;

[42] fine granules of the above [32], which are produced by fluidized-bed granulation method;

[43] fine granules of the above [32], wherein the enteric coating layer comprises an aqueous enteric polymer agent;

[44] fine granules of the above [43], wherein the aqueous enteric polymer agent is a methacrylate copolymer;

[45] fine granules of the above [43], wherein the enteric coating layer further comprise a sustained-release agent;

[46] fine granules of the above [45], wherein the sustained-release agent is a methacrylate copolymer;

[47] fine granules of the above [45], wherein the sustained-release agent is in an amount of 5 to 15 weight % relative to 100 weight % of the aqueous enteric polymer agent;

[48] fine granules of the above [32], wherein the enteric coating layer is in an amount of 50 to 70 weight % relative to 100 weight % of the fine granules;

[49] a tablet, granule, fine granule, capsule, effervescent or suspension preparation which comprises the fine granules of the above [32], and so forth.

In the present specification, "coating" means also partial coating and adhesion or adsorption in addition to coating the whole surface of an object (e.g., core) which is to be coated.

"Spherical" means also forms having a curved surface such as forms having elliptic cross sections, and forms in the shapes of eggplants and drops in addition to spheres.

"Average particle diameter" means volume based distribution median diameter (median diameter: 50% particle diameter from cumulative distribution), unless otherwise specified. It can be measured by, for example, a laser diffraction particle distribution measurement method. Concretely exemplified is a method using Raser Diffraction Analyzer, type: HEROS RODOS [trade name; manufactured by Sympatec (Germany)].

"An orally disintegrable tablet" of the present invention comprises (i) fine granules having an average particle diameter of 400 μm or less, which fine granules comprise a composition coated by an enteric coating layer, said composition having 10 weight % or more of an acid-labile physiologically active substance and (ii) an additive.

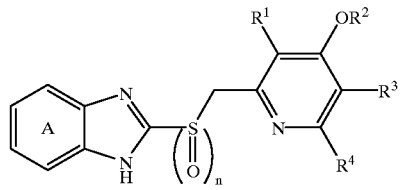
In the present invention, "fine granules having an average particle diameter of 400 μm or less, which fine granules comprise a composition coated by an enteric coating layer, said composition having 10 weight % or more of an acid-labile physiologically active substance" have an average particle diameter of about 400 μm or less, in order that roughness is not felt in the mouth. Preferably, the average particle diameter of the fine granules is 300 to 400 μm.

Aside from the average particle diameter of the above "fine granules", regarding the maximum particle size, the particle diameter is practically 425 μm or less, and preferably practically 400 μm or less. Preferably, the particle diameter is practically 300 to 425 μm, more preferably 300 to 400 μm.

"Practically" as used in "the particle diameter is practically 425 μm or less" and "the particle diameter is practically 400 μm or less" means that the particles may include a small quantity (about 5 weight % or less) of particles whose particle diameter Is out of above described range to Include the inevitable contaminant particles.

"An acid-labile physiologically active substance" includes a compound being unstable in an acidic region and/or a compound inactivated by an acid, especially a pharmaceutical ingredient. Concretely mentioned are vitamins such as vitamin B_{12}, fursultiamine, folic acid, vitamin A, vitamin D, as well as a known benzimidazole compound having an antiulcer activity of the formula (I) below, or a salt thereof.

Formula (I)



wherein ring A may be substituted; R^1, R^3 and R^4 are the same or different and each is a hydrogen, an alkyl or an alkoxy; R^2 is C_{1-4} alkyl which may be substituted by a substituent(s) selected from the group consisting of halogen, hydroxy and C_{1-4} alkoxy; and n is 0 or 1.

In the above formula (I), "substituent(s)" of the "substituted ring A" include, for example, halogen, C_{1-10} alkyl which may be substituted, C_{3-7} cycloalkyl which may be substituted, C_{2-16} alkenyl which may be substituted, C_{1-10} alkoxy which may be substituted, cyano, carboxy, C_{1-7} alkoxycarbonyl, C_{1-4} alkoxycarbonyl-C_{1-4} alkyl, carbamoyl, carbamoyl-C_{1-14} alkyl, hydroxy, hydroxy-C_{1-7} alkyl, C_{1-6} acyl, carbamoyloxy, nitro, C_{2-6} acyloxy, C_{6-12} aryl, C_{6-12} aryloxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, etc.

The "substituent" of the above "C_{1-10} alkyl which may be substituted", "C_{3-7} cycloalkyl which may be substituted", or "C_{2-16} alkenyl which may be substituted" includes, for example, (1) halogen, (2) nitro, (3) amino which may be substituted by 1 or 2 of C_{1-4} alkyl and C_{1-4} acyl, etc., (4) amidino, (5) guanidino, (6) carbamoyl, etc. The number of these substituents is 1 to 3.

The "substituent" of the above "C_{1-10} alkoxy which may be substituted" includes, for example, (1) halogen, (2) nitro, (3) amino which may be substituted by 1 or 2 of C_{1-4} alkyl and C_{1-4} acyl, etc., (4) amidino, (5) guanidino, etc. The number of these substituents is 1 to 3.

The above "C_{1-6} acyl" includes, for example, C_{2-6} alkanoyl such as formyl, acetyl, propionyl, etc.

The above "C_{1-4} acyl" includes, for example, formyl and C_{2-4} alkanoyl such as acetyl, propionyl, etc.

The above "C_{2-6} acyloxy" includes, for example, C_{2-6} alkanoyloxy such as acetyloxyl, etc.

The above "C_{6-12} aryl" includes, for example, phenyl, naphthyl, etc.

The above "C_{6-12} aryloxy" includes, for example, phenoxy, naphthyloxy, etc.

The "alkyl" for R^1, R^3 or R^4 includes, for example, a straight-chain or branched C_{1-10} alkyl such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl,

decyl, etc. Among others, preferred is a straight-chain or branched C_{1-6} alkyl. More preferred is a straight-chain or branched C_{1-3} alkyl.

The "alkoxy" for R^1, R^3 or R^4 includes, for example, C_{1-10} alkoxy such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, n-pentoxy, isopentoxy, neopentoxy, hexyloxy, heptyloxy, octyloxy, nonyloxy, cyclobutoxy, cyclopentoxy, cyclohexyloxy, etc. Among others, preferred is C_{1-6}alkoxy. More preferred is C_{1-3} alkoxy.

The "C_{1-4} alkyl" of the "C_{1-4} alkyl which may be substituted by a substituent(s) selected from the group consisting of halogen, hydroxy and C_{1-4} alkoxy" for R^2 includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, etc.

The "C_{1-4} alkoxy" of the above "C_{1-4} alkyl which may be substituted by a C_{1-4} alkoxy" includes, for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, etc.

The number of the substituents which the "C_{1-4} alkyl" has is preferably 1 to 3.

Salts of the benzimidazole compound include pharmaceutically acceptable salts such as alkali metal salts, e. g., sodium salts and potassium salts, alkaline earth metal salts e. g., calcium salts and magnesium salts, etc.

Such benzimidazole compounds having an antiulcer activity, or salts thereof include, for example, a compound or a salt thereof disclosed in JP-A-52-62275, JP-A-54-141783 JP-A-57-53406, JP-A-58-135881, JP-A-58-192880, JP-A-59-181277, JP-A-61-50978, JP-A-62-116576, JP-A-62-277322, JP-A-62-258320, JP-A-62-258316, JP-A-64-6270, JP-A-64-79177, JP-A-5-59043, JP-A-62-111980, JP-A-5-117268, EP-A-166287, EP-A-519365, and so forth.

The "physiologically active substance" of the present invention preferably is a benzimidazole compound or a salt thereof such an tenooprdzole, omneirazole, rabmprazole, pantoprazole, perprazole, leminoprazole, TU-199, etc. Preferred is lansoprazole and omeprazole, etc. More preferred is lansoprazole.

The amount of the "acid-labile physiologically active substance" in the "composition" is, for example, about 10 weight % or more, preferably about 20 weight % or more, more preferably about 23 weight % or more, especially preferably about 25 weight % or more. Among others, preferred is 20 to 50 weight %.

In the "composition", a basic inorganic salt is preferably incorporated with the acid-labile physiologically active substance.

The "basic inorganic salt" includes, for example, a basic inorganic salt of sodium, potassium, magnesium and/or calcium, preferably a basic inorganic salt of magnesium and/or calcium. Among others, preferred is a basic inorganic salt of magnesium.

The basic inorganic salt of sodium includes, for example, sodium carbonate, sodium hydrogencarbonate, etc.

The basic inorganic salt of potassium includes, for example, potassium carbonate, potassium hydrogencarbonate, etc.

The basic inorganic salt of magnesium includes, for example, heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metagilicate aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite [$Mg_6Al_2(OH)_{16}.CO_3.4H_2O$], aluminum magnesium hydroxide [$2.5MgO.Al_2O_3.xH_2O$], etc. Among others, preferred is heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, etc.

The basic inorganic salt of calcium includes, for example, precipitated calcium carbonate, calcium hydroxide, etc.

The preferable examples of the "basic inorganic salt" include heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, etc.

Such basic inorganic salt of magnesium or calcium, etc. has a basic pH (not less than 7) when it is in the form of a 1% aqueous solution or suspension.

Two or more of these basic inorganic salts (preferably a basic inorganic salt of magnesium, a basic inorganic salt of calcium, etc.) can be used as a mixture in a given ratio. The amount of the basic inorganic salt to be used is appropriately selected depending on the kind of the basic inorganic salt and is, for instance, about 0.3 to 200 weight %, preferably about 1 to 100 weight %, more preferably about 10 to 50 weight %, especially preferably about 20 to 40 weight % relative to the benzimidazole compound or a salt thereof.

The "composition" may contain water-soluble polymers, the following binders, lubricants, and excipients, etc. in common use as pharmaceutical materials. The amount of such water-soluble polymers, binders, lubricants, and excipients is selected from amounts commonly employed in the manufacture of preparations in general dosage forms.

The "water-soluble polymer" includes, for example, a water-soluble polymer which is soluble in ethanol (i.e., an ethanol-soluble water-soluble polymer) such as a cellulose derivative (e.g., hydroxypropyl cellulose, which may be referred to as "HPC" hereinafter), poly(vinylpyrrolidone), etc.; a water-soluble polymer which is insoluble in ethanol (i.e., an ethanol-insoluble water-soluble polymer) such as a cellulose derivative (e.g., hydroxypropylmethyl cellulose, which may be referred to as "HPMC" hereinafter, methyl cellulose, carboxymethyl cellulose sodium, etc.), sodium polyacrylate, polyvinyl alcohol, sodium alginate, and guar gum, etc.

When such water-soluble polymers are used, the dissolution of drugs (physiologically active substances) can be controlled by employing them in combination with the ethanol-soluble water-soluble polymer and ethanol-insoluble water-soluble polymer or by employing them in combination with some water-soluble polymers having different viscosity.

In the present invention, the "water-soluble polymer" is preferably, a cellulose derivative such as HPC, HPMC, and methyl cellulose, and polyvinyl alcohol. More preferred is a cellulose derivative such as HPC, HPMC.

The "HPC" contains, for example, about 53.4 to 77.5 weight %, more preferably about 60 to 70 weight %, of hydroxypropoxyl group. The viscosity of 2 weight % aqueous solution of HPC at 20° C. is usually about 1 to 150,000 cps (centipoise). As the above HPC, hydroxypropyl cellulose defined in Japanese Pharmacopoeia may be employed. Hereinafter, all viscosity of HPC is a value of 2 weight % aqueous solution at 20° C.

The "HPMC" is a mixed ether which is connected by a methoxy group and a hydroxypropoxy group. The content of the methoxy group of HPMC is, for example, about 19 to 30 weight %, The content of the hydroxypropoxy group is, for example, about 4 to 12 weight %. The viscosity of 2 weight % aqueous solution of HPMC at 20° C. is usually about 1 to 40,000 centistokes. As such HPMC may be employed hydroxypropylmethyl cellulose 2208 defined by Japanese Pharmacopoeia, hydroxypropylmethyl cellulose 2906 defined by Japanese Pharmacopoeia, hydroxypropylmethyl cellulose 2910 defined by Japanese Pharmacopoeia, and so forth. Hycroxypropyl cellulose(s) may be employed alone or in admixture of two or more thereof.

The content of the water-soluble polymer such as HPC and/or HPMC is usually about 0.1 to 50 weight %, preferably about 1 to 30 weight %, as against the whole "composition" containing the physiologically active substance, in order to control the dissolution of the physiologically active substance in the composition containing the physiologically active substance and retain a high content of the physiologically active substance.

The above "enteric coating layer" which coats the "composition having 10 weight % or more of an acid-labile physiologically active substance" includes, for example, an aqueous enteric polymer agent such as cellulose acetate phthalate (CAP), hydroxypropylmethyl cellulose phthalate (hereinafter, referred to as HP-55), hydroxymethyl cellulose acetate succinate, methacrylate copolymer [e.g., Eudragit L30D-55 etc. (trade name; manufactured by Rohm GmbH (Germany)), KollICoat MAE30DP (trade name; manufactured by BASF (Germany)), Polyquid PA-30 (trade name; manufactured by SanyoKasei (Japan)), etc.], carboxymethyl cellulose, shellac, etc.; a sustained-release agent such as methacrylate copolymer [e.g., Eudragit NE30D (trade name), Eudragit RL30D (trade name), Eudragit RS30D (trade name), etc.]; a water-soluble polymer; plasticizers such as triethyl citrate, polyethylene glycol, acetylatedmonoglyceride, triacetin, castor oil, etc. and mixtures thereof.

The "aqueous enteric polymer agent" is preferably a methacrylate copolymer. The "sustained-release agent" is preferably a methacrylate copolymer.

The "sustained-release agent" is used in an amount of 5 to 30 weight %, preferably 5 to 15 weight %, relative to 100 weight % of the "aqueous enteric polymer agent". The "plasticizers" is used in an amount of 5 to 30 weight% relative to 100 weight % of the "aqueous enteric polymer agent".

The "additives" of the "orally disintegrable tablet which. comprises (i) fine granules having an average particle diameter of 400 μm or less, which fine granules comprise a composition coated by an enteric coating layer, said composition having 10 weight % or more of an acid-labile physiologically active substance and (ii) an additive" may be ones commonly employed as pharmaceutical materials. The amount of such additives to be used is selected from amounts commonly employed in the manufacture of preparations in general dosage forms.

The "additives" include, for example, a water-soluble sugar alcohol, a crystalline cellulose, a low-substituted hydroxypropyl cellulose, as well as, binders, acids, foaming agents, artificial sweeteners, flavorants, lubricants, colorants, stabilizers, excipients, disintegrants, and so forth.

The "water-soluble sugar alcohol" means a water-soluble sugar alcohol which needs water in an amount of less than 30 ml when 1 g of water-soluble sugar alcohol is added to water and dissolved within about 30 minutes at 20° C. by strongly shaking every 5 minutes for 30 seconds.

The "water-soluble sugar alcohol" includes, for example, sorbitol, mannitol, maltitol, reduced starch saccharide, xylitol, reduced paratinose, erythritol, etc. Two or more of these water-soluble sugar alcohols can be used as a mixture in a given ratio.

The "water-soluble sugar alcohol" is preferably mannitol, xylitol and erythritol. More preferred is mannitol and erythritol. Especially preferred is mannitol. As erythritol, one that is produced by fermentation with yeasts using glucose as the starting material, and that has a particle size of at most 50 mesh is used. Such erythritol is available on the market, e.g. as manufactured by Nikken Chemical Co., Ltd. (Japan).

The "water-soluble sugar alcohol" is usually employed in an amount of about 5 to 97 weight %, preferably about 10 to 90 weight % relative to 100 weight % of the orally disintegrable tablet apart from the fine granules, in order to obtain sufficient strength of the preparation and sufficient disintegration or dissolution in the oral cavity.

For example, mannitol or erythritol is usually employed in an amount of about 5 to 90 weight %, preferably about 10 to 80 weight %, more preferably about 20 to 80 weight %, especially preferably about 50 to 80 weight % relative to 100 weight % of the orally disintegrable tablet apart from the fine granules.

The "crystalline cellulose" includes refined one having partially α-cellulose depolymerization. Such crystalline cellulose includes one called microcrystalline cellulose. Examples of the "crystalline cellulose" include CEOLUS KG801, avicel PH101, avicel PH102, avicel PH301, avicel PH302, avicel RC-591 (crystalline cellulose carmellose sodium), etc. Among these, preferably employed is CEOLUS KG801 which is also called crystalline cellulose of high compressibility. Two or more of the crystalline cellulose can be used as a mixture in a given ratio. Such crystalline cellulose is available on the market, for example, as manufactured by Asahi Chemical Co., Ltd. (Japan).

The "crystalline cellulose" is used, for instance, in an amount of about 3 to 50 weight %, preferably about 5 to 40 weight %, more preferably about 5 to 20 weight % relative to 100 weight % of the orally disintegrable tablet apart from the fine granules.

The "low-substituted hydroxypropyl cellulose" means a low-substituted hydroxypropyl cellulose wherein the content of hydroxypropoxyl group in the hydroxypropyl cellulose (hereinafter,maybe abbreviated to "the content of HPC group") is about 5.0 to 9.9 weight %, preferably a low-substituted hydroxypropyl cellulose wherein the content of HPC group is about 5.0 to 7.0 weight %, a low-substituted hydroxypropyl cellulose wherein the content of HPC group is about 7.0 to 9.9 weight %, and so forth.

The "low-substituted hydroxypropyl cellulose wherein the content of HPC group is about 7.0 to 9.9% includes, for example, LH-22, LH-32 and mixtures thereof, which are commercially available [Shin-Etsu Chemical Co., Ltd. (Japan)]. Also, they can be produced in accordance with per se known methods, for example, methods described in JP-B-82 53100 or analogous thereto.

The low-substituted hydroxypropyl cellulose wherein the content of HPC group is about 5.0 to 7.0% includes, for example, LH-23, LH-33 and mixtures thereof, described in the following Reference Examples. They can be produced in accordance with per se known methods, for example, methods described in JP-B-82 53100 or analogous thereto.

At first, alkaline cellulose containing free alkaline and propylene oxide is reacted to obtain the crude low-substituted hydroxypropyl cellulose containing free alkaline.

Concretely, for example, raw material pulp such as wood pulp and cotton leader is immersed in about 10 to 50% concentration of an aqueous solution of sodium hydroxide, and pressed to obtain alkaline cellulose of which NaOH/cellulose ratio is about 0.1 to 1.2 (ratio by weight). Next, crude low-substituted hydroxypropyl cellulose containing free alkaline is obtained by reacting the resulting alkaline cellulose and propylene oxide with stirring at about 20 to 90° C. for about 2 to 8 hours. Propylene oxide is used in an amount so that the content of hydroxypropoxyl group in the desired low-substituted hydroxypropyl cellulose can be 5 or more weight % to less than 7 weight % (in case of the

low-substituted hydroxypropyl cellulose wherein the content of HPC group is about 5.0 to 7.0 weight %), 7 or more weight % to less than 9.9 weight % (in case of the low-substituted hydroxypropyl cellulose wherein the content of HPC group is about 7.0 to 9.9 weight %).

The crude low-substituted hydroxypropyl cellulose containing free alkaline is dispersed in water or hot water containing about 5 to 80% of acid necessary to neutralize all the alkaline, and a part of the crude low-substituted hydroxypropyl cellulose containing free alkaline is dissolved therein. Acid is further added to neutralize the remaining alkaline.

After the neutralization, some processes such as drainage, drying and grinding are performed in accordance with conventional methods to obtain the desired low-substituted hydroxypropyl cellulose.

The particle diameter of "the low-substituted hydroxypropyl celluloses wherein the content of hydroxypropoxyl group is 5.0 to 7.0 weight %" to be used in the present invention is, for example, about 5 to 60 Sm. preferably about 10 to 40 μm, as a average particle diameter.

In the above ranges, in case that low-substituted hydroxypropyl celluloses (L-HPC) having a relatively large particle diameter (for example, L-HPC having about 26 to 40 μm of the average particle diameter) is employed, a pharmaceutical preparation superior in disintegrability can be produced. On the other hand, in case that L-HPC having a relatively small particle diameter (for example, L-HPC having about 10 to 25 μm of the average particle diameter) is employed, a pharmaceutical preparation superior in strength of the preparation can be produced. Accordingly, the particle diameter of L-HPC can be suitably selected according to the characteristics of the desired pharmaceutical preparation.

The "low-substituted hydroxypropyl cellulose wherein the content of HPC group is 5.0 to 7.0 weight %" or the "low-substituted hydroxypropyl cellulose wherein the content of HPC group is 7. 0 to 9.9%" is usually employed in an amount of about 3 to 50 weight %, preferably about 5 to 40 weight %, relative to 100 weight % of the orally disintegrable tablet apart from the fine granules, in order to obtain sufficient oral disintegrability and sufficient strength of the preparation.

The "binders" include, for example, hydroxypropyl cellulose, hyaroxypropylmethylcellulose, crystalline cellulose, α starch (pregelatinized starch), polyvinylpyrrolidone, gum arabic powder, gelatin, pullulan, low-substituted hydroxypropyl cellulose, etc. The use of crystalline cellulose as the binders provides a solid preparation which exhibits more excellent strength of a preparation while retaining excellent disintegration and dissolution in the oral cavity.

The "acids" include, for example, citric acid (e.g., citric acid anhydrous), tartaric acid, malic acid, etc.

The "foaming agents" include, for example, sodium hydrogen carbonate, etc.

The "artificial sweeteners" include, for example, saccharin sodium, dipotassium glycyrrhizinate, aspartame, stevia, thaumatin, etc.

The "flavorants" include synthetic flavorants or natural flavorants, such as lemon, lime, orange, menthol, strawberry, etc.

The "lubricants" include, for example, magnesium stearate, sucrose fatty acid ester, polyethyleneglycol, talc, stearic acid, etc.

The "colorants" include, for example, various food colorants such as Food Yellow No. 5, Food RED No. 2, Food Blue No. 2, etc., food lakes, red iron oxide, etc.

The "stabilizers" include, for example, the above-mentioned "basic inorganic salt".

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

The "disintegrants" include those conventionally used in the pharmaceutical field, such as (1) crospovidone, (2) super disintegrants such as croscarmellose sodium [FMC-Asahi Chemical Co., Ltd. (Japan)], carmellose calcium [Gotoku Chemical(Yakuhin), (Japan)], (3) carboxymethylstarch sodium [e.g., Matsutani Chemical Co., Ltd. (Japan)], (4) low-substituted hydroxyDropyl cellulose e.g., Shin-Etgu Chemical Co., Ltd. (Japan)], (5) corn starch, etc. Among others, preferred is, for example, crospovidone.

The "crospovidone" includes polyvinylpolypyrrolidone (PVPP), 1-vinyl-2-pyrrolidinone homopolymer, 1-ethenyl-2-pyrrolidinone homopolymer, etc, such as Kollidon CL [manufactured by BASF (Germany)], Polyplasdone XL [manufactured by ISP Ltd. (Japan)], Polyplasdone XL-10 [manufactured by ISP Ltd. (Japan)], Polyplasdone INF-10 [manufactured by ISP Ltd. (Japan)], etc. Usually crospovidone having a molecular weight of at least 1,000,000 is used.

Two or more of these disintegrants can be as a mixture in a given ratio. For example, (i) crospovidone solely, or (ii) crospovidone and another disintegrant(s) is preferably employed.

The "disintegrants" are used, for instance, in an amount of about 1 to 15 weight %, preferably about 1 to 10 weight %, more preferably about 3 to 7 weight %, relative to 100 weight % of the orally disintegrable tablet apart from the fine granules.

In the present invention, the "fine granules" may contain, for example, titanium oxide as a masking agent.

The diameter of the "orally disintegrable tablet" of the present invention is about 5 to 20 mm, preferably about 7 to 15 mm, more preferably about 8 to 13 mm.

The "orally disintegrable tablet" may comprise no lubricant inside the tablet.

The "orally disintegrable tablet" of the present invention exhibits fast disintegrability or dissolubility in the oral cavity, and also an appropriate strength of preparation.

The oral disintegration time of the "orally disintegrable tablet" of the present invention (the time for healthy male or female adults to complete disintegration by buccal saliva) is one minute or less, usually about 50 seconds or less, preferably about 40 seconds or less, more preferably about 30 seconds or less.

The strength of the "orally disintegrable tablet" of the present invention (measurement with a tablet hardness tester) is usually about 1 to 20 kg, preferably about 2 to 15 kg, more preferably 3 to 8 kg.

In the above-mentioned fine granules, "fine granules having an average particle diameter of 400 pzn or less, which comprise a composition coated by an enteric coating layer, said composition having (i) 25 weight % or more of an acid-labile physiologically active substance and (ii) a basic inorganic salt" are novel.

The "fine granules" have an average particle diameter of about 400 μm or less, preferably 350 μm or less. Preferably; the average particle diameter of the fine granules is 300 to 400 μm. Aside from the average particle diameter of the "fine granules", regarding the maximum particle size, the particle diameter is practically 425 μm or less, and preferably practically 400 μm or less. Preferably, the particle diameter is practically 300 to 400 μm or less.

Regarding the fine granule of the present invention, the dissolution of the physiologically active substance can be

controlled by formulating the coat (coating layer) to have different viscosity or content of the water-soluble polymer (e.g., HPC, HPMC and so forth) or by formulating the coat to have a controlled ratio of the ethanol-soluble water-soluble polymer (e.g., HPC) and the ethanol-insoluble water-soluble polymer (e.g., HPMC). The dissolution of the physiologically active substance is not very influenced by liquidity, which can be suitably controlled.

As a pharmaceutical preparation which comprises the "fine granules" of the present invention, there may be employed, for example a solid preparation such as tablet, granule, fine granule, capsule, effervescent, etc; a liquid preparation such as suspension preparation, etc. Among others, preferred is a tablet, more preferred is an orally disintegrable tablet.

When the "fine granule" of the present invention is used for a tablet except for an orally disintegrable tablet, the diameter of the tablet is about 5 to 10 mm, preferably about 5 to 8 mm. When the fine granule of the present invention is used for a capsule, the size of the capsule is preferably a #2 capsule or less.

The "orally disintegrable tablet" of the present invention is and the "pharmaceutical preparation which comprises the fine granules of the present invention" may contain a foaming component to impart a refreshing feeling at administration. Also, with an effervescent comprising the foaming component, the dissolution can be precisely controlled compared to the case of a fine granule alone. As the foaming component, various compounds can be employed as long as safety is not interfered with. Examples of the foaming component include alkaline metal carbonate (e.g., sodium carbonate, potassium carbonate, etc.), alkaline metal hydrogencarbonate (e.g., sodium hydrogencarbonate, potassium hydrogencarbonate, etc.) and ammonium carbonate and so forth. The foaming component(s) may be employed alone or in an admixture of two or more thereof. The preferable foaming component includes sodium carbonate, sodium hydrogencarbonate, ammonium carbonate and so forth. The ratio of the foaming component can be selected within the range in which it is possible to impart the foam, for example, about 10 to 2500 weight %, preferably about 50 to 2000 weight % (e.g., about 75 to 1500 weight %), more preferably about 100 to 1000 weight %, relative to 100 weight % of the fine granule.

In employing the effervescent and the fine granule having small particle diameter, it is advantageous to quickly prepare a homogeneous aqueous solution or suspension, and to maintain the dispersed condition. But, in case that the particle diameter is too small, the problem tends to occur that the fine granule adheres to the wall of a machine by static electricity during production processes.

The specific volume of the above fine granule is about 3 ml/g or less, preferably about 2 ml/g or less. In order to maintain the homogeneous condition of the fine granule in the suspension obtained by adding the foaming agent composition, the specific volume can be suitably selected in the above range according to the specific gravity (specific volume) of the dispersion medium.

The "composition" in the present invention can be produced by a known granulation method.

The "granulation method" includes, for example, rolling granulation method (e.g., centrifugal rolling granulation, etc.), fluidized-bed granulation (e.g., rolling fluidized bed granulation, fluidized granulation, etc.), stirring granulation and so forth. Among others, preferred is fluidized-bed granulation method, more preferred is rolling fluidized-bed granulation method.

Concrete example of the "rolling granulation method" includes a method using "CF apparatus" manufactured by Freund Industrial Co., Ltd. (Japan) and so forth. Concrete examples of the "rolling fluidized-bed granulation method" include methods using "SPIR-A-FLOW", "multi plex" manufactured by Powrex Corp. (U.S.A.), "New-Marumerizer" manufactured by Fuji Paudal Co., Ltd. (Japan), and so forth. The method for spraying the mixture can be suitably selected in accordance with the kind of granulator, and may be, for example, any one of a top spray method, a bottom spray method, a tangential spray method, and so forth. Among others, a tangential spray method is preferred.

The "composition" in the present invention. can be produced in accordance with, for example, a method which comprises coating a core comprising crystalline cellulose and lactose with an acid-labile physiologically active substance.

For example, employed is a method described in JP-A-5-92918 (coating method), which comprises coating a core comprising crystalline cellulose and lactose with an acid-labile physiologically active substance, if necessary together with a basic inorganic salt, binders, lubricants, excipients, a water-soluble polymer, etc. (hereinafter, may be abbreviated to "coating layer"). For example, employed is a method which comprises coating a core with an acid-labile physiologically active substance and a basic inorganic salt, and then further with binders, lubricants, excipients, a water-soluble polymer, etc.

The average particle diameter of the "cores" is about 250 μm or less, preferably about 50 to 250 μm, more preferably about 100 to 250 μm, especially preferably about 100 to 200 μm. The "cores" having the above average particle diameter include particles which all pass through a #50 sieve (300 μm), particles where about 5 w/w % or less of the total remain on a #60 sieve (250 μm), and particles where about 10 w/w % or less of the total pass through a #282 sieve (53 μm) The specific volume of the "core" is about 5 ml/g or less, preferably about 3 ml/g or less.

Examples of the "core" include

(1) a spherical granulated product comprising crystalline cellulose and lactose, (2) a spherical granulated product being about 150 to 250 μm and comprising crystalline cellulose (avicel SP, manufactured by Asahi Chemical Co., Ltd. (Japan)), (3) a stirring granulated product being about 50 to 250 μm and comprising lactose (9 parts) and a starch (1 part), (4) a micro particle being about 250 μm or less classified as a spherical granule comprising micro crystalline cellulose described in JP-A-61-213201, (5) a processed product such as wax formed to a sphere by spraying or melting granulation, (6) a processed product such as gelatin beads comprising oil component, (7) calcium silicate, (8) starch, (9) a porous particle such as chitin, cellulose, chitosan, etc, and (10) a bulk product such as granulated sugar, crystalline lactose or sodium chloride, and processed preparations thereof. Further, these cores may be produced in accordance with per se known grinding method or granulation method, and sifted to prepare the particles having the desired particle diameter.

The above "spherical granulated product comprising crystalline cellulose and lactose" includes, for example (i) a spherical granulated product being 100 to 200 μm and comprising crystalline cellulose (3 parts) and lactose (7 parts) [e.g., Nonpareil 105 (70–140) (particle diameter of 100 to 200 μm), manufactured by Freund Industrial Co., Ltd. (Japan)], (ii) a spherical granulated product being about 150

to 250 μm and comprising crystalline cellulose (3 parts) and lactose (7 parts) [e.g., Nonpareil NP-7:3, manufactured by Freund Industrial Co., Ltd. (Japan)], (iii) a spherical granulated product being 100 to 200 μm and comprising crystalline cellulose (4.5 parts) and lactose (5.5 parts) [e.g., Nonpareil 105T (70–140) (particle diameter of 100 to 200 μm), manufactured by Freund Industrial Co., Ltd. (Japan)], (iv) a spherical granulated product being about 150 to 250 μm and comprising crystalline cellulose (5 parts) and lactose (5 parts) [e.g., Nonpareil NP-5:5, manufactured by Freund Industrial Co., Ltd. (Japan)], and so forth.

In order to produce a pharmaceutical preparation which is superior in dissolution while retaining suitable strength, the "core" includes, for example, preferably the spherical granulated product comprising crystalline cellulose and lactose, more preferably the spherical granulated material comprising crystalline cellulose and lactose and containing 50 weight % or more of lactose. Among others, preferred in a core comprising 40 to 50 weight % of crystalline cellulose and 50 to 60 weight % of lactose.

As the "core" employed in the present invention, in particular, there may be employed the spherical granulated product comprising crystalline cellulose and lactose, more preferably the spherical granulated product with a diameter of about 100 to 200 μm and comprising crystalline cellulose (4.5 parts) and lactose (5.5 parts).

The "core" may contain the physiologically active substance such as the above described pharmaceutical ingredient. Also, the "core" may not contain the physiologically active substance because the release of the physiologically active substance can be controlled by a coating layer containing the physiologically active substance.

The "core" is preferably as uniform a sphere as possible, for reducing the irregularity of the coating, in addition to being a powdery core.

The ratio of the "coating layer" to the "core" can be selected within the range in which it is possible to control dissolution of the physiologically active substance and particle size of the composition, for example, usually about 50 to 400 weight % relative to 100 weight % of the core.

The coating layer may be constructed by plural layers. At least one layer of the plural layers must contain the physiologically active substance. The combination of various layers such as a coating layer not containing the active ingredient, a base coating layer, and an enteric coating layer which constitute the coating layer can be suitably selected.

In case that the "core" is coated, for example, the above physiologically active substance and the water-soluble polymer can be employed in admixture thereof. The admixture may be a solution or a dispersion, and can be prepared by using an organic solvent such as water or ethanol or an admixture thereof.

The concentration of the water-soluble polymer in the admixture varies according to the ratio of the physiologically active substance and the excipients, and is usually about 0.1 to 50 weight %, preferably about 0.5 to 10 weight %, in order to retain the binding strength of the physiologically active substance to the core and maintain the viscosity of the mixture so as not to reduce the workability.

Where the coating layer comprises plural layers, the concentration of the physiologically active substance in each layer may be changed successively or gradually by selecting for the content ratio or viscosity of the water-soluble polymer or by successive coating with mixtures varying in the ratio of the physiologically active substance and the other excipients. In the above case, it may be coated with a mixture in which the content ratio of the water-soluble polymer is out of the range of about 0.1 to 50 weight %, as long as the coating layer as a whole contains about 0.1 to 50 weight % of the water-soluble polymer. Further, in forming the inactive coat according to known methods, the coating layer may comprise some layers such that the inactive layer may block each layer containing the physiologically active substance.

Also, in case of two or more physiologically active substances not suited in the compatibility, the core may be coated by employing each mixture together or separately.

The above coated material is dried, and passed through sieves to obtain a "composition" having uniform size. Because the form of the powder is usually according to the core, a fine granule being in the form of a rough sphere may be obtained. As the sieve may be employed, for example a #50 circular sieve (3001 μm). The composition is obtained by selecting those which pass through the #50 circular sieve.

The "fine granule" in the present invention can be produced in accordance with in the same manner as above granulation method, for example, a method which comprises coating the composition with an enteric coating layer, in order to protect the acid-labile physiologically active substance or to impart enteric dissolution. If necessary, the composition coated with an enteric coating layer may be further coated by a water-soluble sugar alcohol, preferably mannitol. In such case, the strength of the orally disintegrable tablet comprising fine granules is improved.

The "enteric coating layer" is preferably a layer having about 20 to 70 μm, preferably about 30 to 50 μm of thickness and coating the whole surface of the composition containing the physiologically active substance. Accordingly, the smaller particle diameter of the composition, the higher the weight % of the enteric coating layer in the whole fine granule. In the fine granule of the present invention, the "enteric coating layer" is about 30 to 70 weight %, preferably about 50 to 70 weight %, of the fine granule as a whole.

The "enteric coating layer" may be constructed by plural (e.g., 2 or 3) layers. For example, employed is a method which comprises coating a composition with an enteric coating layer having polyethyleneglycol, and then with an enteric coating layer having triethyl citrate, followed by being coated with an enteric coating layer having polyethyleneglycol.

The "orally disintegrable tablet" of the present invention can be produced in accordance with a conventional method in the pharmaceutical field. Such methods include, for instance, a method which comprises blending the "fine granules" and the "additives", and molding, if necessary followed by drying. Concretely mentioned is a method which comprises blending the fine granules and the additives, if necessary with water, and molding, if necessary followed by drying.

The "blending procedure" can be carried out by any of the conventional blending techniques such as admixing, kneading, granulating, etc. The above "blending procedure" is carried out, for instance, by using an apparatus such as Vertical Granulator GV10 [manufactured by Powrex Corp. (Japan)], Universal Kneader [manufactured by Hata Iron Works Co., Ltd. (Japan)], fluidized bed granulator LAB-1 and FD-3S [manufactured by Powrex Corp. (Japan)], V-shape mixer, tumbling mixer, and so forth.

Preferred example of the method for the "orally disintegrable tablet" of the present invention is a method which comprises:

(i) coating a core comprising crystalline cellulose and lactose with an acid-labile physiologically active substance and a basic inorganic salt, followed by being

coated with a coating layer comprising a water-soluble polymer to obtain a composition,

(ii) coating the resultant composition with an enteric coating layer having polyethyleneglycol, and then with an enteric coating layer having triethyl citrate, and then with an enteric coating layer having polyethyleneglycol, followed by being coated by mannitol to obtain fine granule, and

(iii) blending the resultant fine granule with an additive, followed by molding.

Where the pharmaceutical preparation of the present invention, especially an orally disintegrable tablet, is one which comprises no lubricant inside the preparation or tablet, such preparation can be preferably produced in accordance with methods described in JP-A-56-14098, Japanese Patent No. 2681601, etc. Such preparation, especially an orally disintegrable tablet, has sufficient strength. The above lubricant includes, for example, magnesium stearate, sucrose fattyacid ester, polyethyleneglycol, talc, stearic acid, etc.

The pharmaceutical preparations such as solid preparation (e.g., tablets, granules, fine granules, capsules, effervescents, etc.) and liquid preparation such as suspending preparation, which comprises the "fine granules" of the present invention can be produced in accordance with a conventional method.

The solid pharmaceutical preparation containing the "fine granules" of the present invention and the "orally disintegrable tablet" of the invention can also be produced by the wet tabletting method. As the above method, it is preferably employed the methods described in JP-A-5-271054 and so forth. They can also be produced by drying after humidification. As the above method, preferably employed are the methods described in JP-A-9-48726, JP-A-8-291051 and so forth. Namely, it is effective to humidify before tabletting or after tabletting and then to dry, in order to enhance the hardness.

The "molding procedure" can be carried out, for instance, by tabletting with a pressure of 0.5 to 3 ton/cm^2, preferably 1 to 2 ton/cm^2 by using a single-punch tabletting machine [Kikusui Seisakusho (Japan)] or a rotary type tabletting machine [Kikusui Seisakusho (Japan)] when a solid preparation is a tablet, especially an orally disintegrable tablet.

The "drying procedure" can be carried out by any of the techniques used commonly in the art, such as vacuum drying, fluidized-bed drying, etc.

The "fine granules" of the invention can be used for a pharmaceutical preparation. The pharmaceutical preparation includes, for example, a solid preparation such as tablet, granule, fine granule, capsule, effervescent, etc.; a liquid preparation such as a suspension preparation, etc. Among others, a tablet is preferred. Such tablet preferably has suitable strength so as to be stable through production processes and distributions.

A solid pharmaceutical preparation comprising the fine granule of the invention is used for an orally disintegrable tablet and can be administered without water or together with water.

As administration methods, there are listed (1) a method of administration by dissolution or disintegration together with a little water, or without water and with saliva in the oral cavity, not to be swallowed as it is, or (2) a method of administration with water, where it is swallowed as it is. Also, the tablet may be administered dissolved or disintegrated with water.

The "orally disintegrable tablet" of the present invention is advantageously used in (a) cases where administration without water is necessary, (b) cases of administration to a patients who have difficulty in swallowing tablets, or (c) cases of administration to the aged or to children where there is a fear of blocking the throat if it is in usual tablet form.

In case of the above (a), the orally disintegrable tablet is preferably used for antipyretic agents, analgesic agents, anti-inflammatory agents, antianxiety drugs, antitussive-expectorants, anti motion sickness agents, drugs for prevention and treatment for car-sickness, and so forth.

In case of the above (b), the orally disintegrable tablet is preferably used for preventing and/or treating hypertension, hyperlipemia, diabetes, bronchial asthma, cerebrovascular diseases, and so forth.

The "orally disintegrable tablet" of the present invention and the pharmaceutical preparation which comprises the "fine granules" of the present invention can be safely administered orally to mammals such as mice, rats, rabbits, cats, dogs, bovines, horses, monkeys, humans, etc.

With the dosage of the "orally disintegrable tablet" of the present invention and the pharmaceutical preparation which comprises the "fine granules" of the present invention, varies depending on the pharmaceutically active ingredient, subject, kinds of diseases, etc., the dosage can be selected so that the dosage of the pharmaceutically active ingredient is an effective amount.

For instance, when a benzimidazole compound (I) or a salt thereof such as lansoprazole is employed as an acid-labile physiologically active substance, especially a pharmaceutically active ingredient, the "orally disintegrable tablet" of the present invention and the pharmaceutical preparation which comprises the "fine granules" of the present invention is useful for treatment and prevention of digestive ulcer (e.g., gastric ulcer, duodenal ulcer, anastomotic ulcer, Zollinger-Ellison syndrome, etc), gastritis, reflux esophagitis, etc.; eradication of *H. pylori;* suppression of gastrointestinal bleeding caused by digestive ulcer, acute stress ulcer and hemorrhagic gastritis; suppression of gastrointestinal bleeding caused by invasive stress (e.g., stress caused by cerebrovascular disease, head injury, failure of many organs, burn injury of a wide range, which necessitate a large-scale operation necessitating the following intensive management, or intensive care); treatment and prevention of ulcer caused by non-steroidal anti-inflammatory agent; treatment and prevention of gastric hyperacidity and ulcer caused by postoperative stress; administration before anesthesia, etc. The dosage of the preparation per an adult (body weight: 60 kg) is about 0.5 to 1,500 mg/day, preferably about 5 to 150 mg/day, as a benzimidazole compound (I) or a salt thereof such as lansoprazole.

The "orally disintegrable tablet" of the present invention and the pharmaceutical preparation which comprises the "fine granules" of the present invention can be administered once a day, or two or three times separately a day.

BEST MODE FOR CARRYING OUT THE INVENTION

The following Examples and Reference Examples are further illustrative but by no means limitative of the present invention.

Unless otherwise specifically indicated, the following "%" means weight %.

Also, the content of the hydroxypropoxyl group is measured in accordance with the methods described in Japanese Pharmacopoeia (13th edition).

The physical properties of the tablets and granules prepared in Examples were determined by the following test methods.

(1) Hardness Test

Determination was carried out with a tablet hardness tester [manufactured by Toyama Sangyo, Co. Ltd. (Japan)]. The test was performed in 10 runs and mean values were shown.

(2) Oral Disintegration Time

Time for complete disintegration only by saliva in the oral cavity was determined.

(3) Remaining Ratio

According to the 2nd method of the dissolution test defined in Japanese Pharmacopoeia, the dissolution test was performed by using 500 ml of 0.1N HCl (75 rpm) for 1 hour. Then, the enteric fine granule was collected by means of the sieve. The content of the drug in the collected fine granule was measured by the HPLC method. The remaining ratio was calculated according to the following expression with the content of the drug in the tablet which is measured separately by HPLC method.

Remaining ratio=(Content of the drug in the collected fine granule after the dissolution test using 0.1N HCl for 1 hour)/(Content of the drug in the tablet)

(4) Acid-resistance: Dissolution using 0.1N HCl

According to the 2nd method of the dissolution test defined in Japanese Pharmacopoeia, the dissolution test was performed by using 500 ml f 0.1N HCl (75 rpm) for hour. Then, test medium was collected and filtered by using a 0.45 μm membrane filter. The absorbance way measured to calculate the dissolution of the drug into 0.1N HCl.

(5) Average Particle Diameter: Volume Based Distribution Median Diameter (median diameter: 50% Particle Diameter from Cumulative Distribution)

Determination was carried out with Raser Diffraction Analyzer, type; HEROS RODOS [trade name, manufactured by Sympatec (Germany)].

EXAMPLES

Example 1

(1) Production of Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] is charged with 300 g of Nonpareil 105 (70–140) (particle diameter of 100 to 200 μm). With the inlet air temperature and the temperature of the loading being controlled at 85° C. and about 28° C. respectively, the Nonpareil is coated by spraying a bulk liquid of the following composition prepared in advance in accordance with the tangential spray method at a spray rate of 20 g/min. The spraying operation is stopped when the specified amount of the bulk liquid has been sprayed, and then drying is carried out in the granulator for 7 minutes. The resulting granules are sieved through a #60 circular sieve (250 Am) and a #100 circular sieve (150 μm) to provide 750 g of granules having a core.

Bulk Liquid:

Lansoprazole	300 g
Magnesium carbonate	100 g
L-HPC	50 g
HPC (Type SSL)	100 g
Water	1650 g

(2) Production of Film-undercoated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] is charged with 680 g of the above granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 70°0 C. and about 36° C., respectively, an undercoating liquid of the following composition prepared in advance is sprayed in accordance with the tangential spray method at a spray rate of 10 g/min. to provide 650 g of film-undercoated granules having a core.

Undercoating Liquid:

HPMC (Type 2910, viscosity: 3 centistokes)	32 g
Talc	8 g
Water	760 g

(3) Production of Enteric Coated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] is charged with 450 g of the above film-undercoated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 65° C. and about 36° C., respectively, an enteric film coating liquid of the following composition prepared in advance is sprayed in accordance with the tangential spray method at a spray rate of 17 g/min. The coated powders are dried in vacuum at 40° C. for 16 hours, and sieved through a #42 circular sieve (355 μm) and a #80 circular sieve (177 μm) to provide 950 g of enteric coated granules having a core.

Enteric Film Coating Liquid:

Eudragit L30D-55	1078.3 g
Eudragit NE30D	138.5 g
Triethyl citrate	46.0 g
Glyceryl monostearate	23.1 g
Talc	16.0 g
Polysorbate 80	9.0 g
Yellow iron oxide	0.5 g
Water	2038.5 g

Sieve	weight ratio
#18 (850 μm) on	0%
#30 (500 μm) on	0%
#200 (75 μm) on	100%
#200 (75 μm) pass	0%

(4) Production of Granulated Powders

A fluidized bed granulator [manufactured by Powrex Corp. (Japan), LAB-1] is charged with 1321.2 g of erythritol [manufactured by Nikken Chemical Co., Ltd. (Japan)], 360.0 g of low-substituted hydroxypropyl cellulose LH-32 [hydroxypropoxyl group contents of 8.8 %, manufactured by Shin-Etsu Chemical Co., Ltd. (Japan)], 18.0 g of citric acid anhydrous, and 1.8 g of aspartame, and granulation is carried out while spraying a solution which is prepared by dissolving 3.6 g of polyethylene glycol (PEG-6000) in 896.4 ml of purified water. The granules are dried to provide granulated powders. To the granulated powders are added 90.0 g of crospovidone and 5.4 g of magnesium stearate, which is admixed in a bag to give mixed powders.

(5) Production of Orally Disintegrable Tablets

Hereinafter, the above "enteric coated granules having a core" is referred to as "enteric coated powders".

200.0 g of the above enteric coated powders and 300.0 g of the above mixed powders are tabletted using Autograph (trade name; compressing force measurement apparatus) with a punch having a beveled edge, 11 mm in diameter, at a tabletting pressure of 1.0 ton/cm^2 to provide tablets each weighing 500 mg.

Reference Example 1

An alkaline cellulose comprising 24.1% of NaOH, 1.7% of Na_2CO_3, 42.9% of cellulose, 31.8% of H_2O was obtained by immersing a wood pulp in 49% aqueous solution of sodium hydroxide and then by pressing it. A reactor was charged with 100 weight parts of the alkaline cellulose. Then, nitrogen gas replacement was carried out. After the replacement, 5 weight parts of propylene oxide was charged in the reactor and reacted with stirring at 40° C. for 1 hour, at 50° C. for 1 hour and at 70° C. for 1 hour to obtain 103 weight parts of a reactant.

On the other side, a kneader was charged with 2.5 weight parts of hot water at 65° C. and 0.13 weight parts of glacial acetic acid (about 40 weight % against equivalent for neutralization, initial neutralized acid) and therein, 1 weight part of the above resulting alkaline cellulose was dispersed. Then, the temperature was set at 30° C. to dissolve a part of the reactant, and 0.20 weight part of glacial acetic acid (the remainder of an equivalent for neutralization, complete neutralized acid) to obtain a processed fiber product containing a part of dissolution and a part of deposit.

The resulting product was washed with hot water at about 80° C., drained, dried, ground by means of a high rolling impact grinder, and sifted by means of a 100 mesh sieve to obtain the powder of low-substituted hydroxypropyl cellulose LH-33 (the content of hydroxypropoxyl group: 5.8 weight %, the average particle diameter: 17.8 μm).

Reference Example 2

Powders of low-substituted hydroxypropyl cellulose LH-23 (hydroxypropoxyl group contents: 5.7 weight %, average particle diameter: 30.8 μm) were obtained in the same manner as in Reference Example 1.

Example 2

(1) Production of Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 300 g of Nonpareil 105 [(trade name) particle diameter: 100 to 200 μm]. With the inlet air temperature and the temperature of the loading being controlled at 70° C. and about 30° C., respectively, the Nonpareil was coated by spraying a spray liquid of the following composition prepared in advance in accordance with the tangential spray method at a spray rate of 22 g/min., and then drying was carried out in the granulator for 10 minutes. The resulting granules were sieved through a #48 circular sieve (300 μm) and a #100 circular sieve (150 μm) to provide 2186 g of powders (150 to 300 μm) having a core.

Spray Liquid:

Lansoprazole	927 g
Magnesium carbonate	309 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 wt %) (average particle diameter: 17.57 μm)	154.5 g
Hydroxypropyl cellulose (Type SSL)	309 g
Purified water	3955 g

(2) Production of Film-undercoated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 2040 g of the above granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 75° C. and about 40° C., respectively, an undercoating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 13 g/min. to provide 2145 g of film-undercoated granules having a core.

Undercoating Liquid:

Hydroxypropylmethylcellulose (Type 2910, viscosity: 3 centistokes)	264 g
Purified water	5016 g

(3) Production of Enteric Coated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 1710 g of the above film-undercoated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 70° C. and about 40° C., respectively, an enteric film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 17 g/min., and dried for 7 minutes, and then sieved through a #42 circular sieve (355 μm) and a #80 circular sieve (177 μm) to provide 2393 g of enteric coated powders (177 to 355 μm) having a core.

Enteric Film Coating Liquid:

Eudragit L30D-55	5016.4 g
Eudragit NE30D	559.0 g
Triethyl citrate	333.7 g
Glyceryl monostearate	106.5 g
Polysorbate 80	34.8 g
Red iron oxide	1.8 g
Purified water	2547.1 g

(4) Production of Enteric Coated and Mannitol Coated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 600 g of the above enteric coated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 65° C. and about 32° C., respectively, an film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 11 g/min., and then dried for 7 minutes to provide 617 g of enteric coated and mannitol coated granules having a core.

The average particle diameter of the obtained granules was 334.1 μm.

Film Coating Liquid:

Mannitol	33 g
Purified water	297 g

(5) Production of Mannitol-granulated Powders

A fluidized bed granulator [manufactured by Powrex Corp. (Japan), LAB-1] was charged with 800 g of mannitol [manufactured by Merck Japan Co., Ltd.], and granulation was carried out while spraying 315 g of purified water. The granules were dried to provide 727.3 g of granulated powders.

(6) Production of Mixed Powders

To 97.3 g of the above mannitol-granulated powders were added 105 g of the above enteric coated and mannitol coated granules having a core, 15.0 g of low-substituted hydrox-

ypropyl cellulose LH-33 (hydroxypropoxyl group contents: 5.8 weight %, average particle diameter: 17.8 μm), 22.5 g of crystalline cellulose [CEOLUS KG-801 (trade name), manufactured by Asahi Chemical Co., Ltd. (Japan)], 7.5 g of crospovidone, 1.5 g of citric acid anhydrous, 0.45 g of aspartame and 0.75 g of magnesium stearate, which was admixed in a bag to give mixed powders.

(7) Production of Orally Disintegrable Tablets

250.0 g of the above mixed powders were tabletted using Autograph (trade name; compressing force measurement apparatus) with a punch (15R), 11 mm in diameter, at a tabletting pressure of 1.5 ton/cm^2, to provide tablets each weighing 500 mg.

The hardness and oral disintegration time of each tablet thus obtained were 5.9 kg and 30 seconds, respectively.

Example 3

(1) Production of Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 900 g of Nonpareil 105 (trade name) (particle diameter of 100 to 200 μm). With the inlet air temperature and the temperature of the loading being controlled at 75° C. and about 29° C. respectively, the Nonpareil was coated by spraying a bulk liquid of the following composition prepared in advance in accordance with the tangential spray method at a spray rate of 22 g/min. The spraying operation was stopped when the specified amount 5654.7 g of the bulk liquid had been sprayed, and then drying was carried out in the granulator for 10 minutes. The resulting granules were sieved through a #60 circular sieve (250 μm) and a #100 circular sieve (150 μm) to provide 2424 g of granules having a core.

Bulk Liquid:

Lansoprazole	1080 g
Magnesium carbonate	360 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	180 g
Hydroxypropyl cellulose (Type SSL)	360 g
Purified water	4608 g

(2) Production of Film-undercoated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)) was charged with 2337.5 g of the above granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 80° C. and about 41° C., respectively, an undercoating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 18 g/min. The spraying operation was stopped when the specified amount 6050 g of the undercoating liquid had been sprayed, and then drying was carried out in the granulator for 10 minutes to provide 2551 g of film-undercoated granules having a core.

Undercoating Liquid:

Hydroxypropyl methylcellulose (Type 2910, viscosity: 3 centistokes)	332.5 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %) (average particle diameter: 17.57 μm)	17.5 g
Purified water	6650 g

(3) Production of Enteric Coated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 570 g of the above film-undercoated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 75° C. and about 40° C., respectively, an enteric film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 18 g/min. The spraying operation was stopped when the specified amount 2646 g of the enteric film coating liquid had been sprayed, and then drying was carried out in the granulator for 8 minutes. The coated powders were sieved through a #42 circular sieve (355 μm) and a #70 circular sieve (212 μm) to provide 1116 g of enteric coated granules having a core.

The average particle diameter of the obtained granules was 326.9 μm.

Enteric Film Coating Liquid:

Eudragit L30D-55	1911 g
Eudragit NE30D	212.9 g
Triethyl citrate	127.1 g
Glyceryl monostearate	40.6 g
Polysorbate 80	13.3 g
Red iron oxide	0.8 g
Purified water	970.3 g

(4) Production of Mixed Powders

To 200 g of the above enteric coated granules having a core were added 189.7 g of mannitol, 30.0 g of low-substituted hydroxypropyl cellulose LH-23 (hydroxypropoxyl group contents: 5.8 weight %, average particle diameter: 17.8 μm), 60.0 g of crystalline cellulose RCEOLUS KG-801 (trade name), manufactured by Asahi Chemical Co., Ltd. (Japan)], 15.0 g of crospovidone, 2.8 g of citric acid anhydrous and 25 g of magnesium stearate, which was admixed in a bag to give mixed powders.

(5) Production of Orally Disintegrable Tablets

250.0 g of the above mixed powders were tabletted using Autograph (trade name; compressing force measurement apparatus) with a punch (15R), 11 mm in diameter, at a tabletting pressure of 1.5 ton/cm^2, to provide tablets each weighing 500 mg.

The hardness and oral disintegration time of each tablet thus obtained were 4.2 kg and 24 seconds, respectively.

Example 4

(1) Production of Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (TyDp 2)] was charged with 900 g of Nonpareil 105 (trade name) (particle diameter of 100 to 200 μm). With the inlet air temperature and the temperature of the loading being controlled at 75° C. and about 32° C. respectively, the Nonpareil was coated by spraying a bulk liquid of the following composition prepared in advance in accordance with the tangential spray method at a spray rate of 20 g/min. The spraying operation was stopped when the specified amount 5654.7 g of the bulk liquid had been sprayed, and then drying was carried out in the granulator for 10 minutes. The resulting granules were sieved through a #48 circular sieve (300 μm) and a #100 circular sieve (150 μm) to provide 2280 g of granules having a core.

Bulk Liquid:

Lansoprazole	1080 g
Magnesium carbonate	360 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	180 g
Hydroxypropyl cellulose (Type SSL)	360 g
Purified water	4608 g

(2) Production of Film-undercoated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 1020 g of the above granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 85° C. and about 40° C., respectively, an undercoating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 15 g/min. The spraying operation was stopped when the specified amount 1980 g of the undercoating liquid had been sprayed, and then drying was carried out in the granulator for 10 minutes to provide 1330.5 g of film-undercoated granules having a core.

Undercoating Liquid:

Hydroxypropylmethylcellulose (Type 2910, viscosity: 3 centistokes)	120 g
Titanium oxide (TiO_2)	240 g
Sterilized Talc (trade name) [produced by Matsumura Sangyo Co. Ltd. (Japan)]	240 g
Magnesium carbonate	120 g
Purified water	2880 g

(3) Production of Enteric Coated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan)], MP-10 (Type 2)1 was charged with 460 g of the above film-undercoated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 80° C. and about 41° C., respectively, an enteric film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 13 g/min. The spraying operation was stopped when the specified amount 2205 of the enteric film coating liquid had been sprayed.

Enteric Film Coating Liquid:

Eudragit L30D-55	2290 g
Eudragit NE30D	253 g
Triethyl citrate	153 g
Glyceryl monostearate	20 g
Polysorbate 80	8 g
Titanium oxide (TiO_2)	53 g
Sterilized Talc H (trade name) [produced by Matsumura Sangyo Co. Ltd. (Japan)]	53 g
Purified water	2420 g

(4) Production of Enteric Coated and Mannitol Coated Granules Having a Core

Following (3), with the inlet air temperature and the temperature of the loading being controlled at 80° C. and about 35° C., respectively, an film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 16 g/min. using a centrifugal fluidized coating granulator [manufactured by Powrex dorD. (Japan), MP-10 (Type 2)].

The spraying operation was stopped when the specified amount 824 g of the film coating liquid had been sprayed, and then drying was carried out in the granulator for 10 minute. The resulting granules were sieved through a #42 circular sieve (355 μm) and a #60 circular sieve (250 μm) to provide 806 g of enteric coated and mannitol coated granules having a core.

The average particle diameter of the obtained granules was 326.6 μm.

Film Coating Liquid:

Mannitol	320 g
Purified water	2880 g

(5) Production of Mixed Powders

To 120 g of the above enteric coated and mannitol coated granules having a core were added 87.75 g of mannitol, 8.5 g of low-substituted hydroxypropyl cellulose LH-23 (hydroxypropoxyl group contents: 5.8 weight %), 4.5 g of low-substituted hydroxypropyl cellulose LH-33 (hydroxypropoxyl group contents: 5.8 weight %), 19.5 g of crystalline cellulose [CEOLUS KG-801 (trade name), manufactured by Asahi Chemical Co., Ltd. (Japan)], 6.5 g of crospovidone, 1.3 g of citric acid anhydrous, 1.3 g of aspartame and 0.65 g of magnesium stearate, which was admixed in a bag to give mixed powders.

(6) Production of Orally Disintegrable Tablets

250.0 g of the above mixed powders were tabletted using Autograph (trade name; compressing force measurement apparatus) with a punch (15R), 11 mm in diameter, at a tabletting pressure of 1.5 ton/cm^2, to provide tablets each weighing 500 mg.

The hardness and oral disintegration time of each tablet thus obtained were 3.9 kg and 20.5 seconds, respectively.

The remaining ratio of the obtained tablet after acid-resistance test was 97%.

Example 5

(1) Production of Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 900 g of Nonpareil 1.05 (trade name) (particle diameter of 100 to 200 μm). With the inlet air temperature and the temperature of the loading being controlled at 65° C. and about 30° C. respectively, the Nonpareil was coated by spraying a bulk liquid of the following composition prepared in advance in accordance with the tangential spray method at a spray rate of 22 g/min. The spraying operation was stopped when the Specified amount 5661 g of the bulk liquid had been sprayed, and then drying was carried out in the granulator for 8 minutes The resulting granules were sieved through a #42 circular sieve (350 μm) and a #100 circular sieve (150 μm) to provide 2074 g of granules having a core.

Bulk Liquid:

Lansoprazole	1080 g
Magnesium carbonate	360 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	180 g
Hydroxypropyl cellulose (Type SSL)	360 g
Purified water	4680 g

(2) Production of Film-undercoated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged

with 2074 g of the above granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 78° C. and about 40° C., respectively, an undercoating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 22 g/min. The spraying operation was stopped when the specified amount 1980 g of the undercoating liquid had been sprayed, and then drying was carried out in the granulator for 9 minutes. The resulting granules were sieved through a #42 circular sieve (350 μm) and a #100 circular sieve (150 μm) to provide 2555 g of film-undercoated granules having a core.

Undercoating Liquid:

Hydroxypropylmethylcellulose (Type 2910, viscosity: 3 centistokes)	252 g
Titanium oxide (TiO_2)	108 g
Sterilized Talc (trade name) [produced by Matsumura Sangyo Co. Ltd. (Japan)]	108 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	180 g
Mannitol	252 g
Purified water	3600 g

(3) Production of Enteric Coated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 1320 g of the above film-undercoated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 80° C. and about 42° C., respectively, an enteric film coating liquid (A) of the following composition prepared in advance was sprayed in accordance With the tangential spray method at a spray rate of 22 g/min. The specified amount 1638 g of the enteric film coating liquid had been sprayed.

Enteric Film Coating Liquid (A):

Eudragit L30D-55	1219.2 g
Eudragit NE30D	134.4 g
Polyethylene glycol 6000	40.8 g
Glyceryl monostearate	24.0 g
Polysorbate 80	7.2 g
Ferric oxide	0.24 g
Ferric oxide (yellow)	0.24 g
Citric acid anhydrous	0.48 g
Purified water	1693 g

Following this, with the inlet air temperature and the temperature of the loading being controlled at 76° C. and about 42° C., respectively, an enteric film coating liquid (B) of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 22 g/min. The specified amount 6552 g of the enteric film coating liquid had been sprayed.

Enteric Film Coating Liquid (B):

Eudragit L30D-55	4032 g
Eudragit NE30D	447.8 g
Triethyl citrate	269.3 g
Glyceryl monostearate	86.4 g
Polysorbate 80	25.9 g
Ferric oxide	0.86 g
Ferric oxide (yellow)	0.86 g

-continued

Citric acid anhydrous	0.72 g
Purified water	2624 g

Following this, with the inlet air temperature and the temperature of the loading being controlled at 80° C. and about 42° C., respectively, an enteric film coating liquid (A) of the above mentioned composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 22 g/min. The specified amount 819 g of the enteric film coating liquid had been sprayed.

(4) Production of Enteric Coated and Mannitol Coated Granules Having a Core

Following (3), with the inlet air temperature and the temperature of the loading being controlled at 85° C. and about 35° C., respectively an f film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 22 g/min. using a centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)]. The spraying operation was stopped when the specified amount 882 g of the film coating liquid had been sprayed, and then drying was carried out in the granulator for 10 minutes. The resulting granules were sieved through a #35 circular sieve (420 μm) and a #60 circular sieve (250 μm) to provide 1964 g of enteric coated and mannitol coated granules having a core.

The average particle diameter of the obtained granules was 333.7 μm.

Film coating liquid:

Mannitol	180 g
Purified water	1080 g

(5) Production of Mixed Powders

To 270 g of the above enteric coated and mannitol coated granules having a core were added 204.0 g of mannitol, 30 g of low-substituted hydroxypropyl cellulose LH-33 (hydroxypropoxyl group contents: 5.8 weight %), 30 g of crystalline cellulose [CEOLUS KG-801 (trade name), manufactured by Asahi Chemical Co., Ltd. (Japan)], 15 g of crospovidone, 3 g of citric acid anhydrous, 9 g of aspartame, 6 g of magnesium stearate and 3 g of flavor [STRAWBERRY DURAROME (trade name), manufactured by Nihon Filmenich Co., Ltd. (Japan)], which was admixed in a bag to give mixed powders.

(6) Production of Orally Disintegrable Tablets

570 g of the above mixed powders were tabletted using Autograph (trade name; compressing force measurement apparatus) with a punch having a beveled edge, 13 mm in diameter, at a tabletting pressure of 1.5 ton/Cm^2, to provide tablets each weighing 570 mg.

The hardness and oral disintegration time of each tablet thus obtained were 2.6 kg and 20 seconds, respectively.

The acid-resistance of the obtained tablet was 3.5%.

Example 6

(1) Production of Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 750 g of Nonpareil 105 (trade name) (particle diameter of 100 to 200 μm). With the inlet air temperature and the temperature of the loading being controlled at 65° C. and about 30° C. respectively, the Nonpareil was coated by

spraying a bulk liquid of the following composition prepared in advance in accordance with the tangential spray method at a spray rate of 22 g/min. The spraying operation was stopped when the specified amount 4717. 5 g of the bulk liquid had been sprayed, and then drying was carried out in the granulator for 8 minutes. The resulting granules were sieved through a #42 circular sieve (350 μm) and a #100 circular sieve (150 μm) to provide 1811 g of granules having a core.

Bulk Liquid:

Lansoprazole	900 g
Magnesium carbonate	300 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	150 g
Hydroxypropyl cellulose (Type SSL)	300 g
Purified water	3900 g

(2) Production of Film-undercoated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 1811 g of the above granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 78° C. and about 38° C., respectively, an undercoating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray imethod at a spray rate of 22 g/min. The spraying operation was stopped when the specified amount 5274 g of the undercoating liquid had been sprayed, and then drying was carried out in the granulator for 9 minutes. The resulting granules were sieved through a #42 circular sieve (350 μm) and a #100 circular sieve (150 μm) to provide 2628 g of film-undercoated granules having a core.

Undercoating Liquid:

Hydroxypropylmethylcellulose (Type 2910, viscosity: 3 centistokes)	378 g
Titanium oxide (TiO_2)	162 g
Sterilized Talc (trade name) [produced by Matsumura Sangyo Co. Ltd. (Japan)]	162 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	270 g
Mannitol	378 g
Purified water	5400 g

(3) Production of Enteric Coated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 1560 g of the above film-undercoated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 70° C. and about 40° C., respectively, an enteric film coating liquid (A) of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 19 g/min. The specified amount 6048 g of the enteric film coating liquid had been sprayed.

Enteric Film Coating Liquid (A):

Eudragit L30D-55	4032 g
Eudragit NE30D	447.8 g
Triethyl citrate	269.3 g
Glyceryl monostearate	86.4 g
Polysorbate 80	25.9 g
Ferric oxide	0.86 g
Ferric oxide (yellow)	0.86 g
Citric acid anhydrous	0.72 g
Purified water	2624 g

Following this, with the inlet air temperature and the temperature of the loading being controlled at 72° C. and about 42° C, respectively, an enteric film coating liquid (B) of the following composition preepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 19 g/min. The specified amount 819 g of the enteric film coating liquid had been sprayed.

Enteric Film Coating Liquid (B):

Eudragit L30D-55	609.6 g
Eudragit NE30D	68.0 g
Polyethylene glycol 6000	20.4 g
Glyceryl monostearate	12.0 g
Polysorbate 80	3.6 g
Ferric oxide	0.12 g
Ferric oxide (yellow)	0.12 g
Citric acid anhydrous	0.24 g
Purified water	846.7 g

(4) Production of Enteric Coated and Mannitol Coated Granules Having a Core

Following (3), while the inlet air temperature and the temperature of the loading being controlled at 65° C. and about 38° C., respectively, an film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 19 g/min. using a centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)]. The spraying operation was stopped when the specified amount 882 g of the film coating liquid had been sprayed, and then drying was carried out in the granulator for 17 minutes. The resulting granules were sieved through a #35 circular sieve (420 μm) and a #60 circular sieve (250 μm) to provide 2825 g of enteric coated and mannitol coated granules having a core.

The average particle diameter of the obtained granules was 330.5 μm.

Film Coating Liquid:

Mannitol	180 g
Purified water	1080 g

(5) Production of Mixed Powders

To 270 g of the above enteric coated and mannitol coated granules having a core were added 204.0 g of mannitol, 30 g of low-substituted hydroxypropyl cellulose LH-33 (hydroxypropoxyl group contents: 5.8 weight %), 30 g of crystalline cellulose [CEOLUS KC-801 (trade name), manufactured by Asahi Chemical Co., Ltd. (Japan)], 15 g of crospovidone, 3 g of citric acid anhydrous, 9 g of aspartame, 6 g of magnesium stearate and 2 g of flavor [STRAWBERRY DURAROME (trade name), manufactured by Nihon Filmenich Co., Ltd. (Japan)], which was admixed in a bag to give mixed powders.

(6) Production of Orally Disintegrable Tablets

570 g of the above mixed powders were tabletted using Autograph (trade name; compressing force measurement apparatus) with a punch having a beveled edge, 13 mm in diameter, at a tabletting pressure of 1.5 ton/cm^2, to provide tablets each weighing 570 mg.

The hardness and oral disintegration time of each tablet thus obtained were 3.1 kg and 22 seconds, respectively.

The acid-resistance of the obtained tablet was 2.5%.

Example 7

(1) Production of Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 750 g of Nonpareil 105 (trade name) (particle diameter of 100 to 200 μm). With the inlet air temperature and the temperature of the loading being controlled at 75° C. and about 30° C. respectively, the Nonpareil was coated by spraying a bulk liquid of the following composition prepared in advance in accordance with the tangential spray method at a spray rate of 20 g/min. The spraying operation was stopped when the specified amount 4717.5 g of the bulk liquid had been sprayed, and then drying was carried out in the granulator for 10 minutes to provide 1842 g of granules having a core.

Bulk Liquid:

Lansoprazole	900 g
Magnesium carbonate	300 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	150 g
Hydroxypropyl cellulose (Type SSL)	300 g
Purified water	3900 g

(2) Production of Film-undercoated Granules Having a Core

A centrifugal fliudized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 1842 g of the above granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 74° C. and about 38° C., respectively, an undercoating liquid of the following composition prepared an advance was sprayed in accordance with the tangential spray method at a spray rate of 19 g/min. The spraying operation was stopped when the specified amount 5365 g of the undercoatingliquid had been sprayed, and then drying was carried out in the granulator for 9 minutes. The resulting granules were sieved through a#42 circular sieve (350 μm) and a #100 circular sieve (150 μm) to provide 2770 g of film-undercoated granules having a core.

Undercoating Liquid:

Hydroxypropylmethylcellulose (Type 2910, viscosity: 3 centistokes)	378 g
Titanium oxide (TiO_2)	162 g
Sterilized Talc (trade name) [produced by Matsumura Sangyo Co. Ltd. (Japan)]	162 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	270 g
Mannitol	378 g
Purified water	5400 g

(3) Production of Enteric Coated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 1300 g of the above film-undercoated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 78° C. and about 39° C., respectively, an enteric film coating liquid (A) of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 21 g/min. The spraying operation was stopped when the specified amount 5040 g of the enteric film coating liquid had been sprayed, and then drying was carried out in the granulator for 16 minutes. The resulting granules were sieved through a #35 circular sieve (420 μm) and a #60 circular sieve (250 μm) to provide 2453 g of enteric coated granules having a core.

Enteric Film Coating Liquid (A):

Eudragit L30D-55	4032 g
Eudragit NE30D	447.8 g
Triethyl citrate	269.3 g
Glyceryl monostearate	86.4 g
Polysorbate 80	25.9 g
Ferric oxide	0.86 g
Ferric oxide (yellow)	0.86 g
Citric acid anhydrous	0.72 g
Purified water	2624 g

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 1000 g of the above enteric coated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 80° C. and about 38° C., respectively, an enteric film coating liquid (B) of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 19 g/min. The specified amount 273 g of the enteric film coating liquid had, been sprayed.

Enteric Film Coating Liquid (B):

Eudragit L30D-55	610.4 g
Eudragit NE30D	68.0 g
Polyethylene glycol 6000	20.4 g
Glyceryl monostearate	12.0 g
Polysorbate 80	3.6 g
Ferric oxide	0.12 g
Ferric oxide (yellow)	0.12 g
Citric acid anhydrous	0.24 g
Purified water	845.12 g

(4) Production of Enteric Coated and Mannitol Coated Granules Having a Core

Following (3), while the inlet air temperature and the temperature of the loading being controlled at 75° C. and about 35° C., respectively, an film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 20 g/min. using a centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)]. The spraying operation was stopped when the specified amount 294 g of the film coating liquid had been sprayed, and then drying was carried out in the granulator for 10 minutes. The resulting granules were sieved through a #35 circular sieve (420 μm) and a #60 circular sieve (250 μm) to provide 1061 g of enteric coated and mannitol coated granules having a core.

The average particle diameter of the obtained granules was 307.1 μm.

Film Coating Liquid:

Mannitol	120 g
Purified water	720 g

(5) Production of Mixed Powders

To 270 g of the above enteric coated and mannitol coated granules having a core were added 207 g of mannitol, 30 g

of low-substituted hydroxypropyl cellulose LH-33 (hydroxypropoxyl group contents: 5.8 weight %), 30 g of crystalline cellulose [CEOLUS KG-801 (trade name), manufactured by Asahi Chemical Co., Ltd. (Japan)], 15 g of crospovidone, 3 g of citric acid anhydrous, 9 g of aspartame, 6 g of magnesium stearate and 3 g of flavor [STRAWBERRY DURAROME (trade name), manufactured by Nihon Filmenich Co., Ltd. (Japan)], which was admixed in a bag to give mixed powders.

(6) Production of Orally Disintegrable Tablets

570 g of the above mixed powders were tabletted using Autograph (trade name; compressing force measurement apparatus) with a punch having a beveled edge, 13 mm in diameter, at a tabletting pressure of 1.5 ton/cm^2, to provide tablets each weighing 570 mg.

The hardness and oral disintegration time of each tablet thus obtained were 3.2 kg and 24 seconds, respectively.

Example 8

(1) Production of Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 900 g of Nonpareil 105T (trade name) (particle diameter of 100 to 200 m). With the inlet air temperature and the temperature of the loading being controlled at 71 to 78° C. and about 31° C. respectively, the Nonpareil was coated by spraying a bulk liquid of the following composition prepared in advance in accordance with the tangential spray method at a spray rate of 21 g/min. The spraying operation was stopped when the specified amount 5550 g of the bulk liquid had been sprayed, and then drying was carried out in the granulator for 21 minutes. The resulting granules were sieved through a #42 circular sieve (350 μm) and a #100 circular sieve (150 μm) to provide 1723 g of granules having a core.

Bulk Liquid:

Lansoprazole	1080 g
Magnesium carbonate	360 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	180 g
Hydroxypropyl cellulose (Type SSL)	360 g
Purified water	4680 g

(2) Production of Film-undercoated Granules Having a Core

A centrifugal fluided coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 2074 g of the above granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 77° C. and about 41° C., respectively, an undercoating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 21 g/min. The spraying operation was stopped when the specified amount 2787 g of the undercoating liquid had been sprayed, and then drying was carried out in the granulator for 13 minutes. The resulting granules were sieved through a #42 circular sieve (350 μm) and a #100 circular sieve (150 μm) to provide 1958 g of film-undercoated granules having a core.

Undercoating Liquid:

Hydroxypropylmethylcellulose (Type 2910, viscosity: 3 centistokes)	252 g
Titanium oxide (TiO_2)	108 g
Sterilized Talc (trade name) [produced by Matsumura Sangyo Co. Ltd. (Japan)]	108 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	180 g
Mannitol	252 g
Purified water	3600 g

(3) Production of Enteric Coated Granules Having a Core

A centrifugal fluidized Goating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 1100 g of the above film-undercoated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 80° C. and about 41° C., respectively, an enteric film coating liquid (A) of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 22 g/min. The specified amount 1365 g of the enteric film coating liquid had been sprayed.

Enteric Film Coating Liquid (A):

Eudragit L30D-55	1017.3 g
Eudragit NE30D	113.3 g
Polyethylene glycol 6000	34.0 g
Glyceryl monostearate	20.0 g
Polysorbate 80	6.0 g
Ferric oxide	0.2 g
Ferric oxide (yellow)	0.2 g
Citric acid anhydrous	0.4 g
Purified water	1410.8 g

Following this, with the inlet air temperature and the temperature of the loading being controlled at 76° C. and about 41° C., respectively, an enteric film coating liquid (B) of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 22 g/min. The specified amount 5040 g of the enteric film coating liquid had been sprayed.

Enteric Film Coating Liquid (B):

Eudragit L30D-55	3360 g
Eudragit NE30D	373.2 g
Triethyl citrate	224.4 g
Glyceryl monostearate	72.0 g
Polysorbate 80	21.6 g
Ferric oxide	0.72 g
Ferric oxide (yellow)	0.72 g
Citric acid anhydrous	0.6 g
Purified water	1706.8 g

Following this, with the inlet air temperature and the temperature of the loading being controlled at 80° C. and about 42° C., respectively, an enteric film coating liquid (A) of the above mentioned composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 21 g/min. The specified amount 682.5 g of the enteric film coating liquid had been sprayed.

(4) Production of Enteric Coated and Mannitol Coated Granules Having a Core

Following (3), with the inlet air temperature and the temperature of the loading being controlled at 80° C. and about 36° C., respectively, an film coating liquid of the

following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 22 g/min. using a centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)]. The spraying operation was stopped when the specified amount 735 g of the film coating liquid had been sprayed, and then drying was carried out in the granulator for 10 minutes. The resulting granules were sieved through a #35 circular sieve (420 μm) and a #60 circular sieve (250 μm) to provide 2319.5 g of enteric coated and mannitol coated granules having a core.

The average particle diameter of the obtained granules; was 392.7 μm.

Film Coating Liquid:

Mannitol	100 g
Purified water	600 g

(5) Production of Mixed Powders

To 270 g of the above enteric coated and mannitol coated granules having a core were added 204.0 g of mannitol, 30 g of low-substituted hyaroxypropyl cellulose LH-33 (hydroxypropoxyl group contents: 5.8 weight %), 30 g of crystalline cellulose [CEOLUS KG-801 (trade name), manufactured by Asahi Chemical Co., Ltd. (Japan)], 15 g of [crospovidone, 3 g of citric acid anhyaroug, 9 g of dspartame, 6 g of magnesium stearate and 3 g of flavor [STRAWBERRY DURAROME (trade name), manufactured by Nihon Filmenich Co., Ltd. (Japan)], which was admixed in a bag to give mixed powders.

(6) Production of Orally Disintegrable Tablets

570 g of the above mixed powders were tabletted using Autograph (trade name; compressing force measurement apparatus) with a punch having a beveled edge, 12 mm in diameter, at a tabletting pressure of 1.5 ton/cm^2, to provide tablets each weighing 570 mg.

The hardness and oral disintegration time of each tablet thus obtained were 3.7 kg and 35 seconds, respectively.

The acid-resistance of the obtained tablet was 3.4%.

Example 9

(1) Production of Granules Having a Core

A centrifugal fluidized coating granulator (manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 300 g of Nonpareil 105 (70–140) (particle diameter of 100 to 200 μm). With the inlet air temperature and the temperature of the loading being controlled at 85° C. and about 28° C. respectively, the Nonpareil was coated by spraying a bulk liquid of the following composition prepared in advance in accordance with the tangential spray method at a spray rate of 20 g/min. The spraying operation was stopped when the specified amount of the bulk liquid had been sprayed, and then drying was carried out in the granulator for 7 minutes. The resulting granules were sieved through a #48 circular sieve (300 μm) and a #100 circular sieve (150 μm) to provide 757 g of granules having a core.

Bulk Liquid:

Lansoprazole	300 g
Magnesium carbonate	100 g
L-HPC	50 g
HPC (Type SSL)	100 g
Water	1650 g

(2) Production of Film-undercoated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 680 g of the above granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 70° C. and about 36° C., respectively, an undercoating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 10 g/min. to provide 672 g of film-undercoated granules having a core.

Undercoating Liquid:

HPMC (Type 2910, viscosity: 3 centistokes)	32 g
Talc	8 g
Water	760 g

(3) Production of Enteric Coated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 450 g of the above film-undercoated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 65° C. and about 36° C., respectively, an enteric film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a sprayer rate of 17 g/min. The Coated powders were dried in vacuum at 40° C. for 16 hours, and sieved through a #42 circular sieve (355 μm) and a #80 circular sieve (177 μm) to provide 950 g of enteric coated granules having a core.

The average particle diameter of the obtained granules was 285.4 μm.

Enteric Film Coating Liquid:

Eudragit L30D-55	1078.3 g
Eudragit NE30D	138.5 g
Triethyl citrate	46.0 g
Glyceryl monostearate	16.5 g
Talc	16.0 g
Polysorbate 80	9.0 g
Iron oxide	0.5 g
Water	2038.5 g

Sieve	weight ratio
#18 (850 μm) on	0%
#30 (500 μm) on	0%
#200 (75 μm) on	100%
#200 (75 μm) pass	0%

(4) Production of Granulated Powders

A fluidized bed granulator [manufactured by Powrex Corp., (Japan), LAB-1] was charged with 1321.2 g of erythritol [manufactured by Nikken Chemical Co., Ltd. (Japan)], 360.0 g of low-substituted hydroxypropyl cellulose LH-32 [hydroxypropoxyl group contents of 8.8%, manufactured by Shin-PteU Chemical Co., Ltd. (Japan)], 18.0 g of citric acid anhydrous, and 1.8 g of aspartame, and granulation was carried out while spraying a solution which was prepared by dissolving 3.6 g of polyethylene glycol (PEG-6000) in 896.4 ml of purified water. The granules were dried

to provide granulated powders. To the granulated powders were added 90.0 g of crospovidone and 5.4 a of magnesium stearate, which was admixed in a bag to give mixed powders.

(5) Production of Orally Disintegrable Tablets

200.0 g of the above enteric coated granules having a core and 300.0 g of the above mixed powders were tabletted using Autograph (trade name; compressing force measurement apparatus) with a punch having a beveled edge, 11 mm in diameter, at a tabletting pressure of 1.0 ton/cm^2, to provide tablets each weighing 500 mg.

The hardness, the oral disintegration time and remaining ratio after acid-resistance test of each tablet thus obtained were 4.2 kg, 27 seconds and 96.3%, respectively.

INDUSTRIAL APPLICABILITY

The orally disintegrable tablet of the present invention has superior disintegrability or dissolution so that it can be used for treatment or prevention of various diseases, as an orally disintegrable tablet capable of being administered to the aged of children and easily administered without water. Also, because the orally disintegrable tablet of the present invention contains fine granules having the average particle diameter and an enteric coating layer such that it will not impart roughness in mouth, it can be administered easily without discomfort at the administration and has superior acid-resistance.

Further, because the orally disintegrable tablet of the present invention has a suitable strength such that it will not be substantially damaged through production processes or circulation processes, it is superior in stability for long-term storage and easy of use at the administration.

Further, because the fine granule of the present invention is characterized in that it stably retains the acid-labile physiologically active substance, contains the physiologically active substance in high content, be small and has superior stability, it can be used for producing various compact pharmaceutical preparations such as tablets, capsules, suspensions and so forth. Such preparations are easy of use at the administration. In addition, the fine granule of the present invention has superior acid-resistance after compression.

What is claimed is:

1. An orally disintegrable tablet which comprises

(i) fine granules having an average particle diameter of 400 μm or less, which fine granules comprise a composition coated by an enteric coating layer comprising a first component which is an enteric coating agent and a second component which is a sustained-release agent, said composition having 10 weight % or more of an acid-labile physiologically active substrate that is lansoprazole and (ii) an additive wherein said tablet having a hardness strength of about 1 to about 20 kg, is orally disintegrable.

2. An orally disintegrable tablet of claim **1**, wherein the average particle diameter of the fine granule is 300 to 400 μm.

3. An orally disintegrable tablet of claim **1**, wherein the fine granules further comprise a basic inorganic salt.

4. An orally disintegrable tablet of claim **1**, wherein the additive comprises a water-soluble sugar alcohol.

5. An orally disintegrable tablet of claim **1**, wherein the composition coated by an enteric coating layer is further coated by a coating layer which comprises a water-soluble sugar alcohol.

6. An orally disintegrable tablet of claim **4**, wherein the additive comprises (1) crystalline cellulose and/or (ii) low-substituted hydroxypropyl cellulose.

7. An orally disintegrable tablet of claim **1**, wherein the particle diameter of the fine granules is practically 425 μm or less.

8. An orally disintegrable tablet of claim **1**, wherein the particle diameter of the fine granules is practically 400 μm or less.

9. An orally disintegrable tablet of claim **3**, wherein the basic inorganic salt is a salt of magnesium and/or a salt of calcium.

10. An orally disintegrable tablet of claim **1**, wherein the composition comprises a core being coated by a benzimidazole compound and a basic inorganic salt, said core comprising crystalline cellulose and lactose.

11. An orally disintegrable tablet of claim **10**, wherein the core comprises 50 weight % or more of lactose.

12. An orally disintegrable tablet of claim **10**, wherein the core comprises 40 to 50 weight % of crystalline cellulose and 50 to 60 weight % of lactose.

13. An orally disintegrable tablet of claim **1**, wherein the composition comprises 20 weight % or more of an acid-labile physiologically active substance.

14. An orally disintegrable tablet of claim **1**, wherein the composition comprises 20 to 50 weight % of an acid-labile physiologically active substance.

15. An orally disintegrable tablet of claim **1**, wherein the fine granules are produced by fluidized-bed granulation method.

16. An orally disintegrable tablet of claim **1**, wherein the enteric coating layer comprises an aqueous enteric polymer agent.

17. An orally disintegrable tablet of claim **16**, wherein the aqueous enteric polymer agent is a methacrylate copolymer.

18. An orally disintegrable tablet of claim **1**, wherein the sustained-release agent is a methacrylate copolymer.

19. An orally disintegrable tablet of claim **16**, wherein the sustained-release agent is in an amount of 5 15 weight % relative to 100 weight % of the aqueous enteric polymer agent.

20. An orally disintegrable tablet of claim **4**, wherein the water-soluble sugar alcohol is erythritol.

21. An orally disintegrable tablet of claim **4**, wherein the water-soluble sugar alcohol si mannitol.

22. An orally disintegrable tablet of claim **5**, wherein the water-soluble sugar alcohol is in an amount of 5 to 97 weight % relative to 100 weight % of the orally disintegrable tablet apart from the fine granules.

23. An orally disintegrable tablet of claim **4**, wherein the crystalline cellulose is in an amount of 3 to 50 weight % relative to 100 weight % of the tablet apart from the fine granule.

24. An orally disentegrable tablet of claim **6**, wherein the content of hydroxypropoxyl group in the low-substituted hydroxypropyl cellulose is 7.0 to 9.9 weight %.

25. An orally disintegrable tablet of claim **6**, wherein the content of hydroxypropoxyl group in the low-substituted hydroxypropoxyl cellulose is 5.0 7.0 weight %.

26. An orally disintegrable tablet of claim **1**, which further comprises crosprovidone.

27. An orally disintegrable tablet of claim **1**, wherein the oral disintegration time is one minute or less.

28. An orally disintegrable tablet of claim **1**, which comprises no lubricant inside the tablet.

29. Fine granules having an average particle diameter of 400 μm or less, which comprise a composition coated by an enteric coating layer comprising a first component which is an enteric coating agent and a second component which is a sustained-release agent, said composition having (i) 25

weight % or more of an acid-liable physiologically active substance that is lansoprazole and (ii) a basic inorganic salt.

30. Fine granules of claim **28**, wherein the average particle diameter of the fine granules is 300 to 400 μm.

31. Fine granules of claim **28**, wherein the particle diameter of the fine granules is practically 425 μm or less.

32. Fine granules of claim **28**, wherein the particle diameter of the fine granules is practically 400 μm or less.

33. Fine granules of claim **28**, wherein the basic inorganic salt is a salt of magnesium and/or a salt of calcium.

34. Fine granules of claim **28**, wherein the composition comprises a core being coated by a benzimidazole compound and a basic inorganic salt, said core comprising crystalline cellulose and lactose.

35. Fine granules of claim **34**, wherein the core comprises 50 weight % or more of lactose.

36. Fine granules of claim **28**, wherein the composition comprises 25 to 40 weight % of an acid-labile physiologically active substance.

37. Fine granules of claim **28**, which are produced by fluidized-bed granulation method.

38. Fine granules of claim **28**, wherein the enteric coating layer comprises an aqueous enteric polymer agent.

39. Fine granules of claim **38**, wherein the aqueous enteric polymer agent is a methacrylate copolymer.

40. Fine granules of claim **28**, wherien the sustained-release agent is a methacrylate copolymer.

41. Fine granules of claim **28**, wherein the sustained-release agent is in an amount of 5 to 15 weight % relative to 100 weight % of the aqueous enteric polymer agent.

42. Fine granules of claim **28**, wherein the enteric coating layer is in an amount of 50 to 70 weight % relative to 100 weight % of the fine granules.

43. A tablet, granule, fine granule, capsule, effervescent or suspension preparation which comprises the fine granules of claim **28**.

44. An orally disintegrable tablet of claim **16**, wherein the sustained-release agent is in an amount of 5 to 30 weight % relative to 100 weight % of the aqueous enteric polymer agent.

45. Fine granules of claim **38**, wherein the sustained-release agent is in an amount of 5 to 30% relative to 100 weight % of the aqueous enteric polymer agent.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,328,994 B1
DATED : December 11, 2001
INVENTOR(S) : Toshihiro Shimizu, Shuji Morimoto and Tetsuo Tabata

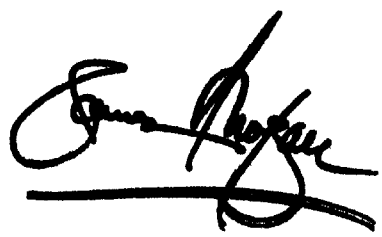
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 37,
Line 8, the word "substrate" should read -- substance --

Column 38,
Line 2, the word "si" should read -- is --

Signed and Sealed this

Fifth Day of August, 2003



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

JS 44 (Rev. 11/04)

CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. (SEE INSTRUCTIONS ON THE REVERSE OF THE FORM.)

I. (a) PLAINTIFFS Takeda Pharmaceutical Company Limited, Tap Pharmaceutical Products Inc., and Ethypharm, S.A.

(b) County of Residence of First Listed Plaintiff _____
(EXCEPT IN U.S. PLAINTIFF CASES)

(c) Attorney's (Firm Name, Address, and Telephone Number) Mary B. Graham
Morris, Nichols, Arsht & Tunnell LLP
1201 N. Market St., Wilmington, DE 19899 302.658.9200

DEFENDANTS
Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd.

County of Residence of First Listed Defendant _____
(IN U.S. PLAINTIFF CASES ONLY)
NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE LAND INVOLVED.

Attorneys (If Known)

II. BASIS OF JURISDICTION (Place an "X" in One Box Only)

- ☐ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question (U.S. Government Not a Party)
- ☐ 2 U.S. Government Defendant
- ☐ 4 Diversity (Indicate Citizenship of Parties in Item III)

III. CITIZENSHIP OF PRINCIPAL PARTIES (Place an "X" in One Box for Plaintiff and One Box for Defendant)
(For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	☐ 1	☐ 1	Incorporated *or* Principal Place of Business In This State	☐ 4	☐ 4
Citizen of Another State	☐ 2	☐ 2	Incorporated *and* Principal Place of Business In Another State	☐ 5	☐ 5
Citizen or Subject of a Foreign Country	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

IV. NATURE OF SUIT (Place an "X" in One Box Only)

CONTRACT
- ☐ 110 Insurance
- ☐ 120 Marine
- ☐ 130 Miller Act
- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment & Enforcement of Judgment
- ☐ 151 Medicare Act
- ☐ 152 Recovery of Defaulted Student Loans (Excl. Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
- ☐ 160 Stockholders' Suits
- ☐ 190 Other Contract
- ☐ 195 Contract Product Liability
- ☐ 196 Franchise

REAL PROPERTY
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Ejectment
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

TORTS

PERSONAL INJURY
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault, Libel & Slander
- ☐ 330 Federal Employers' Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury

PERSONAL INJURY
- ☐ 362 Personal Injury - Med. Malpractice
- ☐ 365 Personal Injury - Product Liability
- ☐ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth in Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

CIVIL RIGHTS
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 444 Welfare
- ☐ 445 Amer. w/Disabilities - Employment
- ☐ 446 Amer. w/Disabilities - Other
- ☐ 440 Other Civil Rights

PRISONER PETITIONS
- ☐ 510 Motions to Vacate Sentence

Habeas Corpus:
- ☐ 530 General
- ☐ 535 Death Penalty
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition

FORFEITURE/PENALTY
- ☐ 610 Agriculture
- ☐ 620 Other Food & Drug
- ☐ 625 Drug Related Seizure of Property 21 USC 881
- ☐ 630 Liquor Laws
- ☐ 640 R.R. & Truck
- ☐ 650 Airline Regs.
- ☐ 660 Occupational Safety/Health
- ☐ 690 Other

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Mgmt. Relations
- ☐ 730 Labor/Mgmt.Reporting & Disclosure Act
- ☐ 740 Railway Labor Act
- ☐ 790 Other Labor Litigation
- ☐ 791 Empl. Ret. Inc. Security Act

BANKRUPTCY
- ☐ 422 Appeal 28 USC 158
- ☐ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ☐ 820 Copyrights
- ☒ 830 Patent
- ☐ 840 Trademark

SOCIAL SECURITY
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g))

FEDERAL TAX SUITS
- ☐ 870 Taxes (U.S. Plaintiff or Defendant)
- ☐ 871 IRS—Third Party 26 USC 7609

OTHER STATUTES
- ☐ 400 State Reapportionment
- ☐ 410 Antitrust
- ☐ 430 Banks and Banking
- ☐ 450 Commerce
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced and Corrupt Organizations
- ☐ 480 Consumer Credit
- ☐ 490 Cable/Sat TV
- ☐ 810 Selective Service
- ☐ 850 Securities/Commodities/ Exchange
- ☐ 875 Customer Challenge 12 USC 3410
- ☐ 890 Other Statutory Actions
- ☐ 891 Agricultural Acts
- ☐ 892 Economic Stabilization Act
- ☐ 893 Environmental Matters
- ☐ 894 Energy Allocation Act
- ☐ 895 Freedom of Information Act
- ☐ 900Appeal of Fee Determination Under Equal Access to Justice
- ☐ 950 Constitutionality of State Statutes

V. ORIGIN (Place an "X" in One Box Only)

☒ 1 Original Proceeding ☐ 2 Removed from State Court ☐ 3 Remanded from Appellate Court ☐ 4 Reinstated or Reopened ☐ 5 Transferred from another district (specify) ☐ 6 Multidistrict Litigation ☐ 7 Appeal to District Judge from Magistrate Judgment

VI. CAUSE OF ACTION

Cite the U.S. Civil Statute under which you are filing **(Do not cite jurisdictional statutes unless diversity)**:

Brief description of cause: Suit for patent infringement under 35 U.S.C. Section 271.

VII. REQUESTED IN COMPLAINT:

☐ CHECK IF THIS IS A CLASS ACTION UNDER F.R.C.P. 23

DEMAND $

CHECK YES only if demanded in complaint:
JURY DEMAND: ☐ Yes ☒ No

VIII. RELATED CASE(S) IF ANY

(See instructions): JUDGE Robinson DOCKET NUMBER C.A. No. 06-33-SLR

DATE May 25, 2007

SIGNATURE OF ATTORNEY OF RECORD Mary B. Graham

FOR OFFICE USE ONLY

RECEIPT # _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____

AO FORM 85 RECEIPT (REV. 9/04)

United States District Court for the District of Delaware

Civil Action No. 07-331

ACKNOWLEDGMENT OF RECEIPT FOR AO FORM 85

NOTICE OF AVAILABILITY OF A UNITED STATES MAGISTRATE JUDGE TO EXERCISE JURISDICTION

FILED
CLERK U.S. DISTRICT COURT
DISTRICT OF DELAWARE
2007 MAY 25 PM 12:25

I HEREBY ACKNOWLEDGE RECEIPT OF 5 COPIES OF AO FORM 85.

MAY 25 2007

(Date forms issued)

(Signature of Party or their Representative)

Aaron Johnston

(Printed name of Party or their Representative)

Note: Completed receipt will be filed in the Civil Action