IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

TAKEDA PHARMACEUTICAL COMPANY, LTD., a Japanese Corporation, and TAP PHARMACEUTICAL PRODUCTS INC., a Delaware Corporation, Plaintiffs,	)	
v.	)	C.A. No. _____
TEVA PHARMACEUTICALS USA, INC. a Delaware Corporation, Defendant.	)	

COMPLAINT

Plaintiffs Takeda Pharmaceutical Company Ltd. and TAP Pharmaceutical Products Inc. (collectively "Plaintiffs"), for their Complaint against defendant Teva Pharmaceuticals USA, Inc., allege as follows:

THE PARTIES

1. Plaintiff Takeda Pharmaceutical Company Ltd. ("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. On information and belief, Teva Pharmaceuticals USA, Inc. ("Teva") 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.

JURISDICTION AND VENUE

4. 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).

5. Teva is subject to personal jurisdiction in this District.

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

FACTS PERTINENT TO ALL CLAIMS FOR RELIEF

7. 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.

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

9. 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.

10. On June 25, 1991, the PTO issued U.S. Patent No. 5,026,560 ("the '560 Patent"), entitled "Spherical Granules Having Core and Their 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 '560 Patent, and Plaintiff TAP is the exclusive licensee. A copy of the '560 Patent is attached hereto as Exhibit B.

11. 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 C.

12. On March 3, 1992, the PTO issued U.S. Patent No. 5,093,132 ("the '132 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 '132 Patent, and Plaintiff TAP is the exclusive licensee. A copy of the '132 Patent is attached hereto as Exhibit D.

13. On July 18, 1995, the PTO issued U.S. Patent No. 5,433,959 ("the '959 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 '959 Patent, and Plaintiff TAP is the exclusive licensee. A copy of the '959 Patent is attached hereto as Exhibit E.

14. On May 10, 1995, the United States Food and Drug Administration ("FDA") approved New Drug Application ("NDA") No. 20-406 for lansoprazole delayed release capsules, 15 and 30 mg. TAP is the holder of NDA No. 20-406 for lansoprazole delayed release capsules, which it sells under the registered name PREVACID®.

15. The '098, '560, '321, '132 and '959 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®, lansoprazole delayed release capsules, 15 and 30 mg.

16. On information and belief, Teva submitted to FDA an amendment to Abbreviated New Drug Application ("ANDA") No. 77-255 seeking approval to engage in the commercial manufacture, use and sale of lansoprazole delayed release capsules, 15 and 30 mg, prior to the expiration of the patents in suit.

17. Plaintiffs have received a letter dated December 5, 2005 from Teva notifying them that Teva amended ANDA No. 77-255 to include a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (a "Paragraph IV certification") that, in Teva'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 capsule products described in ANDA No. 77-255.

18. Plaintiffs commenced this action within 45 days of the date they received Teva's notice of ANDA No. 77-255 containing the Paragraph IV certification.

FIRST CLAIM FOR RELIEF
(Infringement of the '098 Patent)

19. Plaintiffs repeat and reallege each and every allegation contained in paragraphs 1 through 18 hereof, as if fully set forth herein.

20. By amending ANDA No. 77-255 to contain a Paragraph IV certification seeking FDA approval to engage in the commercial manufacture, use and sale of the lansoprazole delayed release capsule 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).

21. On information and belief, Teva was aware of the existence of the '098 Patent prior to amending ANDA No. 77-255 but took such action knowing that it would constitute an infringement of the '098 Patent.

22. 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.

23. Teva does not dispute that the lansoprazole delayed release capsule products described in ANDA No. 77-255 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.

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

25. Plaintiffs will be irreparably harmed if Teva is not enjoined from infringing the '098 Patent.

SECOND CLAIM FOR RELIEF
(Infringement of the '560 Patent)

26. Plaintiffs repeat and reallege each and every allegation contained in paragraphs 1 through 18 hereof, as if fully set forth herein.

27. By amending ANDA No. 77-255 to contain a Paragraph IV certification seeking FDA approval to engage in the commercial manufacture, use and sale of lansoprazole delayed release capsules, 15 and 30 mg, prior to the expiration of the '560 Patent, it is believed that Teva has infringed the '560 Patent under 35 U.S.C. § 271(e)(2).

28. On information and belief, Teva was aware of the existence of the '560 Patent prior to amending ANDA No. 77-255 but took such action knowing that it would constitute an infringement of the '560 Patent.

29. On information and belief, Teva acted without a reasonable basis for a good faith belief that it would not be liable for infringing the '560 Patent.

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

31. Plaintiffs will be irreparably harmed if Teva is not enjoined from infringing the '560 Patent.

THIRD CLAIM FOR RELIEF
(Infringement of the '321 Patent)

32. Plaintiffs repeat and reallege each and every allegation contained in paragraphs 1 through 18 hereof, as if fully set forth herein.

33. By amending ANDA No. 77-255 to contain a Paragraph IV certification seeking FDA approval to engage in the commercial manufacture, use and sale of lansoprazole delayed release capsules, 15 and 30 mg, prior to the expiration of the '321 Patent, it is believed that Teva has infringed the '321 Patent under 35 U.S.C. § 271(e)(2).

34. On information and belief, Teva was aware of the existence of the '321 Patent prior to amending ANDA No. 77-255 but took such action knowing that it would constitute an infringement of the '321 Patent.

35. 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.

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

37. Plaintiffs will be irreparably harmed if Teva is not enjoined from infringing the '321 Patent.

FOURTH CLAIM FOR RELIEF
(Infringement of the '132 Patent)

38. Plaintiffs repeat and reallege each and every allegation contained in paragraphs 1 through 18 hereof, as if fully set forth herein.

39. By amending ANDA No. 77-255 to contain a Paragraph IV certification seeking FDA approval to engage in the commercial manufacture, use and sale of lansoprazole delayed release capsules, 15 and 30 mg, prior to the expiration of the '132 Patent, it is believed that Teva has infringed the '132 Patent under 35 U.S.C. § 271(e)(2).

40. On information and belief, Teva was aware of the existence of the '132 Patent prior to amending ANDA No. 77-255 but took such action knowing that it would constitute an infringement of the '132 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 '132 Patent.

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

43. Plaintiffs will be irreparably harmed if Teva is not enjoined from infringing the '132 Patent.

FIFTH CLAIM FOR RELIEF
(Infringement of the '959 Patent)

44. Plaintiffs repeat and reallege each and every allegation contained in paragraphs 1 through 18 hereof, as if fully set forth herein.

45. By amending ANDA No. 77-255 to contain a Paragraph IV certification seeking FDA approval to engage in the commercial manufacture, use and sale of lansoprazole delayed release capsules, 15 and 30 mg, prior to the expiration of the '959 Patent, it is believed that Teva has infringed the '959 Patent under 35 U.S.C. § 271(e)(2).

46. On information and belief, Teva was aware of the existence of the '959 Patent prior to amending ANDA No. 77-255 but took such action knowing that it would constitute an infringement of the '959 Patent.

47. On information and belief, Teva acted without a reasonable basis for a good faith belief that it would not be liable for infringing the '959 Patent.

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

49. Plaintiffs will be irreparably harmed if Teva is not enjoined from infringing the '959 Patent.

WHEREFORE, Plaintiffs respectfully request the following relief:

A. An order adjudging and decreeing that Teva has infringed the patents in suit;

B. An order pursuant to 35 U.S.C. § 271(e)(4)(A) decreeing that the effective date of any approval of ANDA No. 77-255 be no earlier than May 10, 2009, the date on which the '098 Patent expires, or the date of the last to expire of the patents in suit;

C. A permanent injunction pursuant to 35 U.S.C. § 271(e)(4)(B) restraining and enjoining Teva, its 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. 77-255 until May 10, 2009 or the date of the last to expire of the patents in suit;

D. 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;

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

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January 17, 2006

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

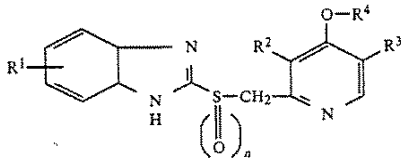
FOREIGN PATENT DOCUMENTS

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.

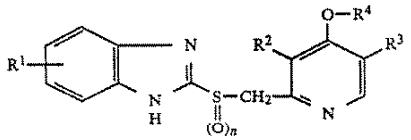
However, while these known compounds have an acid-secretion-inhibiting action, their gastric mucous membrane protecting action is insufficient, thus being hardly considered satisfactory as anti-ulcer agents. Besides, these compounds are possessed of such drawbacks in the physico-chemical properties as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

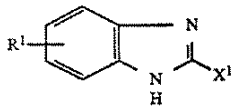
(1) pyridine derivatives of the formula (I)



(I)

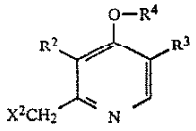
wherein R^1 is hydrogen, methoxy or trifluoromethyl, R^2 and R^3 are independently hydrogen or methyl, R^4 is a C_{2-5} fluorinated alkyl, and n denotes 0 or 1, or their pharmacologically acceptable salts and

(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.

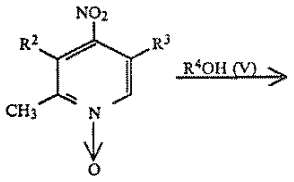
The object compound (I) produced by the above reaction can be isolated and purified by conventional means e.g. recrystallization and chromatography.

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.

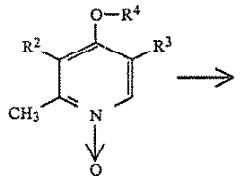
Among the compounds (I), those of n=0 give stable salts, while those of n=1 may exist as an aqueous solution though unstable.

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

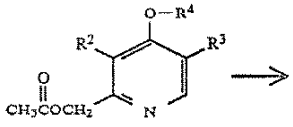
(Process 1)



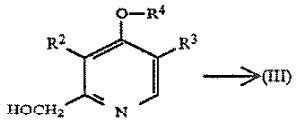
(IV)



(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.

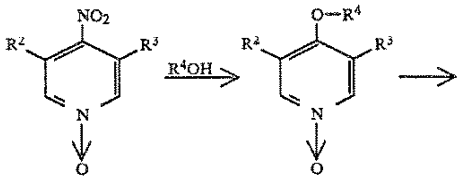
The thus-obtained compound (VI) is subjected to heating (about 80° to about 120° C.) in the presence of acetic anhydride singly or together with a mineral acid e.g. sulfuric acid and perchloric acid to give a 2-acetoxymethylpyridine derivative of the formula (VII) [wherein R^2, R^3 and R^4 are of the 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.

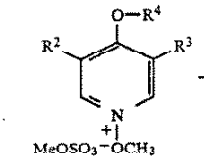
The amount of the organic sulfonic acid chloride or organic phosphoric acid chloride used for the reaction is usually in equivalent to a little excess, and the reaction is usually conducted in the presence of a base. The base is exemplified by organic base e.g. triethylamine and tributylamine, or inorganic 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.

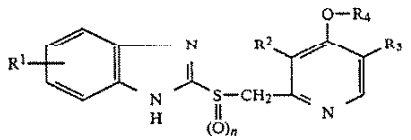
Further, the compound (XI) is allowed to react with a radical source such as ammonium persulfate or any other persulfate in methanol to give the above-mentioned compound (VIII). The reaction temperature is within the range of from about 20° C. to about 80° C., and the reaction time ranges from about 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$\frac{1}{2}H_2O$ (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

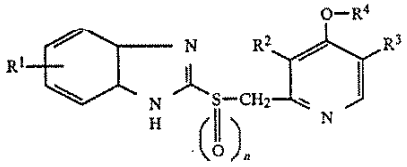
-continued

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.

* * * * *

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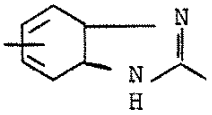
CERTIFICATE OF CORRECTION

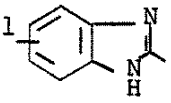
PATENT NO. : 4,628,098

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

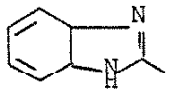
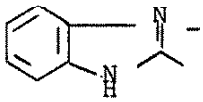
CERTIFICATE OF CORRECTION

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 "" and insert ----.

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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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: 5,026,560**

[45] **Date of Patent: Jun. 25, 1991**

[54] **SPHERICAL GRANULES HAVING CORE AND THEIR PRODUCTION**

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[58] **Field of Search** 424/490, 494, 480

[56] **References Cited**

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[57] **ABSTRACT**

The spherical granules having a core coated with spraying powder containing a drug and low substituted hydroxypropylcellulose, because of their excellent hardness, can be coated further evenly, (e.g. sustained release coating, gastric coating, enteric coating), and at the time the granules are excellent in disintegration.

30 Claims, No Drawings

SPHERICAL GRANULES HAVING CORE AND THEIR PRODUCTION

This invention relates to spherical granules having a core excellent in hardness and disintegration, and to their production.

Recently many studies have been made on drug delivery systems; especially as the dosage form for oral administration, granules coated with various coating agents, i.e. so-called coating granules have been used increasingly frequently, and the granules as they are or capsules produced by filling the granules in capsules have been developed.

As reasons for this fact may be mentioned that granules, as compared with tablets biopharmaceutically, reduce individual variations in gastric emptying rate, absorption, etc. and little affected by food (intake).

For production of spherical granules, the method wherein after granulation by extrusion the granules are made spherical with a marumerizer is most commonly used, but the granules thus produced are mostly not perfect spheres and the granule size distribution is wide; therefore it is said that uniform coating is so difficult that pharmaceutical preparations for precisely controlled release are difficult to be obtained.

On the other hand, recently a centrifugal fluidized-bed coating-granulator (sometimes abbreviated as CF granulator hereinafter) has been developed, and a method to make the granules spherical with this granulator has been tried.

In this method the surface of a spherical seed core or core is coated, while being sprayed with water or a solution containing a binder, with a spraying powder containing a drug, and thus spherical granules of high perfect sphere content and narrow granule size distribution are obtained. [See Drug Development and Industrial Pharmacy, 11(8), 1523–1541 (1985).]

To produce pharmaceutical preparations for controlled release the surface of the resulting spherical granules is coated with wax or polymer for the purpose of control of release of the drug. The coating is performed generally by fluidized-bed coating.

In the initial phase of the process of the fluidized-bed coating, there occur frequently troubles such as breaking and scraping of the spherical granules. These troubles not only damage the drug release control function but also affect greatly the yield in production of granules: thus a method for production of spherical granules excellent in hardness and disintegration has been desired

Under these circumstances, the inventors investigated the method for production of spherical granules excellent in hardness and disintegration by using the CF granulator, and have completed this invention.

This invention relates to

(1) spherical granules having a core coated with spraying powder containing a drug and low substituted hydroxypropylcellulose, and to

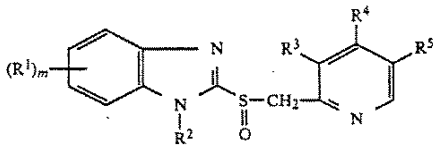
(2) a method for producing spherical granules having a core characterized in that seed cores are coated, while being sprayed with an aqueous binder, with spraying powder containing a drug and low substituted hydroxypropylcellulose.

The content of the hydroxypropoxyl group in the low substituted hydroxypropylcellulose (sometimes abbreviated as L-HPC hereinafter) used in this invention is generally about 4–20%, preferably 5.0–16.0%, more preferably 10.0–13.0%. The mean particle size of the L-HPC may generally be not more than 200 μm in diameter, preferably not more than 100 μm, more preferably not more than 30μm.

The drugs are not particularly defined as far as they can be used in the form of granules, including drugs for the central nervous system such as diazepam, idebenone, aspirin, ibuprofen, paracetamol, naproxen, piroxicam, diclofenac, indomethacin, sulindac, lorazepam, nitrazepam, phenytoin, acetaminophen, ethenzamide, and ketoprofen; drugs for the circulatory system such as molsidomine, vinpocetine, propranolol, methyldopa, dipyridamole, furosemide, triamterene, nifedipine, atenolol, spironolactone, metoprolol, pindolol, captopril, and isosorbide nitrate, drugs for the respiratory system such as amlexanox, dextromethorphan, theophylline, pseudoephedrine, salbutamol, and guaifenesin; drugs for the digestive system such as benzimidazoles described below, cimetidine, ranitidine, pancreatin, and 5-aminosalicylic acid; antibiotics and chemotherapeutic agents such as cephalexin, cefaclor, cefradine, amoxicillin, pivampicillin, bacampicillin, dicloxacillin, erythromycin, erythromycin stearate, lincomycin, doxycycline, trimethoprim, and sulfamethoxazole; drugs for metabolic system such as serrapeptase, glibenclamide, and potassium chloride; and vitamin drugs such as vitamin B_1, vitamin B_2, vitamin B_6, vitamin C, and fursultiamine.

The said benzimidazoles include those described in U.S. Pat. No. 4045563, U.S. Pat. No. 4255431, European Patent Publication No. 45200 U.S. Pat. No. 4472409, European Patent Publication No. 5129, British Patent Publication No. 2134523, European Patent Publication No. 174726, European Patent Publication No. 175464, and European Patent Publication No. 208452 etc.

The benzimdazoles having antiulcer activity, which are described in the above laid-open patent specifications, for instance are represented by the formula



wherein

R^1 is hydrogen, alkyl, halogen, cyano, carboxy, carboalkoxy, carboalkoxyalkyl, carbamoyl, carbamoylalkyl, hydroxy, alkoxy, hydroxyalkyl, trifuluoromethyl, 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} alk-

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

Referring 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.

More specifically, they include 2-[[3-methyl-4(2,2,2-trifluoroethoxy)-2-pyridyl]methylsulfinyl]benzimidazole, and 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2pyridyl)methylsulfinyl]benzimidazole etc.

The said seed cores include Nonpareil produced by coating sucrose (75 weight parts) with corn starch (25 weight parts) according to the per se known method, and spherical seed cores using crystalline cellulose. The drug may be used as the seed core. The particle size of the said seed cores is generally 14–80 mesh.

The said aqueous binder includes water, ethanol (concentration: preferably 50% (v/v) or less), and solutions of binders in water or in ethanol; the concentration of the said solutions is generally 0.1–80% (w/v), preferably 0.5–70% (w/v). The said binders include sucrose, hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose, polyvinylpyrrolidone, pullulan, and gum arabic, which may be used alone or in combination.

The spraying powder containing the drug and L-HPC in this invention may be combined further with powdery additives. The said additives include excipients (e.g. lactose, corn starch, sucrose, crystalline cellulose, light anhydrous silicic acid), binders (e.g.c -starch, methylcellulose, carboxymethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, pullulan, dextrin, gum arabic), disintegrators (e.g. calcium carboxymethylcellulose, starch), stabilizers (e.g. magnesium carbonate, calcium carbonate, L-cystein), and coloring agents (e.g. talc, iron sesquioxide, tar colors).

The said spraying powder in this invention are obtained by mixing uniformly the drug, L-HPC, and the additives described above, and the particle size is generally not more than about 100 μm, preferably not more than about 50 μm.

The combination ratio of L-HPC to the spraying powder is preferably about 5–90% (w/w), more preferably about 10 –60% (w/w).

The combination ratio of the drug to the spraying powder depends upon the kind and the dose of the drug, being about 2–70% (w/w), preferably about 5–50% (w/w).

In the following the method for production of spherical granules having a core of this invention is described in detail. The conditions under which seed cores are coated with spraying powder while being sprayed with an aqueous binder are: the ratio of the aqueous binder to the spraying powder of about 1:1–1:2 is adequate; the production temperature need not be controlled; being generally room temperature (1–30° C.). Spherical granules having a core of even size are obtained by sieving after drying. For example, 12–32 mesh round sieves are used, and the granules which pass through the 12 mesh sieve but do not pass through the 32 mesh sieve are selected.

The spherical granules having a core thus obtained may be coated according to the per se known method for the purpose of taste masking, enteric coating, gastric coating, or prolongation, and/or filled n capsules according to the per se known method.

The said coating agents include hydroxypropylmethylcellulose, ethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, polyoxyethyleneglycol, Tween 80, pluronic F 68, castor oil, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, Eudragit (Röhm Pharma Co., West Germany, acrylate copolymer, amionic in character), carboxymethylethylcellulose, polyvinylacetaldiethylaminoacetate, waxes, and pigments such as talc, titanium oxide, ferric oxide.

The spherical granules having a core of this invention, because of their excellent hardness, can be further coated evenly (e.g. sustained release coating, gastric coating, enteric coating), and at the same time the granules are excellent in disintegration.

In the following, this invention is illustrated in detail with working examples and experimental examples, which however should not limit this invention.

EXAMPLE

Nonpareils (20–28 mesh), 2250 g, were the CF granulator (CF-360, Freund Industrial Co., Ltd., Japan), and coated, while being sprayed with 2000 ml of hydroxy propylcellulose solution (3% (w/v)) at 25 ml/min, first with the spraying powder 1 and then the spraying powder 2, both of which had been prepared by mixing the ingredients listed below, at the rate of 45 g/min at room temperature with a rotor rotating at 200 rpm, dried under reduced pressure at 40° C. for 16 hours, and sieved through round sieves, to give spherical granules having a core of 12–32 mesh.

[spraying powder 1]

compound A* :450 g
magnesium carbonate : 450 g
sucrose : 450 g
corn starch : 450 g
L-HPC : 450 g
(degree of substitution with hydroxypropxyl group: 10.0–13.0% (w/w), mean particle size: not more than 30 μm. The particles of the same degree of substitution and particle size were used hereinafter.)

* Compound A: 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methylsulfinyl]benzimidazole

[spraying powder 2]

sucrose : 420 g
corn starch : 360 g
L-HPC : 360 g

EXAMPLE 2

The granules obtained in Example 1, 3800 g, were brought into the fluidized-bed coator (Okawara Co., Japan), subjected to enteric coating by spraying the enteric coating film solution described below at the rate of 50 ml/min under the controlled conditions of inlet air at 50° C. and material temperature at 40° C., to give enteric coated spherical granules having core The said granules were filled into No.2 hard capsules with a capsule filling machine (Parke-Davis Co., USA), to give capsules

[Enteric coating film solution]	
Eudragit L30D-55	628 g
talc	192 g
polyethyleneglycol 6000	64 g
titanium oxide	64 g
Tween 80	32 g
water	4400 ml
[composition of the capsules]	
enteric coated granules	240 mg
No. 2 hard capsule	65 mg
	305 mg (per capsule)

EXAMPLE 3

Nonpareils (20–28 mesh), 85 g, were brought into mini CF granulator(Freund Co.), and coated, while being sprayed with water (50 ml) at 2.5 ml/min. with the spraying powder described below at the rate of 5 g/min with a rotor rotating at 400 rpm, dried under reduced pressure at 40° C. for 16 hours and sieved through round sieves, to give spherical granules having acore of 12–32 mesh.

[spraying powder]

pancreatin : 20 g
sucrose : 40 g
corn starch : 20 g
L-HPC : 20 g

EXAMPLE 4

Nonpareils (24–32 mesh), 2 kg, were brought into a CF granulator (CF-360, Freund Co.), and coated, while being sprayed with 1% (w/v) hydroxypropylcellulose solution (1000 ml) at 20 ml/min, with the the spraying powder described below at the rate of 40 g/min with a rotor rotating at 200 rpm, dried under reduced pressure at 40° C. for 16 hours, and sieved through round sieves, to give spherical granules having a on of 12–32 mesh.

[spraying powder]

serrapeptase : 50 g
sucrose : 1350 g
corn starch : 200 g
L-HPC : 400 g

Then the granules thus obtained, 300 g, were brought into the fluidized-bed coator (Okawara Co., Japan), subjected to enteric coating by spraying the enteric coating film solution described below at the rate of 50 ml/min under the controlled conditions of inlet air at 50° C. and material temperature at 40° C., to give enteric coated spherical granules having a core.

[Enteric coating film solution]

hydroxypropylmethylcellulose phthalate a 1000 g
castor oil : 100 g
talc : 20 g
acetone : 10000 ml

EXAMPLE 5

Nonpareils (24–32 mesh), 85 g, were brought into a mini CF granulator (Freund Co.), and coated, while being sprayed with 50% (w/v) solution of sucrose (50 ml) at 5 ml/min, with the spraying powder described below at the rate of 10 g/min with a rotor rotating at 400 rpm, dried under reduced pressure at 40° C. for 16 hours, and sieved through round sieves, to give spherical granules having a core of 12–32 mesh.

[spraying powder]

molsidomine : 5 g
sucrose : 55 g
corn starch : 20 g
L-HPC : 20 g

EXAMPLE 6

Nonpareils (24–32 mesh), 85 g, were brought into a mini CF granulator(Freund Co.), and coated, while being sprayed with 1% (w/v) solution of hydroxypropylmethylcellulose (50 ml) at 2.5 ml/min, with the spraying powder described below at the rate of 5 g/min with a rotor rotating at 400 rpm, dried under reduced pressure at 40° C. for 16 hours, and sieved through round sieves, to give spherical granules having a core of 12–32 mesh.

[spraying powder]

idebenone : 20 g
sucrose : 20 g
corn starch : 25 g
L-HPC : 35 g

EXAMPLE 7

Spherical seed cores of crystalline cellulose (20–32 mesh), 85 g, were brought into a mini CF granulator (Freund Co.), and coated, while being sprayed with 1% (w/v) solution of pullulan (50 ml) at 2.5 ml/min, with the the spraying powder described below at the rate of 5 g/min with a rotor rotating at 300 rpm, dried under reduced pressure at 40° C. for 16 hours, and sieved through round sieves, to give spherical granules having a core of 12–32 mesh.

[spraying powder]

amlexanox : 25 g
hydroxypropylmethylcellulose : 20 g
corn starch : 25 g
L-HPC : 30 g

EXAMPLE 8

Crystals of vitamin C (42–60 mesh), 80 g, were brought into a mini CF granulator(Freund Co.), and coated, while being sprayed with 2% (w/v) solution of hydroxypropylcellulose (60 ml) at 2.5 ml/min, with the spraying powder described below at the rate of 5 g/min with a rotor rotating at 400 rpm, dried under reduced pressure at 40° C. for 16 hours, and sieved through round sieves, to give spherical granules having a core of 12–32 mesh.

[spraying powder]

cefaclor : 50 g
sucrose : 20 g
corn starch : 10 g

L-HPC : 40 g

EXAMPLE 9

Crystals of sucrose (42–60 mesh), 85 g, were brought into a mini CF granulator(Freund Co.), and coated, while being sprayed with water (50 ml) at 2.5 ml/min, with the the spraying powder described below at the rate of 5 g/min with a rotor rotating at 400 rpm, dried under reduced pressure at 40° C. for 16 hours, and sieved through round sieves, to give spherical granules having a core of 12–32 mesh.

[spraying powder]

fursultiamine : 5 g
sucrose : 35 g
corn starch : 30 g
L-HPC : 30 g

EXAMPLE 10

Nonpareils (20–28 mesh), 1650 g, were brought into the CF granulator (CF-360, Freund Co.), and coated, while being sprayed with 1050 ml of hydroxypropylcellulose solution (2% (w/v)) at 30 ml/min, first with the spraying powder 1 and then the spraying powder 2, both of which had been prepared by mixing the ingredients listed below, at the rate of 60 g/min at room temperature with a rotor rotating at 250 rpm, dried under reduced pressure at 40° C. for 16 hours, and sieved through round sieves, to give spherical granules having a core of 14–32 mesh.

[spraying powder 1]

compound A*: 450 g
magnesium carbonate : 336 g
sucrose : 297 g
corn starch : 300 g
L-HPC : 354 g

* Compound A: 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)2-pyridyl]methylsulfinyl]benzimidazole

[spraying powder 2]

sucrose : 300 g
corn starch : 246 g
L L-HPC : 354 g

EXAMPLE 11

The granules obtained in Example 10, 3800 g, Were brought into the fluidized-bed coator (Okawara Co.; Japan), subjected to enteric coating by spraying the enteric coating film solution described below at the rate of 50 ml/min under the controlled conditions of inlet air at 65° C. and material temperature at 40° C., to give enteric coated spherical granules having core. To the said granules were added talc and light anhydrous silicic acid, then filled into No. 1 hard capsules with a capsule filling machine (Parke-Davis Co., USA) to give capsules.

[Enteric coating film solution]

Eudragit L30D-55: 2018 g (solid: 605 g)
talc: 1832 g
polyethyleneglycol 6000 : 60 g
titanium oxide: 60 g
Tween 80 : 27 g
water : 4230 ml

[composition of the capsules]

enteric coated granules	348.8	mg
compound A	30.0	mg
magnesium carbonate	22.4	mg
Nonpareils	110.0	mg
sucrose	39.8	mg
corn starch	36.4	mg
L-HPC	40.0	mg
hydroxypropylcellulose	1.4	mg
Eudragit L 30D-55	44.6	mg
talc	13.4	mg
polyethyleneglycol 6000	4.4	mg
titanium oxide	4.4	mg
Tween 80	2.0	mg
talc	0.6	mg
light anhydrous silicic acid	0.6	mg
No. 1 hard capsule	79.0	mg
	429.0	mg (per capsule)

EXPERIMENTAL EXAMPLE 1

In the method of Example 3 , coating was performed with the spraying powder containing the ingredients listed in Table 1 in place of L-HPC to produce spherical granules having core. The said granules thus obtained (12–32 mesh). 5 g. were brought into a 50 ml stainless steel cylinder (50 ml, 32 mm in diameter), shaken in a mill (Spex Co., .Spexmill) for 30 minutes, and sieved through a 32 mesh round sieve. The residual amount on the sieve was measured to calculate friability for evaluation of hardness of the granules. In addition, disintegration time was also determined according to the method described in the 11th Japanese Pharmacopoeia. Table 1 Hardness and Disintegration Time of the Granules

		Hardness (%)	Disintegration time
This invention	L-HPC	98	1 min
Controls	crystalline cellulose	87	2 min
	α-starch	89	not less than 30 min
	hydroxypropylcellulose	90	10 min
	hydroxypropylmethyl-cellulose	89	6 min
	polyvinylpyrrolidone	85	4 min
	pullulan	88	1.5 min
	methylcellulose	84	2 min
	dextrin	85	1 min
	gum arabic	82	1 min
	carboxymethylcellulose	86	2 min

These results show evidently that the spherical granules having a ogre of this invention are excellent in hardness and disintegration.

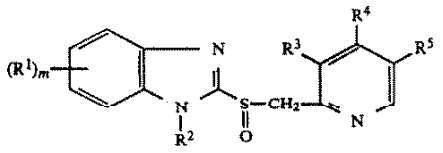
What is claimed is:

1. Spherical granules having a core coated with a binder and spraying powder containing a drug and low substituted hydroxypropylcellulose having a mean particle diameter not more than 200 μm, wherein the low substituted hydroxypropylcellulose contains 4 to 20% of a hydroxypropoxyl group.

2. The spehrical granules having a core according to claim 1, wherein the drug is a drug for the digestive system.

3. The spherical granules having a core according to claim 2, wherein the drug for the digestive system is a benzimidazole compound having antiulcer activity, cimetidine, ranitidine, pancreatin or 5-aminosalicylic acid.

4. The spherical granules having a core according to claim 3, wherein the benzimdazole compound is represented by the formula



wherein

R^1 is hydrogen, alkyl, halogen, cyano, carboxy, carboalkoxy, carboalkoxyalkyl, carbamoyl, carbamoylalkyl, hydroxy, alkoxy, hydroxyalkyl, trifuluoromethyl, acyl, carbamoyloxy, nitro, acyloxy, aryl, aryloxy, alkylthio or alkylsulfinyl,

R^2 is hydrogen, alkyl, acyl, carboalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, alkylcarbonylmethyl, alkoxycarbonylmethyl or alkylsulfon

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.

5. The spherical granules having a core according to claim 3, wherein the benzimidazole compound is 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2pyridyl]methylsulfinyl]benzimidazole or 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)-methylsulfinyl]benzimidazole.

6. The spherical granules having a core according to claim 1, wherein the content is 5.0 to 16.0%.

7. The spherical granules having a core according to claim 1, wherein the content is 10.0 to 13.0%.

8. The spherical granules having a core according to claim 1, wherein the mean particle diameter is not more then 100 μm.

9. The spherical granules having a core according to claim 1, wherein the mean particle diameter is not more than 30 μm.

10. The spherical granules having a core according to claim 1, wherein the granules pass through 12 mesh sieve but do not pass through 32 mesh sieve.

11. The spherical granules having a core according to claim 1, wherein the granules are enteric-coated.

12. A method for producing spherical granules having acore characterized in that seed cores are coated, while being sprayed with an aqueous binder, with spraying powder containing a drug and low substituted hydroxypropylcellulose having a means particle diameter not more than 200 μm, wherein the low substituted hydroxypropylcellulose contains 4 to 20% of a hydroxypropoxyl group.

13. The method according to claim 12, wherein the seed cores are nonpareils produced by coating 75 weight parts of sucrose with 25 weight parts of corn starch

14. The method according to claim 12, wherein the seed cores are made with crystalline cellulose.

15. The method according to claim 12, wherein the aqueous binder is water or ethanol.

16. The method according to claim 12, wherein the aqueous binder is solution of binder in water or in ethanol.

17. The method according to claim 16, wherein the solution has 0.1 to 80.% (w/v) of concentration.

18. The method according to claim 16, wherein the binder is one or more selected from the group consisting of sucrose, hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose, polyvinylpyrrolidone, pullulan and gum arabic.

19. The method according to claim 12, wherein the spraying powder is not more than 100 μm in particle size.

20. The method according to claim 12, wherein the spraying powder contains 5 to 90% (w/w) of low substituted hydroxypropylcellulose.

21. The method according to claim 12, wherein the spraying powder contains 2 to 70% (w/w) of the drug.

22. The method according to claim 12, wherein the ratio of the aqueous binder to the spraying powder is 1:1 to 1:2.

23. The spherical granules having a core according to claim 1, wherein the spraying powder contains magnesium carbonate and/or calcium carbonate.

24. The spherical granules having a core according to claim 1, wherein the coated spherical granules are further coated with spraying powder containing low substituted hydroxypropylcellulose.

25. The spherical granules having a core according to claim 24, wherein the spherical granules are further coated with an enteric coating agent.

26. The spherical granules having a core 3 according to claim 25, wherein the enteric coating agent is acrylate copolymers anionic in charcter or hydroxypropylmethylcellulose phthalate.

27. The method according to claim 12, wherein the spraying powder contains magnesium carbonate and/or calcium carbonate.

28. The methdo according to claim 12, wherein the spherical granules are further coated with spraying powder containing low substituted hydroxypropylcellulose.

29. The method according to claim 28, wherein the spherical granules are further coated with an enteric coating agent.

30. The methdo according to claim 29, wherein the enteric coating agent is acrylate copolymers anionic in character or hydroxyporpylmethylcellulose phthalate.

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EXHIBIT C

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**

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

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[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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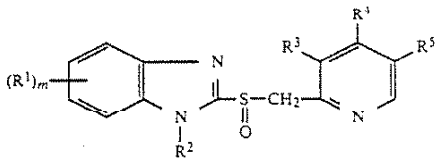
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[57] **ABSTRACT**

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.

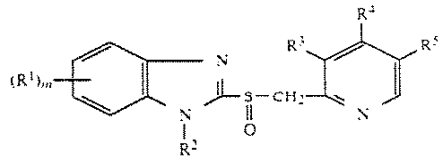
In view of the above, the present inventors made investigations in an attempt to stabilize pharmaceutical preparations containing benzimidazole compounds and, as a result, have completed the present invention.

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



(I)

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.

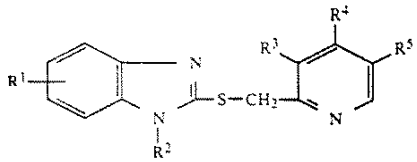
Referring to R^3, the lower alkyl represented thereby is preferably C_{1-8} lower alkoxy such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentyloxy, hexyloxy, heptyloxy or octyloxy and more preferably C_{1-4} lower alkoxy.

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)

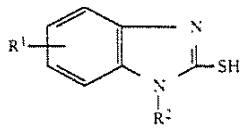
wherein R^1–R^5 are as defined above, to oxidation.

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.

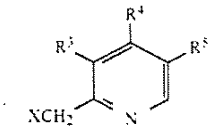
Said compounds may be converted to pharmacologically acceptable salts by conventional means. As such salts, there may be mentioned hydrochloride, hydrobromide, hydroiodide, phosphate, nitrate, sulfate, acetate and citrate, among others.

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.

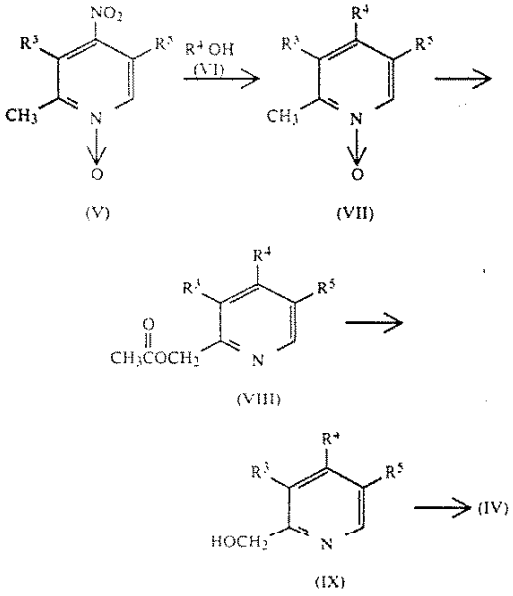
The halogen atom represented by X is, for example, chlorine, bromine or iodine.

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.

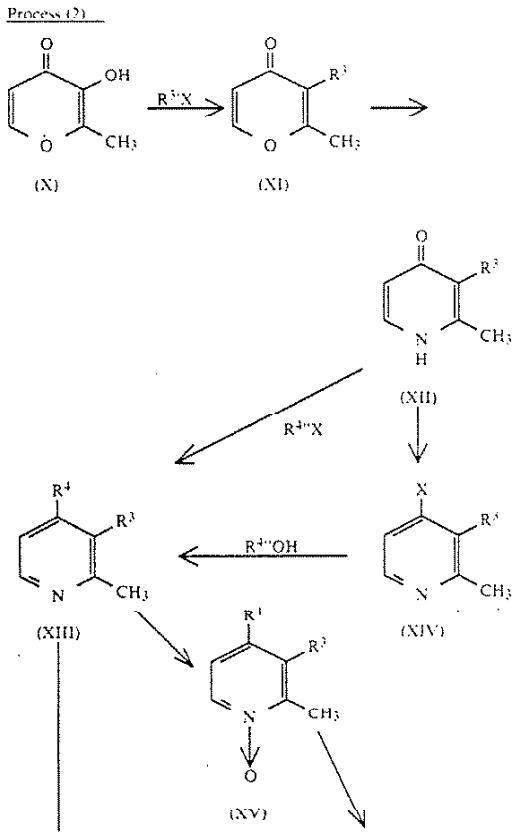
The subsequent alkaline hydrolysis of the compound (VIII) gives a 2-hydroxymethylpyridine derivative of the formula (IX). Sodium hydroxide, potassium hydroxide, potassium carbonate and sodium carbonate, for instance, are usable as alkalis, and methanol, ethanol and water, among others, are usable as 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.

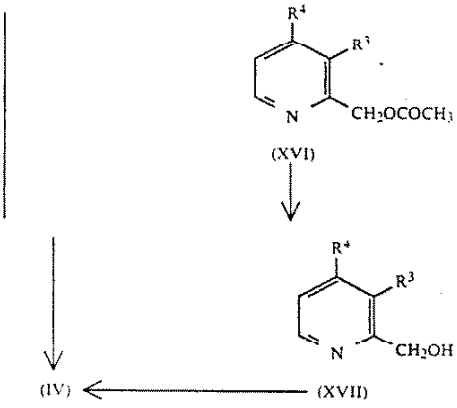
Among the compounds (V), those compounds wherein R^3 is C_{1-8} lower alkoxy, R^4 is alkoxy which may optionally be fluorinated, and R^5 is hydrogen can be produced by the following process:

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), 3.89 (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, brs), 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: 1.05 (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), 4.42 (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 D

US005093132A

United States Patent [19]

Makino et al.

[11] Patent Number: 5,093,132

[45] Date of Patent: * Mar. 3, 1992

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

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[*] Notice: The portion of the term of this patent subsequent to Sep. 3, 2008 has been disclaimed.

[21] Appl. No.: **575,897**

[22] Filed: **Aug. 31, 1990**

Related U.S. Application Data

[63] Continuation of Ser. No. 14,303, Feb. 13, 1987, Pat. No. 5,045,321.

[30] **Foreign Application Priority Data**

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[51] **Int. Cl.**[5] **A61K 9/30**; A61K 9/16; A61K 31/415

[52] **U.S. Cl.** **424/475**; 424/494; 424/495; 514/394; 514/925; 514/970

[58] **Field of Search** 514/394, 395, 925, 927, 514/970; 424/494, 495, 475

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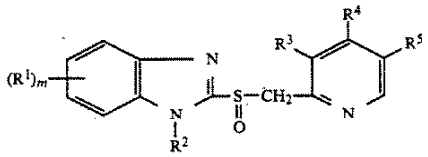
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Attorney, Agent, or Firm—Wegner, Cantor, Mueller & Player

[57] **ABSTRACT**

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



wherein R^1 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, and a basic inorganic salt stabilizing agent, is physically stable. Magnesium and calcium basic inorganic salt stabilizing agents are particularly useful.

11 Claims, No Drawings

STABILIZED PHARMACEUTICAL COMPOSITION AND ITS PRODUCTION

This is a continuation application of United States application Ser. No. 014,303, filed Feb. 13, 1987, now U.S. Pat. No. 5,045,321.

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"), particularly the derivatives 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methylsulfinyl]benzimidazole and 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methylsulfinyl]benzimidazole, or a pharmaceutically acceptable salt thereof, which is useful as an antiulcer agent. The composition is stabilized by incorporation of an effective amount of a basic inorganic salt stabilizing agent, with basic inorganic salts of magnesium, calcium, potassium and sodium being useful, the magnesium can calcium salts being preferred.

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 (polyoxyethylene polyoxypropylene 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.

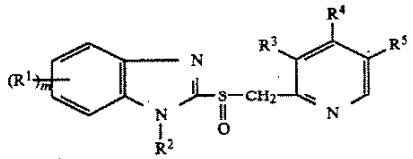
In view of the above, the present inventors made investigations in an attempt to stabilize pharmaceutical preparations containing benzimidazole compounds and, as a result, have completed the present invention.

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



(I)

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 inthe above-cited laid-open patent specifications or modifications thereof.

In the following, brief mention is mad 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} alkoxys as the alkoxy; C_{1-7} alkyls as the alkyl moiety of the hydroxy

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

Referring 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 formula (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 fluroinated 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 C_{1-8} alkoxy, R^4 is C_{1-8} alkoxy which may be fluorinated, 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.

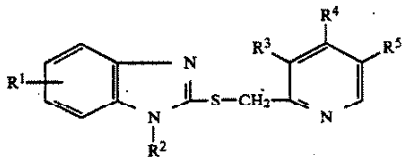
Referring to R^3, the lower alkyl represented thereby is preferably C_{1-8} lower alkoxy such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentyloxy, hexyloxy, heptyloxy or octyloxy and more preferably C_{1-4} lower alkoxy.

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 abvoe 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)

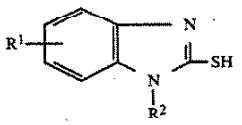
wherein R^1–R^5 are as defined above, to oxidation.

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.

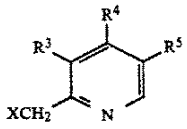
Said compounds may be converted to pharmacologically acceptable salts by conventional means. As such salts, there may be mentioned hydrochloride, hydrobromide, hydroiodide, phosphate, nitrate, sulfate, acetate and citrate, among others.

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.

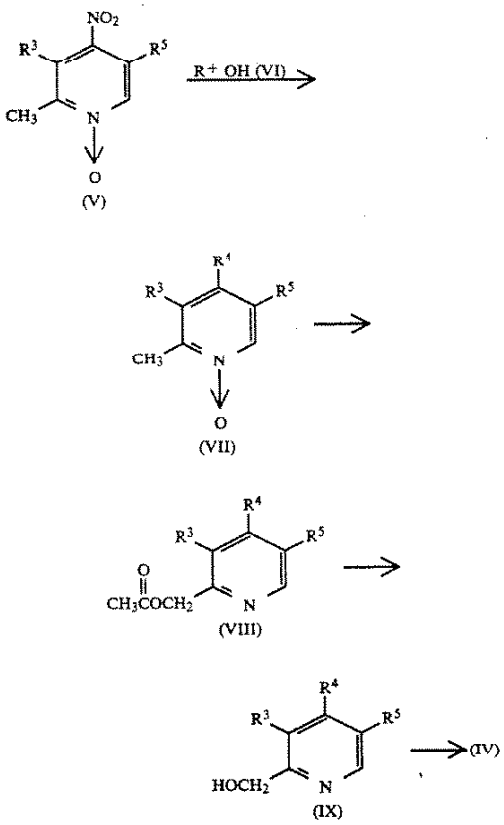
The reaction is carried out advantageously in the presence of a base. As said base, there may be mentioned alkali metal hydrides such as sodium hydride and potassium hydride, alkali metals such as metallic sodium, sodium alcoholates such as sodium methoxide and sodium ethoxide, alkali metal carbonates 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.

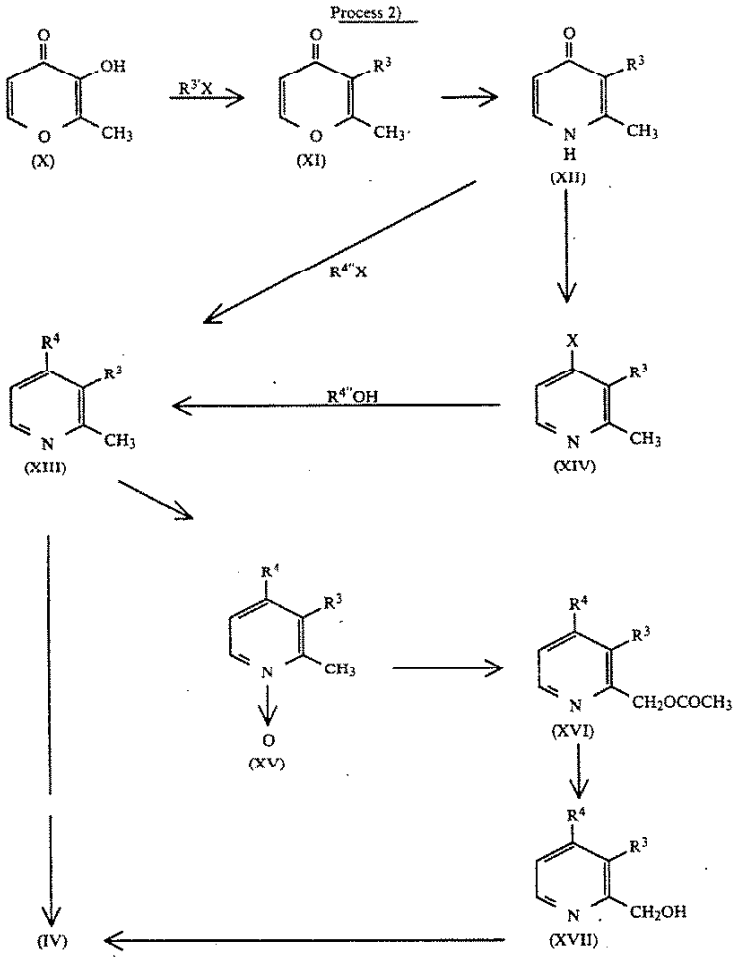
Heating (about 80°–120° C.) of the thus-obtained compound (VII) with acetic anhydride alone or in the presence of an inorganic acid such as sulfuric acid or perchloric acid gives an 2-acetoxymethylpyridine derivative of the formula (VIII) wherein R^3, R^4 and R^5 are as defined above. The reaction period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



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 $R4''OH$ 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 dimethylforamide, 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 stabilizing agents, which are to be used in accordance with the invention, are now described.

Especially useful basic inorganic salt stabilizing agents are basic inorganic salts of magnesium and calcium. 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 [$Mg_6Al_2(OH)_{16}.CO_34H_2O$] 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. Other basic inorganic salts useful as stabilizing agents include sodium and potassium basic inorganic salts such as potassium carbonate, sodium carbonate and sodium hydrogen carbonate, as well as aluminum basic inorganic salts such as aluminum silicate. It is only required of such basic inorganic 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 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, hydroxy propylmethylcellulose, 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 stabilizing agent, 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 stabilizing agent evenly. Thus, for example, the additives may be admixed with a mixture of the benzimidazole compound and the basic inorganic salt stabilizing agent as prepared by preliminary admixing, or the basic inorganic salt stabilizing agent 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, hydroxy methylcellulose, hydroxypropylcellulose, polyoxyethylene glycol, Tween 80, Pluornic F68, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, Eudragit (Rohm, 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 stabilizing agent 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 stabilizing agent, and additives (e.g. sucrose, corn starch, crystalline cellulose, hydroxypropyl-cellulose, methylcellulose, hydroxypropylmethyl-cellulose, 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 (lH, brs), 4.49 (2H, t, J=12 Hz), 4.67 (2H, s), 6.69 (lH, d, J=5 Hz), 8.34 (lH, 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]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 admixing, the whole mixture was made up into tablets each weighing 250 mg on a rotary tableting machine (Kikusui Seisakusho, Japan).

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 mmϕ). The granules were immediately converted to spherical form in a spheronizer (Fuji Powder's Marumerizer, Japan; 1,000 rmp). 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

-continued

Composition per 200 mg of granules	
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 3 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° 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 abvoe, while spraying hydroxypropylcellulose solution [4% (w/w)], to give spherical granules. The spherical granules were dried in vacuum at 40° C. for 16 horus 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 coating composition specified below using 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 240 mg 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 1a

The ingredients given below were mixed well in the proportions 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
Microcystalline cellulose	20 mg
Carboxymethylcellulose calcium	10 mg
Hydroxypropylcellulose	10 mg
Pluronic F68	4 mg
Lactose	26 mg
Water	(0.1 ml)
Total	200 mg

After storage at 50° C. and 75% RH for 1 week, the granules were observed for changes in appearance. The granules of this example showed no change in appearance.

EXPERIMENT EXAMPLE 1b

The ingredients given below were mixed well in the proportions 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
Magnesium Oxide	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

After storage at 50° C. and 75% RH for 1 week, the granules were observed for changes in appearance. The granules of this example showed no change in appearance.

EXPERIMENTAL EXAMPLE 1c

The ingredients given below were mixed well in the proportions 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
Magnesium Metasilicate Aluminate	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

After storage at 50° C. and 75% RH for 1 week, the granules were observed for changes in appearance. The granules of this example showed no change in appearance.

EXPERIMENTAL EXAMPLE 1d

The ingredients given below were mixed well in the proportions 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
Synthetic Hydrotalcite	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

After storage at 50° C. and 75% RH for 1 week, the granules were observed for changes in appearance. The granules of this example showed no change in appearance. Experimental Example 1e

The ingredients given below were mixed well in the proportions 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
Aluminum magnesium hydroxide	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

After storage at 50° C. and 75% RH for 1 week, the granules were observed for changes in appearance. The granules of this example showed no change in appearance.

EXPERIMENTAL EXAMPLE 1f

The ingredients given below were mixed well in the proportions 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 grandules	
Compound (B)	30 mg
Magnesium silicate	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

After storage at 50° C. and 75% RH for 1 week, the granules were observed for changes in appearance. The granules of this example showed no change in appearance.

EXPERIMENTAL EXAMPLE 1g

The ingredients given below were mixed well in the proportions 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
Precipitated calcium 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

After storage at 50° C. and 75% RH for 1 week, the granules were observed for changes in appearance. The granules of this example showed no change in appearance.

Experimental Example 1h

The ingredients given below were mixed well in the proportions 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
Magnesium hydroxide	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

After storage at 50° C. and 75% RH for 1 week, the granules were observed for changes in appearance. The granules of this example showed no change in appearance.

EXPERIMENTAL EXAMPLE 1i

The ingredients given below were mixed well in the proportions 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
Sodium 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

After storage at 50° C. and 75% RH for 1 week, the granules were observed for changes in appearance. The granules of this example showed a moderate change in appearance to yellow.

EXPERIMENTAL EXAMPLE 1j

The ingredients given below were mixed well in the proportions 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
Potassium 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

After storage at 50° C. and 75% RH for 1 week, the granules were observed for changes in appearance. The granules of this example showed a moderate change in appearance to yellow.

EXPERIMENTAL EXAMPLE 1k

The ingredients given below were mixed well in the proportions 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
Sodium hydrogen 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

After storage at 50° C. and 75% RH for 1 week, the granules were observed for changes in appearance. The granules of this example showed a moderate change in appearance to yellow.

EXPERIMENTAL EXAMPLE 1l

The ingredients given below were mixed well in the proportions 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
Magnesium chloride	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

After storage at 50° C. and 75% RH for 1 week, the granules were observed for changes in appearance. The granules of this example showed a severe change in appearance, to violet.

Experimental Example 1m

The ingredients given below were mixed well in the proportions 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
Magnesium sulfate	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

After storage at 50° C. and 75% RH for 1 week, the granules were observed for changes in appearance. The granules of this example showed a severe change in appearance, to violet.

EXPERIMENTAL EXAMPLE 1n

The ingredients given below were mixed well in the proportions 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
Calcium chloride	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

After storage at 50° C. and 75% RH for 1 week, the granules were observed for changes in appearance. The granules of this example showed a severe change in appearance, to violet.

EXPERIMENTAL EXAMPLE 1o

The ingredients given below were mixed well in the proportions 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
aluminum silicate	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

After storage at 50° C. and 75% for 1 week, the granules were observed for changes in appearance. The granules of this example showed a moderate change in appearance, to violet.

EXPERIMENTAL EXAMPLE 1p

The ingredients given below were mixed well in the proportions 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
Corn starch	80 mg
Microcrystalline cellulose	20 mg
Carboxymethylcellulose calcium	10 mg
Hydroxypropylcellulose	10 mg
Pluronic F68	4 mg
Lactose	46 mg
Water	(0.1 ml)
Total	200 mg

After storage at 50° C. and 75% RH for 1 week, the granules were observed for changes in appearance. The granules of this example showed a severe change in appearance, to violet.

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	++
Omeporazole	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 compositions were produced in the same manner as in Examples 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 storage 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%

TABLE 2-continued

	Additive		Initial	50° C., 75% RH, 1 week	40° C. 6 months
	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 stabilized pharmaceutical composition for the inhibition of gastric acid secretion, comprising:

an effective amount of a 2-benzimidazole derivative selected from the group consisting of 2-benzimidazole and 5-methoxy-2-benzimidazole, or a pharmaceutically acceptable salt thereof;

a basic inorganic salt stabilizing agent which is present in an amount effective to stabilize the composition, the benzimidazole derivative being in contact with the basic inorganic salt evenly; and

an enteric coating for the composition.

2. The composition of claim 1, wherein the basic inorganic salt stabilizing agent is a basic inorganic salt of magnesium which is effective to stabilize the composition.

3. The composition of claim 1, wherein the basic inorganic salt stabilizing agent is a basic inorganic salt of calcium which is effective to stabilize the composition.

4. The composition of claim 1, wherein the basic inorganic salt stabilizing agent is a basic inorganic salt of potassium which is effective to stabilize the composition.

5. The composition of claim 1, wherein the basic inorganic salt stabilizing agent is a basic inorganic salt of sodium which is effective to stabilize the composition.

6. The composition of claim 1, wherein the composition comprises a plurality of enteric coated granules, each of the granules containing therein said active compound and said basic inorganic salt stabilizing agent.

7. A method for providing a gastic acid secretion inhibitory effect to a subject in need thereof, comprising:

orally administering to the subject a stabilized pharmaceutical composition comprising:

an effective amount of a 2-benzimidazole derivative selected from the group consisting of 2-benzimidazole and 5-methoxy-2-benzimidazole, or a pharmaceutically acceptable salt thereof;

a basic inorganic salt stabilizing agent which is present in an amount effective to stabilize the composition, the benzimidazole derivative being in contact with the basic inorganic salt evenly; and

an enteric coating for the composition.

8. The method of claim 7, wherein the basic inorganic salt stabilizing agent is a basic inorganic salt of magnesium which is effective to stabilize the composition.

9. The method of claim 7, wherein the basic inorganic salt stabilizing agent is a basic inorganic salt of calcium which is effective to stabilize the composition.

10. The method of claim 7, wherein the basic inorganic salt stabilizing agent is a basic inorganic salt of potassium which is effective to stabilize the composition.

11. The method of claim 7, wherein the basic inorganic salt stabilizing agent is a basic inorganic salt of sodium which is effective to stabilize the composition.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,093,132

DATED : March 3, 1992

INVENTOR(S) : Tadashi MAKINO et al.

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

Col. 25 & 26 Claims 1 and 7 should read as follows:

-- 1. A stabilized pharmaceutical composition for the inhibition of gastric acid secretion, comprising:

an effective amount of a 2-[(2-pyridyl)methylsulfinyl]benzimidazole derivative selected from the group consisting of 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methylsulfinyl]benzimidazole and 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methylsulfinyl]benzimidazole, or a pharmaceutically acceptable salt thereof;

a basic inorganic salt stabilizing agent which is present in an amount effective to stabilize the composition, the benzimidazole derivative being in contact with the basic inorganic salt evenly; and

an enteric coating for the composition.

7. A method for providing a gastric acid secretion inhibitory effect to a subject in need thereof, comprising:

orally administering to the subject a stabilized pharmaceutical composition comprising:

an effective amount of a 2-[(2-pyridyl)methylsulfinyl]benzimidazole derivative selected from the group consisting of 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methylsulfinyl]benzimidazole and 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methylsulfinyl]benzimidazole, or a pharmaceutically acceptable salt thereof;

a basic inorganic salt stabilizing agent which is present in an amount effective to stabilize the composition, the benzimidazole derivative being in contact with the basic inorganic salt evenly; and

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,093,132 Page 2 of 2

DATED : March 3, 1992

INVENTOR(S) : Tadashi Makino, et. al.

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

an enteric coating for the composition--.

Signed and Sealed this

Twenty-ninth Day of December, 1992

Attest:

DOUGLAS B. COMER

Attesting Officer

Acting Commissioner of Patents and Trademarks

[redacted]

EXHIBIT E

US005433959A

United States Patent [19]

Makino et al.

[11] Patent Number: 5,433,959

[45] Date of Patent: * Jul. 18, 1995

[54] **STABILIZED PHARMACEUTICAL COMPOSITION**

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

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

[*] Notice: The portion of the term of this patent subsequent to Sep. 3, 2008 has been disclaimed.

[21] Appl. No.: **120,867**

[22] Filed: **Sep. 10, 1993**

Related U.S. Application Data

[60] Continuation of Ser. No. 793,091, Nov. 15, 1991, abandoned, which is a division of Ser. No. 575,897, Aug. 31, 1990, Pat. No. 5,093,132, and a continuation of Ser. No. 14,303, Feb. 13, 1987, Pat. No. 5,045,321.

[30] **Foreign Application Priority Data**

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

[51] **Int. Cl.**[6] **A61K 9/30**; A61K 33/12; A61K 33/10; A61K 33/08

[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** 424/475, 495, 683, 686, 424/692; 514/394, 395, 925, 927

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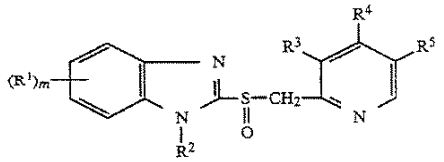
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Primary Examiner—Marianne M. Cintins
Assistant Examiner—K. Weddington
Attorney, Agent, or Firm—Merchant, Gould, Smith, Edell, Welter & Schmidt

[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, 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, and a basic inorganic salt stabilizing agent, is physically stable. Magnesium and calcium basic inorganic salt stabilizing agents are particularly useful.

15 Claims, No Drawings

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STABILIZED PHARMACEUTICAL COMPOSITION

This application is a continuation of U.S. application Ser. No. 07/793,091 filed Nov. 15, 1991, now abandoned; which is a division of Ser. No. 07/575,897 filed Aug. 31, 1990, now U.S. Pat. No. 5,093,132 and a continuation of application Ser. No. 07/014,303, filed Feb. 13, 1987, now U.S. Pat. No. 5,045,321.

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"), particularly the derivatives 2-[[3-methyl-4-(2,2,2-trifluoromethoxy)-2-pyridyl]methylsulfinyl]benzimidazole and 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methylsulfinyl]benzimidazole, or a pharmaceutically acceptable salt thereof, which is useful as an antiulcer agent. The composition is stabilized by incorporation of an effective amount of a basic inorganic salt stabilizing agent, with basic inorganic salts of magnesium, calcium, potassium and sodium being useful, the magnesium can calcium salts being preferred.

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. 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.

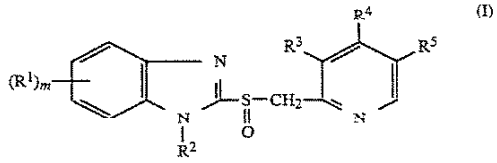
In view of the above, the present inventors made investigations in an attempt to stabilize pharmaceutical preparations containing benzimidazole compounds and, as a result, have completed the present invention.

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 alkylcarbonylmethyl; 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.

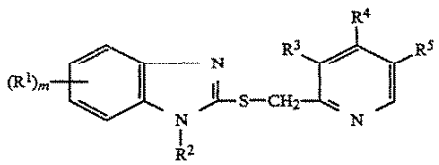
Referring to R^3 the lower alkyl represented thereby is preferably C_{1-8} lower alkoxy such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentyloxy, hexyloxy, heptyloxy or octyloxy and more preferably C_{1-4} lower alkoxy.

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)

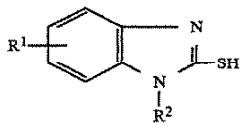
wherein R^1–R^5 are as defined above, to oxidation.

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.

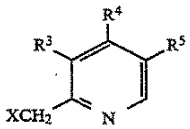
Said compounds may be converted to pharmacologically acceptable salts by conventional means. As such salts, there may be mentioned hydrochloride, hydrobromide, hydroiodide, phosphate, nitrate, sulfate, acetate and citrate, among others.

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.

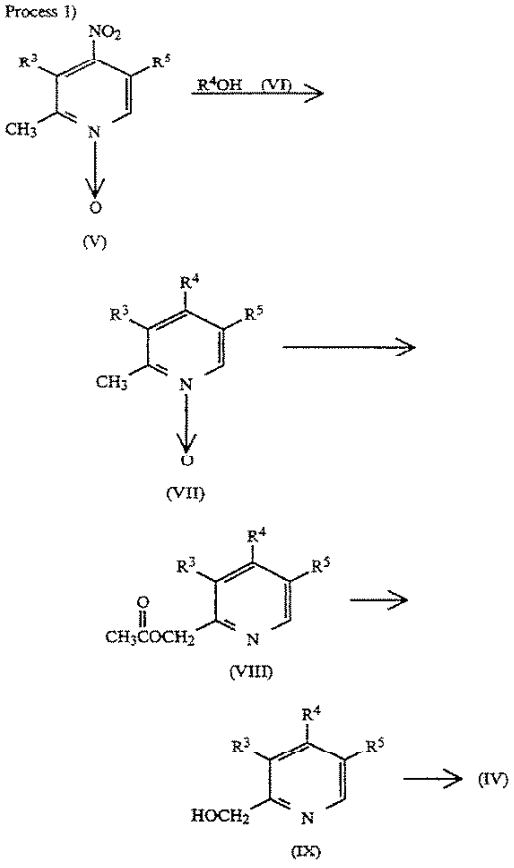
The reaction is carried out advantageously in the presence of a base. As said base, there may be mentioned alkali metal hydrides such as sodium hydride and potassium hydride, alkali metals such as metallic so-

dium, 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 hexamethlphosphoric 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.

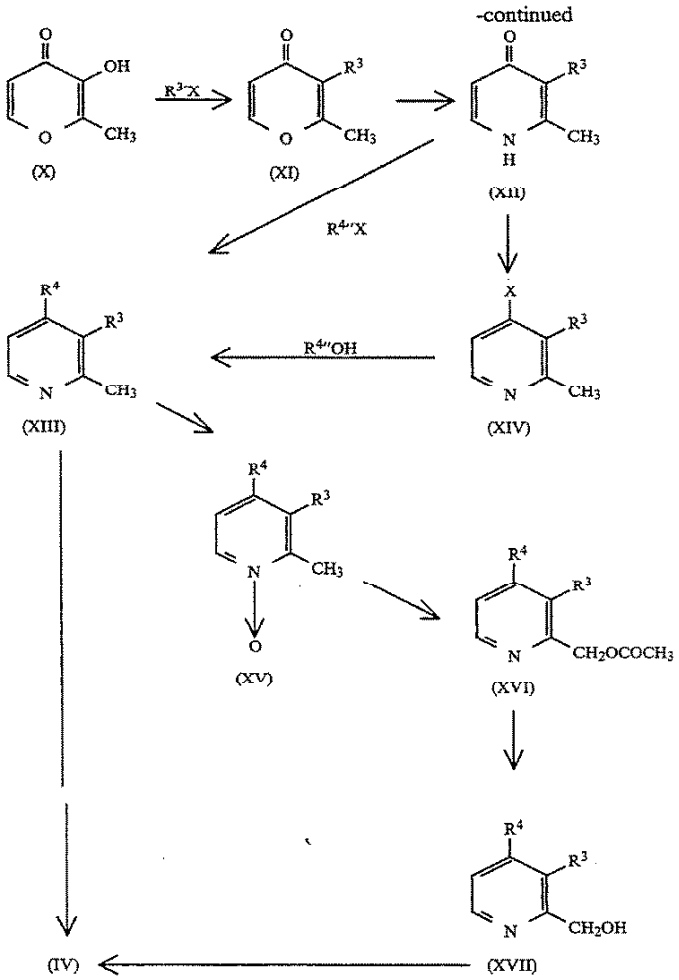
The compound (IX) is further halogenated with a chlorinating agent such as thionyl chloride to give a 2-halomethylpyridine derivative of the formula (IV) wherein R^3, R^4 and R^5 are as defined above and X is chlorine, bromine or iodine. Usable as solvents are, for example, chloroform, dichloromethane 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



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 $R^{4''}OH$ 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, aides 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 stabilizing agents, which are to be used in accordance with the invention, are now described.

Especially useful basic inorganic salt stabilizing agents are basic inorganic salts of magnesium and calcium. 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 [$Mg_6Al_2(OH)_{16}.CO_3.4H_2O$] 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. Other basic inorganic salts useful as stabilizing agents include sodium and potassium basic inorganic salts such as potassium carbonate, sodium carbonate and sodium hydrogen carbonate, as well as aluminum basic inorganic salts such as aluminum silicate. It is only required of such basic inorganic 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 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 stabilizing agent, 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 particle 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 stabilizing agent evenly. Thus, for example, the additives may be admixed with a mixture of the benzimidazole compound and the basic inorganic salt stabilizing agent as prepared by preliminary admixing, or the basic inorganic salt stabilizing agent 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 stabilizing agent 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 stabilizing agent, and additives (e.g. sucrose, corn starch, crystalline cellulose, hydroxypropyl-cellulose, methylcellulose, hydroxypropylmethyl-cellulose, 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), 2N 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]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]methylsulfinyl]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 admixing, 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

-continued

Composition per 200 mg of granules	
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 3 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° 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), magnesium carbonate, sucrose, corn starch and crystalline cellulose were thoroughly mixed together to obtain dusting powder.

Nonpareils were put on a centrifugal fluidized coating-granulator (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 (3)	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 coating composition specified below using 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 240 mg 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 (3)	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	360 g
Composition of enteric granules:	
[Hydroxypropoxy group content: 10.0–13.0% (w/w), average particle size: no more than 30 μm]	

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 1a

The ingredients given below were mixed well in the proportions 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

After storage at 50° C. and 75% RH for 1 week, the granules were observed for changes in appearance. The granules of this example showed no change in appearance.

EXPERIMENT EXAMPLE 1b

The ingredients given below were mixed well in the proportions 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
Magnesium Oxide	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

After storage at 50° C. and 75% RH for 1 week, the granules were observed for changes in appearance. The granules of this example showed no change in appearance.

EXPERIMENTAL EXAMPLE 1c

The ingredients given below were mixed well in the proportions 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
Magnesium Metasilicate Aluminate	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

After storage at 50° C. and 75% RH for 1 week, the granules were observed for changes in appearance. The granules of this example showed no change in appearance.

EXPERIMENTAL EXAMPLE 1d

The ingredients given below were mixed well in the proportions 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
Synthetic Hydrotalcite	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

After storage at 50° C. and 75% RH for 1 week, the granules were observed for changes in appearance. The granules of this example showed no change in appearance.

EXPERIMENTAL EXAMPLE 1e

The ingredients given below were mixed well in the proportions 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
Aluminum magnesium hydroxide	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

After storage at 50° C. and 75% RH for 1 week, the granules were observed for changes in appearance. The granules of this example showed no change in appearance.

EXPERIMENTAL EXAMPLE 1f

The ingredients given below were mixed well in the proportions 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
Magnesium silicate	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

After storage at 50° C. and 75% RH for 1 week, the granules were observed for changes in appearance. The granules of this example showed no change in appearance.

EXPERIMENTAL EXAMPLE 1g

The ingredients given below were mixed well in the proportions 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
Precipitated calcium 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

After storage at 50° C. and 75% RH for 1 week, the granules were observed for changes in appearance. The granules of this example showed no change in appearance.

EXPERIMENTAL EXAMPLE 1h

The ingredients given below were mixed well in the proportions 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
Magnesium hydroxide	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

After storage at 50° C. and 75% RH for 1 week the granules were observed for changes in appearance. The granules of this example showed no change in appearance.

EXPERIMENTAL EXAMPLE 1i

The ingredients given below were mixed well in the proportions 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
Sodium 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

After storage at 50° C. and 75% RH for 1 week, the granules were observed for changes in appearance. The granules of this example showed a moderate change in appearance to yellow.

EXPERIMENTAL EXAMPLE 1j

The ingredients given below were mixed well in the proportions 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
Potassium 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

After storage at 50° C. and 75% RH for 1 week, the granules were observed for changes in appearance. The granules of this example showed a moderate change in appearance to yellow.

EXPERIMENTAL EXAMPLE 1k

The ingredients given below were mixed well in the proportions 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
Sodium hydrogen 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

After storage at 50° C. and 75% RH for 1 week, the granules were observed for changes in appearance. The granules of this example showed a moderate change in appearance to yellow.

EXPERIMENTAL EXAMPLE 1l

The ingredients given below were mixed well in the proportions 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
Magnesium chloride	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

After storage at 50° C. and 75% RH for 1 week, the granules were observed for changes in appearance. The granules of this example showed a severe change in appearance, to violet.

EXPERIMENTAL EXAMPLE 1m

The ingredients given below were mixed well in the proportions 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
Magnesium sulfate	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

After storage at 50° C. and 75% RH for 1 week, the granules were observed for changes in appearance. The granules of this example showed a severe change in appearance, to violet.

EXPERIMENTAL EXAMPLE 1n

The ingredients given below were mixed well in the proportions 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
Calcium chloride	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

After storage at 50° C. and 75% RH for 1 week, the granules were observed for changes in appearance. The granules of this example showed a severe change in appearance, to violet.

EXPERIMENTAL EXAMPLE 1o

The ingredients given below were mixed well in the proportions 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
aluminum silicate	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

After storage at 50° C. and 75% RH for 1 week, the granules were observed for changes in appearance. The granules of this example showed a moderate change in appearance, to violet.

Composition per 200 mg of granules	
Compound (B)	30 mg
Corn starch	80 mg
Microcrystalline cellulose	20 mg
Carboxymethylcellulose calcium	10 mg
Hydroxypropylcellulose	10 mg
Pluronic F68	4 mg
Lactose	46 mg
Water	(0.1 ml)
Total	200 mg

After storage at 50° C. and 75% RH for 1 week, the granules were observed for changes in appearance. The granules of this example showed a severe change in appearance, to violet.

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

EXPERIMENTAL EXAMPLE 1p

The ingredients given below were mixed well in the proportions 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.

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 compositions 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 storage 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			

TABLE 2-continued

	Additive		Initial	50° C., 75% RH, 1 week	40° C., 6 months
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%
Granules 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%	90.6%
	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 stabilized pharmaceutical composition for the inhibition of gastric acid secretion, comprising:

an effective amount of a 2-[(2-pyridyl)methylsulphinyl]benzimidazole compound of a pharmaceutically acceptable salt thereof having a gastric acid secretion inhibitory property;

a basic inorganic salt stabilizing agent which is present in an amount effective to stabilize the composition, the benzimidazole compound or its salt being in contact with the basic inorganic salt evenly; and

an enteric coating for the composition.

2. The composition of claim **1**, wherein the basic inorganic salt stabilizing agent is a basic inorganic salt of magnesium which is effective to stabilize the composition.

3. The composition of claim **1**, wherein the basic inorganic salt stabilizing agent is a basic inorganic salt of calcium which is effective to stabilize the composition.

4. The composition of claim **1**, wherein the basic inorganic salt stabilizing agent is a basic inorganic salt of potassium which is effective to stabilize the composition.

5. The composition of claim **1**, wherein the basic inorganic salt stabilizing agent is a basic inorganic salt of sodium which is effective to stabilize the composition.

6. The composition of claim **1**, wherein the composition comprises a plurality of enteric coated granules, each of the granules containing therein said benzimidazole compound or its salt and the stabilizing agent.

7. A method of providing a gastric acid secretion inhibitory effect to a subject in need thereof, comprising:

orally administering to the subject a stabilized pharmaceutical composition comprising:

an effective amount of a 2-[(2-pyridyl)methylsulphinyl]benzimidazole compound or a pharmaceutically acceptable salt thereof having a gastric acid secretion inhibitory property;

a basic inorganic salt stabilizing agent which is present in an amount effective to stabilize the composition, the benzimidazole compound or its salt being in contact with the basic inorganic salt evenly; and

an enteric coating for the composition.

8. The composition of claim **7**, wherein the basic inorganic salt stabilizing agent is a basic inorganic salt of magnesium which is effective to stabilize the composition.

9. The composition of claim **7**, wherein the basic inorganic salt stabilizing agent is a basic inorganic salt of calcium which is effective to stabilize the composition.

10. The composition of claim **7**, wherein the basic inorganic salt stabilizing agent is a basic inorganic salt of potassium which is effective to stabilize the composition.

11. The composition of claim **7**, wherein the basic inorganic salt stabilizing agent is a basic inorganic salt of sodium which is effective to stabilize the composition.

12. A stabilized pharmaceutical composition for the inhibition of gastric acid secretion, comprising:

an effective amount of a 2-[(2-pyridyl)methylsulphinyl]benzimidazole compound or a pharmaceutically acceptable salt thereof having a gastric acid secretion inhibitory property;

a basic inorganic magnesium or calcium stabilizing agent which is present in an amount effective to stabilize the composition, the benzimidazole compound or its salt being in contact with the basic inorganic salt evenly; and

an enteric coating for the composition.

13. The composition of claim **12**, wherein the stabilizing agent is selected from the group consisting of heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metasilicate aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite, aluminum magnesium hydroxide, precipitated calcium carbonate and calcium hydroxide.

14. A method of providing a gastric acid secretion inhibitory effect to a subject in need thereof, comprising:

orally administering to the subject a stabilized pharmaceutical composition comprising:

an effective amount of a 2-[(2-pyridyl)methylsulphinyl]benzimidazole compound or a pharmaceutically acceptable salt thereof having a gastric acid secretion inhibitory property;

a basic inorganic magnesium or calcium stabilizing agent which is present in an amount effective to stabilize the composition, the benzimidazole compound or its salt being in contact with the basic inorganic salt evenly; and

an enteric coating for the composition.

15. The method of claim **14**, wherein the stabilizing agent is selected from the group consisting of heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metasilicate aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite, aluminum magnesium hydroxide, precipitated calcium carbonate and calcium hydroxide.

* * * * *

JS44

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 the 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, Ltd.

(b) COUNTY OF RESIDENCE OF FIRST LISTED PLAINTIFF _____
EXCEPT IN U.S. PLAINTIFF CASES)
Leatherhead, Surrey, England

(c) ATTORNEYS FIRM NAME, ADDRESS AND PHONE NO.
Connolly Bove Lodge & Hutz LLP, 1007 N. Orange Street, PO Box 2207, Wilmington, DE 19899, Arthur G. Connolly, III. Esq. (302) 658-9141

DEFENDANTS

Teva Pharmaceuticals USA, Inc.

COUNTY OF RESIDENCE OF FIRST LISTED DEFENDANT _____
(IN U.S. PLAINTIFF CASES ONLY)
NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF LAND INVOLVED

ATTORNEYS (IF KNOWN)

II. BASIS OF JURISDICTION (PLACE AN "X" IN ONE BOX ONLY)

☐1 U. S. Government Plaintiff
[X]3 Federal Question (U. S. Government Not A Party)
☐2 U. S. Government Defendant
[] 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)

	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. ORIGIN (PLACE AN "X" IN ONE BOX ONLY)

[X]1 Original Proceeding ☐2 Removed from State Court ☐3 Remanded from Appellate Court ☐4 Reinstated or Reopened ☐5 Another District (specify) Transferred from Litigation ☐6 Multidistrict Litigation Judgment ☐7 Appeal to District Judge from Magistrate

V. 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
[x] 190 Other Contract
☐ 195 Contract Product Liability

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

CIVIL RIGHTS
☐ 441 Voting
☐ 442 Employment
☐ 443 Housing/ Accommodations
☐ 444 Welfare
☐ 440 Other Civil Rights

PERSONAL INJURY
☐ 362 Personal Injury - Med. Malpractice
☐ 365 Personal Injury - Product Liability
☐ 366 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
☐ 370 Other Fraud
☐ 371 Truth in Lending
☐ 380 Other Personal Property Damage
☐ 385 Property Damage Product Liability

PRISONER PETITIONS
☐ 510 Motions to Vacate Sentence Habeas Corpus:
☐ 530 General
☐ 535 Death Penalty
☐ 540 Mandamus & Other
☐ 550 Other

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
☐ 443 Withdrawal 28 USC 157

PROPERTY RIGHTS
☐ 820 Copyrights
[X] 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/ICC Rates/etc.
☐ 460 Deportation
☐ 470 Racketeer Influenced and Corrupt Organizations
☐ 810 Selective Service
☐ 850 Securities/commodities/ Exchange
☐ 875 Customer Challenge 12 USC 3410
☐ 891 Agricultural Acts
☐ 892 Economic Stabilization Act
☐ 893 Environmental Matters
☐ 894 Energy Allocation Act
☐ 895 Freedom of InformationAct
☐ 900 Appeal of Fee Determination Under Equal Access to Justice
☐ 950 Constitutionality of State Statutes
☐ 890 Other Statutory Actions

VI. CAUSE OF ACTION

(CITE THE U.S. CIVIL STATUTE UNDER WHICH YOU ARE FILING AND WRITE A BRIEF STATEMENT OF CAUSE. DO NOT CITE JURISDICTIONAL STATUTES UNLESS DIVERSITY) **28 U.S.C. §§ 1331 and 1338(a)**

VII. REQUESTED IN COMPLAINT:

DEMAND $ Damages and Injunctive relief

CHECK IF THIS IS A **CLASS ACTION** ☐ UNDER F.R.C.P. 23

CHECK YES only if demanded in complaint:
JURY DEMAND: ☐ YES ☒ NO

VIII. RELATED CASE(S) IF ANY (See instructions)

DATE January 17, 2006 SIGNATURE OF ATTORNEY OF RECORD Arthur G. Connolly III (#2667)

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RECEIPT #_____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____

JS 44 Reverse

INSTRUCTIONS FOR ATTORNEYS COMPLETING CIVIL COVER SHEET FORM JS-44

Authority for Civil Cover Sheet

The JS-44 civil cover sheet and the information contained herein neither replaces nor supplements the filings and service of pleading 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. Consequently a civil cover sheet is submitted to the clerk of Court for each civil complaint filed. The attorney filing a case should complete the form as follows:

I. (a) Plaintiffs-Defendants. Enter names (last, first middle initial) of plaintiff and defendant. If the plaintiff or defendant is a government agency, use only the full name or standard abbreviations. If the plaintiff or defendant is an official within a government agency identify first the agency and then the official, giving both name and title.

(b) County of Residence. For each civil case filed, except U.S. plaintiff cases, enter the name of the county where the first listed plaintiff resides at the time of filing. In U.S. plaintiff cases, enter the name of the county in which the first listed defendant resides at the time of filing. (NOTE: In land condemnation cases, the county of residence of the "defendant" is the location of the tract of land involved.)

(c) Attorneys. Enter the firm name, address, telephone number, and attorney of record. If there are several attorneys, list them on an attachment, noting in this section "(see attachment)".

II. Jurisdiction. The basis of jurisdiction is set forth under Rule 8(a), F.R.C.P., which requires that jurisdiction be shown in pleadings. Place an "X" in one of the boxes. If there is more than one basis of jurisdiction, precedence is given in the order shown below.

United States plaintiff. (1) Jurisdiction based on 28 U.S.C. 1345 and 1348. Suits by agencies and officers of the United States are included here

United States defendant. (2) When the plaintiff is suing the United States, its officers or agencies, place an "X" in this box.

Federal question. (3) This refers to suits under 28 U.S.C. 1331, where jurisdiction arises under the Constitution of the United States, an amendment to the Constitution, an act of Congress or a treaty of the United States. In cases where the U.S. is a party, the U.S. plaintiff or defendant code takes precedence, and box 1 or 2 should be marked.

Diversity of citizenship. (4) This refers to suits under 28 U.S.C. 1332, where parties are citizens of different states. When Box 4 is checked, the citizenship of the different parties must be checked. (See Section III below; federal question actions take precedence over diversity cases.)

III. Residence (citizenship) of Principal Parties. This section of the JS-44 is to be completed if diversity of citizenship was indicated above. Mark this section for each principal party.

IV. Cause of Action. Report the civil statute directly related to the cause of action and give a brief description of the cause.

V. Nature of Suit. Place an "X" in the appropriate box. If the nature of suit cannot be determined, be sure the cause of action, in Section IV above, is sufficient to enable thedeputy clerk or the statistical clerks in the Administrative Office to determine the nature of suit. If the cause fits more than one nature of suit, select the most definitive.

VI. Origin. Place an "X" in one of the seven boxes.

Original Proceedings. (1) Cases which originate in the United States district courts.
Removed from State Court. (2) Proceedings initiated in state courts may be removed to the district courts under Title 28 U.S.C., Section 1441. When the petition for removal is granted, check this box.
Remanded from Appellate Court. (3) Check this box for cases remanded to the district court for further action. Use the date of remand as the filing date.

Reinstated or Reopened. (4) Check this box for cases reinstated or reopened in the district court. Use the reopening date as the filing date.

Transferred from Another District. (5) For cases transferred under Title 28 U.S.C. Section 1404(a). Do not use this for within district transfers of multidistrict litigation transfers.

Multidistrict Litigation. (6) Check this box when a multidistrict case is transferred into the district under authority of Title 28 U.S.C. Section 1407. When this box is checked, do not check (5) above.

Appeal to District Judge from Magistrate Judgment. (7) Check this box for an appeal from a magistrate judge's decision.

VII. Requested in Complaint. Class Action. Place an "X" in this box if you are filing a class action under Rule 23, F.R.Cv.P.

Demand. In this space enter the dollar amount (in thousands of dollars) being demanded or indicate other demand such as a preliminary injunction.

Jury Demand. Check the appropriate box to indicate whether or not a jury is being demanded.

VIII. Related Cases. This section of the JS-44 is used to reference related pending cases if any. If there are related pending cases, insert the docket numbers and the corresponding judge names for such cases.
Date and Attorney Signature. Date and sign the civil cover sheet.

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AO FORM 85 RECEIPT (REV. 9/04)

United States District Court for the District of Delaware

Civil Action No. 33

ACKNOWLEDGMENT OF RECEIPT FOR AO FORM 85

NOTICE OF AVAILABILITY OF A UNITED STATES MAGISTRATE JUDGE TO EXERCISE JURISDICTION

I HEREBY ACKNOWLEDGE RECEIPT OF 1 COPIES OF AO FORM 85.

1-17-06
(Date forms issued)

(Signature of Party or their Representative)

Robert Testa
(Printed name of Party or their Representative)

Note: Completed receipt will be filed in the Civil Action