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**

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[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

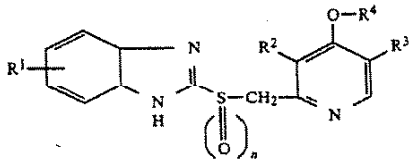
5129	10/1979	European Pat. Off. .
45200	2/1982	European Pat. Off. .
74341	3/1983	European Pat. Off. .
2134523A	8/1984	United Kingdom .

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.

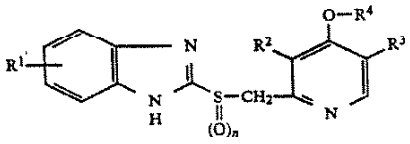
However, while these known compounds have an acid-secretion-inhibiting action, their gastric mucous membrane protecting action is insufficient, thus being hardly considered satisfactory as anti-ulcer agents. Besides, these compounds are possessed of such drawbacks in the physico-chemical properties as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

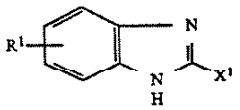
(1) pyridine derivatives of the formula (I)



(I)

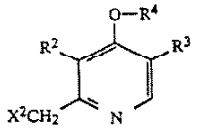
wherein R^1 is hydrogen, methoxy or trifluoromethyl, R^2 and R^3 are independently hydrogen or methyl, R^4 is a C_{2-5} fluorinated alkyl, and n denotes 0 or 1, or their pharmacologically acceptable salts and

(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.

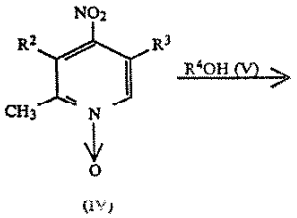
The object compound (I) produced by the above reaction can be isolated and purified by conventional means e.g. recrystallization and chromatography.

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.

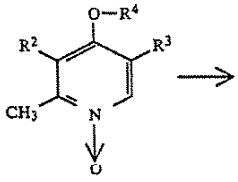
Among the compounds (I), those of n=0 give stable salts, while those of n=1 may exist as an aqueous solution though unstable.

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

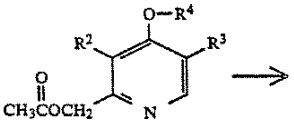
(Process 1)



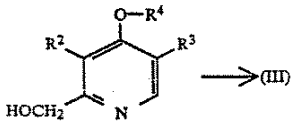
(IV)



(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.

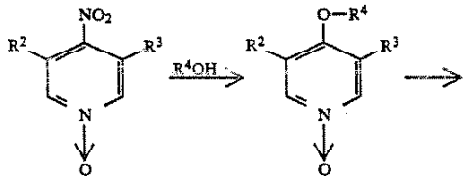
The thus-obtained compound (VI) is subjected to heating (about 80° to about 120° C.) in the presence of acetic anhydride singly or together with a mineral acid e.g. sulfuric acid and perchloric acid to give a 2-acetoxymethylpyridine derivative of the formula (VII) [wherein R^2, R^3 and R^4 are of the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

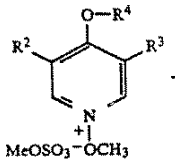
The amount of the organic sulfonic acid chloride or organic phosphoric acid chloride used for the reaction is usually in equivalent to a little excess, and the reaction is usually conducted in the presence of a base. The base is exemplified by organic base e.g. triethylamine and tributylamine, or inorganic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

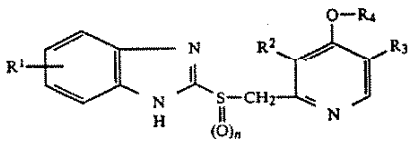
Further, the compound (XI) is allowed to react with a radical source such as ammonium persulfate or any other persulfate in methanol to give the above-mentioned compound (VIII). The reaction temperature is within the range of from about 20° C. to about 80° C., and the reaction time ranges from about 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
*45-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.).

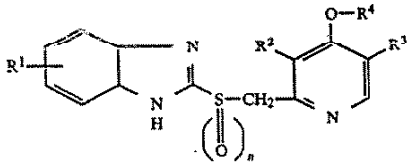
By this process, compounds (I) (n=1) were prepared from compounds (I) (n=0).

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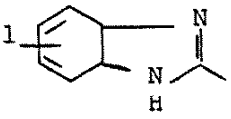
CERTIFICATE OF CORRECTION

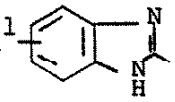
PATENT NO. : 4,628,098

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

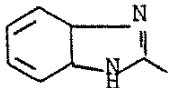
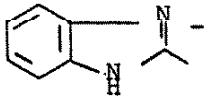
CERTIFICATE OF CORRECTION

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:

Attesting Officer

DONALD J. QUIGG

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

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.
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Bruce A. Lehman

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**

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

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

[21] Appl. No.: **143,957**

[22] Filed: **Jan. 14, 1988**

[30] **Foreign Application Priority Data**

Jan. 29, 1987 [JP] Japan 62-19178

[51] **Int. Cl.**[5] **A61K 9/16;** A61K 9/36; A61K 9/62

[52] **U.S. Cl.** **424/494;** 424/458; 424/461; 424/468; 424/480; 424/489; 424/490; 424/479; 424/493; 424/497; 514/925

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

[56] **References Cited**

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Drug Development and Industrial Pharmacy, 11(8), 1523-1541 (1985).

Primary Examiner—Thurman K. Page
Assistant Examiner—James M. Spear
Attorney, Agent, or Firm—Wegner, Cantor, Mueller & Player

[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

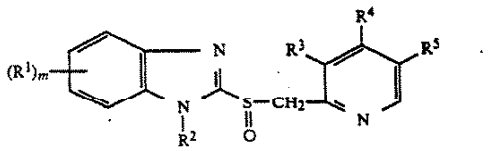
(2) a method for producing spherical granules having a core characterized in that seed cores are coated, while being sprayed with an aqueous binder, with spraying powder containing a drug and low substituted hydroxypropylcellulose.

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, ceilulose 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 hydroxypropylcellulose 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
	hydroxypropylmethylcellulose	89	6 min
	polyvinylpyrrolidone	85	4 min
	pullulan	88	1.5 min
	methylcellulose	84	2 min
	dexirin	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.

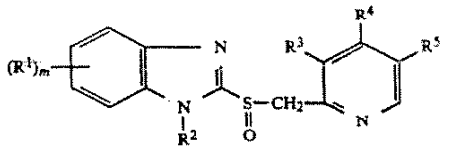
What is claimed is:

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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