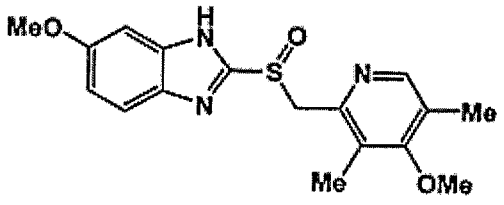
S-OMEPRAZOLE STRONTIUM OR HYDRATE THEREOF, METHOD FOR PREPARING SAME, AND PHARMACEUTICAL COMPOSITION COMPRISING SAME

FIELD OF THE INVENTION

The present invention relates to S-omeprazole strontium or a hydrate thereof having improved optical purity, thermal stability, solubility and non-hygroscopicity, a method for preparing same, and a pharmaceutical composition comprising same.

DESCRIPTION OF THE PRIOR ART

Omeprazole, 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]sulfinyl]-*1H*-benzimidazole having the structure of formula (II) is known as a H^+/K^+-ATPase or proton pump inhibitor which is effective in inhibiting gastric acid secretion to protect gastrointestinals cells (*see* EP Patent No. 0 005 129), and its commercial formulations, Losec® and Prilosec® (AstraZeneca AB), are marketed as medicaments for prevention and treatment of gastric acid-related disorders. This omeprazole should be formulated as enteric coated form because it has a structurally neutral molecule and thus it is thermally and chemically unstable under a condition below neutral pH value.

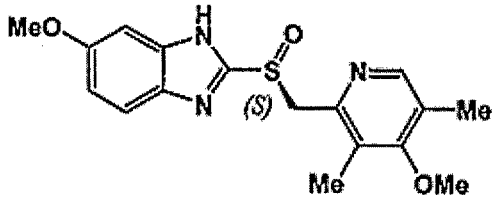


(II)

US Patent No. 4,738,974 discloses omeprazole salts and hydrates thereof, e.g., lithium, sodium, potassium, magnesium, calcium, titanium, ammonium, and guanidine salts. Such omeprazole salts are much more stable than omeprazole in the neutral form.

Omeprazole is a racemic mixture composed of equal amounts of R- and S-enantiomers. S-omeprazole of formula (III) is much more preferred

over the R-isomer in the treatment of gastric or duodenal ulcer, gastroesophageal reflux disease, etc., because the R-isomer tends to be metabolized as inactive metabolites in the irregular variations. Accordingly, there have been many attempts to develop a method for preparing pure S-omeprazole which is substantially free of R-omeprazole.



(III)

For example, racemic omerprazole has been resolved to isolate the S-isomer by a high performance liquid chromatography (*see* Erlandsson et al., Journal of Chromatography, 535, 305-319 (1990)), and a process for preparing each of the omeprazole enantiomers is disclosed in PCT Publication No. WO 1992/08716. However, the separated S-omeprazole products have not been regarded as a stable solid of the pharmaceutically required purity. US patent No. 6,162,816 discloses a crystalline S-omeprazole, but even this crystalline form of S-omeprazole is not sufficiently stable.

US Patent Nos. 5,714,504 and 5,693,818 disclose S-omeprazole salts and hydrates thereof, e.g., lithium, sodium, potassium, magnesium, calcium, and ammonium salts. US Patent Nos. 6,369,085 and 6,511,996 disclose the crystalline potassium salt as well as magnesium salt dihydrate and trihydrate of S-omeprazole, together with their polymorphs. These S-omeprazole salts have stability superior to S-omeprazole itself.

Now, S-omeprazole salts with sodium, potassium and magnesium, or hydrates thereof are commercially marketed with the trade name Nexium® (AstraZeneca AB) as a medicament for prevention and treatment of ulcer. The sodium and potassium salts are preferred for injectable administration because of their good solubility, but they are unsuitable for oral administration due to their hygroscopicity. On the other hand, non-hygroscopic S-omeprazole magnesium trihydate is preferred in terms of oral administration of a solid form of omeprazole, but it is not easy to achieve the optical purity required pharmaceutically. Accordingly, S-omeprazole magnesium trihydate has been subjected to the salt exchange

with the optically pure sodium or potassium salt prepared in advance to achieve satisfactory therapeutic effects (*see* Cotton et al., *Tetrahedron Asymmetry*, 11, 3819-3825 (2000)).

PCT Publication Nos. WO 2004/099182, WO 2005/011692, WO 2003/074514, WO 2005/023796 and WO 2005/023797 disclose S-omeprazole salts of barium, zinc, *t*-butylamine, adamantaneamine and α-methylcyclohexanemethane amine, but, these salts are no better than S-omeprazole magnesium trihydrate in terms of solubility, crystallinity, hygroscopicity, stability and optical purity.

In view of the previous art, therefore, there has been a need to develop an improved salt of S-omeprazole suitable for both oral and injectable administration.

Strontium is an alkaline earth metal of IIA group and it exists in nature in the form of 4 isotopes, ^{88}Sr (82.58%), ^{87}Sr (7.00%), ^{86}Sr (9.86%) and ^{84}Sr (0.56%). It is also known that strontium exerts no safety problems even at a dose of 633 mg/kg/day in rats (*see* P. J. Marie et al., *Mineral & Electrolyte Metabolism*, 11, 5-13 (1985)). Strontium is reported to be ingested by people in an average amount of about 3.3mg/day per 70 kg body weight during the course of everyday life (*see* Report of Toxicological Profile for Strontium, U.S. Department of Health and Human Services, 2004). It is further known that strontium supports calcium metabolism in bone tissues to promote the bone formation and inhibit the resorption of bone tissues (*see* S. P. Nielsen, *Bone*, 35, 583-588 (2004)). As a typical example of strontium salts which have been pharmaceutically used, strontium ranelate, the salt of strontium with ranelic acid is known. However, there is so far no salt of strontium with weak acidic benzimidazole derivatives including omeprazole.

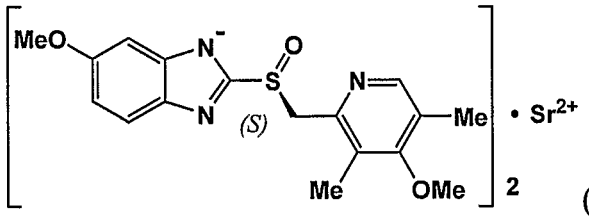
The present inventors have endeavored to develop a novel salt of S-omeprazole and found that S-omeprazole strontium or a hydrate thereof has much improved optical purity, thermo-stability, non-hygroscopicity and solubility over conventional salts.

SUMMARY OF THE INVENTION

It is a primary object of the present invention to provide S-omeprazole

strontium or a hydrate thereof and a method for preparing same.

In accordance with one aspect of the present invention, there is provided S-omeprazole strontium of formula (I) or a hydrate thereof:



(I)

In accordance with another aspect of the present invention, there is provided a method for preparing S-omeprazole strontium of formula (I) or a hydrate thereof, which comprises the step of adding strontium hydroxide or another strontium salt to a neutral or basic solution containing S-omeprazole and stirring the resulting mixture.

In accordance with still another aspect of the present invention, there is provided a pharmaceutical composition comprising S-omeprazole strontium of formula (I) or a hydrate thereof as an active ingredient and a pharmaceutical acceptable carrier for preventing or treating a gastric acid-related disorder.

BRIEF DESCRIPTION OF THE DRAWINGS

The above and other objects and features of the present invention will become apparent from the following description of the invention taken in conjunction with the accompanying drawings, which respectively show:

FIG. 1: an X-ray powder diffraction (XPRD) spectrum of the crystalline S-omeprazole strontium tetrahydrate (Crystalline Form A) obtained according to a preferred embodiment of the present invention in Example 1;

FIG. 2: a differential scanning calorimeter (DSC) curve of the crystalline S-omeprazole strontium tetrahydrate (Crystalline Form A) obtained according to a preferred embodiment of the present invention in Example 1;

FIG. 3: an XPRD spectrum of the crystalline S-omeprazole strontium anhydrate (Crystalline Form B) obtained according to another preferred

embodiment of the present invention in Example 9;

FIG. 4: a DSC curve of the crystalline S-omeprazole strontium anhydrate (Crystalline Form B) obtained according to another preferred embodiment of the present invention in Example 9;

FIG. 5: an XPRD spectrum of the crystalline S-omeprazole strontium hydrate (Crystalline Form C) obtained according to still another preferred embodiment of the present invention in Example 10;

FIG. 6: a DSC curve of the crystalline S-omeprazole strontium hydrate (Crystalline Form C) obtained according to still another preferred embodiment of the present invention in Example 10;

FIG. 7: an XPRD spectrum of the amorphous S-omeprazole strontium obtained according to yet another preferred embodiment of the present invention in Example 11; and

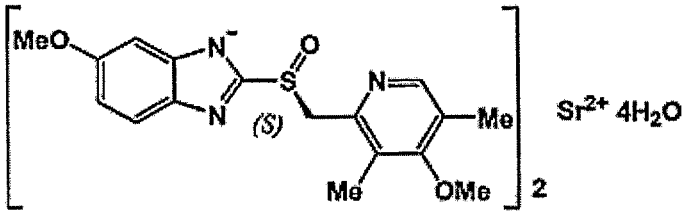
FIG. 8: a DSC curve of the amorphous S-omeprazole strontium obtained according to yet another preferred embodiment of the present invention in Example 11.

DETAILED DESCRIPTION OF THE INVENTION

The inventive S-omeprazole strontium of formula (I) or a hydrate thereof is a novel salt of S-omeprazole, which is optically purer, thermally more stable, less hygroscopic and more soluble than any of the corresponding magnesium salts.

The S-omeprazole strontium according to the present invention has two S-omeprazole molecules coordinated to strontium ion (II), to which at least one H_2O molecule may be coordinated. Such S-omeprazole strontium or a hydrate thereof can be produced in an amorphous form or crystalline form, preferably a crystalline form, which may be confirmed by X-ray powder diffraction (XRD) or differential scanning calorimeter (DSC) analysis.

A preferred embodiment of the present invention is the crystalline tetrahydrate of S-omeprazole strontium, represented by formula (IV):



(IV)

The XRD spectrum of the crystalline S-omeprazole strontium tetrahydrate shows major peaks having I/I_0 values of at least 3% (I is the intensity of each peak; I_0 is the intensity of the highest peak) at 2θ±0.2 of 5.6, 11.1, 13.5, 14.8, 16.2, 17.5, 18.0, 20.1, 20.4, 21.2, 22.2, 24.5, 25.2, 26.3, 27.5, 29.8, 31.1, 32.8 and 36.5 (FIG. 1). Also, a DSC scan of the crystalline tetrahydrate obtained at 5℃/min shows an endothermic peak of about 179 J/g which starts at about 100℃ and reaches its maximum at about 118℃, as well as an exothermic peak of about 451 J/g which starts at about 203℃ and reaches its maximum at about 211℃ (FIG. 2). The actually observed melting point of the crystalline tetrahydrate is around 202℃, and the moisture content thereof determined by loss-on-drying test is 8.0 to 9.5% which is within the experimental error range of 8.49% of the theoretical value.

The present invention also covers a partial or heterogenic crystalline form of S-omeprazole strontium or a hydrate thereof.

Accordingly, another preferred embodiment of the present invention provides a partial or heterogenic crystalline anhydrate of S-omeprazole strontium whose XRD spectrum shows a major peak having an I/I_0 value of 100% at 2θ±0.2 of 5.8 (FIG. 3). A DSC scan of the crystalline anhydrate obtained at 5℃/min shows an exothermic peak which starts at about 186℃ and reaches its maximum at about 197℃ (FIG. 4) while no substantial endothermic peaks are observable. The crystalline anhydrate is observed to decompose at a temperature of about 196℃ or higher.

Still another preferred embodiment of the present invention provides a partial or heterogenic crystalline hydrate of S-omeprazole strontium whose XRD spectrum shows a major peak having an I/I_0 value of 100% at 2θ±0.2 of 25.2 (FIG. 5). A DSC scan of the crystalline hydrate obtained at 5℃/min shows an endothermic peak which starts at about 37℃ and reached its

maximum at about 68℃, as well as an exothermic peak which starts at about 161℃ and reaches its maximum at about 189℃ (FIG. 6). The crystalline hydrate is observed to decompose at a temperature of about 160℃ or higher.

In accordance with yet another preferred embodiment of the present invention, S-omeprazole strontium of formula (I) is also provided in an amorphous form, and its XRD spectrum shows no distinctively characteristic peak (FIG. 7). A DSC scan of the amorphous form obtained at 5℃/min shows an endothermic peak which starts at about 29℃ and reaches its maximum at about 56℃, as well as an exothermic peak which starts at about 183℃ and reaches its maximum at about 208℃ (FIG. 8). This suggests that a phase transition occurs at about 196℃. The amorphous form is observed to decompose at a temperature of about 180℃ or higher.

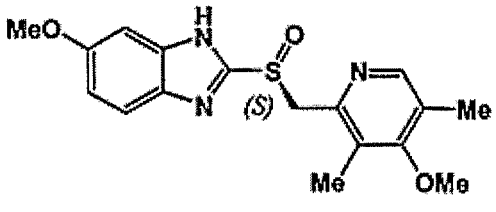
The inventive S-omeprazole strontium of formula (I) or a hydrate thereof satisfies the pharmaceutically required stability since it can maintain the initial moisture content, purity and crystallinity under a long-term storage condition (25℃ under 60% relative humidity), an accelerated aging condition (40℃ under 75% relative humidity) or an stressed condition (60℃ and 75% relative humidity) conducted for 4 weeks or more in a closed state. Particularly, the crystalline S-omeprazole strontium tetrahydrate (crystalline form A) is non-hygroscopic and it is capable of maintaining its initial moisture content under an exposed condition at 25 to 40℃ and 40 to 90% relative humidity for 2 weeks or more.

Further, the inventive S-omeprazole strontium of formula (I) or a hydrate thereof may be pharmaceutically preferred in terms of water solubility over other salts of S-omeprazole. For example, it has a water solubility of about 17.6 mg/ml, which is at least 10 times higher than that of S-omeprazole magnesium trihydrate.

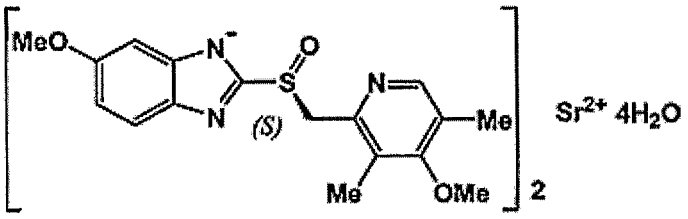
In accordance with the present invention, S-omeprazole strontium of formula (I) or a hydrate thereof may be prepared by adding strontium hydroxide or another strontium salt to a neutral or basic solution containing S-omeprazole, followed by, if necessary, converting the crystal structure thereof.

Specifically, the crystalline S-omeprazole strontium tetrahydrate of formula (IV) may be prepared by adding strontium hydroxide to a neutral solution containing S-omeprazole of formula (III), stirring the resulting

mixture until precipitates form, and filtering and drying the resulting precipitates by a conventional method:



(III)



(IV)

The neutral solution used herein means a solution prepared by dissolving or suspending S-omeprazole in an organic solvent selected from methanol, ethanol, 1-propanol, 2-propanol, acetonitrile, tetrahydrofuran and acetone, preferably, methanol and acetone, or in a mixture of one of said organic solvents and water, preferably, having a mix ratio having a mix ratio of 99:1 to 50:50 (v/v). In the present invention, strontium hydroxide is preferably used in an amount of 0.5 to 0.75 molar equivalent based on S-omeprazole of formula (III). Also, the stirring procedure may be carried out at a temperature ranging from 0℃ to the boiling point of the solvent used for 30 minutes to 24 hours.

Alternatively, the crystalline S-omeprazole strontium tetrahydrate may be prepared by adding a reactive strontium salt to a basic solution of S-omeprazole of formula (III) containing a base, stirring the resulting mixture until precipitates form, and filtering and drying the resulting precipitates by a conventional method. The reactive strontium salt may be selected from strontium chloride, strontium bromide, strontium sulfate, strontium nitrate, strontium perchlorate, strontium acetate, strontium carbonate and strontium oxalate, preferably strontium chloride and strontium acetate. The basic solution means a solution prepared by dissolving or suspending S-omeprazole and a base in an organic solvent selected from methanol, ethanol, 1-propanol, 2-propanol, acetonitrile, tetrahydrofuran and

acetone, preferably, methanol and acetone or in a mixture of one of said organic solvents and water, preferably, having a mix ratio of 99:1 to 50:50 (v/v). The base may be selected from lithium hydroxide, sodium hydroxide, potassium hydroxide, ammonia, methylamine, ethylamine, propylamine, dimethylamine, diethylamine, trimethylamine and triethylamine, preferably sodium hydroxide and potassium hydroxide. In this embodiment, the base is preferably used in an amount ranging from 1 to 3 molar equivalents based on 1 mole of S-omeprazole of formula (III) and the amount of the reactive strontium salt is preferably in the range of 0.5 to 0.75 molar equivalent based on the base. The stirring may be conducted at a temperature ranging from 0℃ to the boiling point of the solvent used for 30 minutes to 24 hours.

It is preferred that the neutral or basic solution contains 1g of S-omeprazole of formula (III) in a volume of 1 to 20㎖, preferably 3 to 10㎖.

In accordance with the above method of the present invention, S-omeprazole salts having high optical purity can be obtained even when an optically impure S-omeprazole is used as a starting material.

Meanwhile, the partial or heterogenic crystalline anhydrate of S-omeprazole strontium may be prepared by drying the crystalline S-omeprazole strontium tetrahydrate at 80 to 130℃ for 30 minutes to 24 hours to dehydrate, if necessary, under a reduced pressure.

The partial or heterogenic crystalline hydrate of S-omeprazole strontium may be prepared by suspending such crystalline anhydrate in water, stirring the suspension at room temperature for 1 to 24 hours, and filtering and drying the resultant by a conventional method.

Also, the amorphous form of S-omeprazole strontium may be prepared by dissolving the crystalline S-omeprazole strontium tetrahydrate in an organic solvent such as acetone and removing the organic solvent from the resulting solution by evaporation under a reduced pressure or spray drying.

The inventive S-omeprazole strontium of formula (I) or a hydrate thereof as mentioned above has a high optical purity of at least 99.0% enantiomeric excess (ee), non-hygroscopicity and good stability against moisture and heat, so that it can be pharmaceutically used for the prevention or treatment of gastric acid-related disorders such as gastroesophageal reflux disease, gastroenteritis and gastric ulcer due to hyperacidity.

Accordingly, the present invention provides a pharmaceutical composition comprising the inventive S-omeprazole strontium of formula (I) or a hydrate thereof as an active ingredient.

The pharmaceutical composition according to the present invention may be administered via various routes including oral, rectal and injectable application, preferably the oral route.

For oral administration, the pharmaceutical composition of the present invention may be in the form of tablets, capsules, pills, and the like, and may be formulated with pharmaceutically acceptable carriers, diluents or excipients. Examples of suitable carriers, diluents and excipients are excipients such as starches, sugar and mannitol; filling agents or increasing agents such as calcium phosphate and silica derivatives; binding agents such as cellulose derivatives of carboxymethylcellulose or hydroxypropylcellulose, gelatin, arginic acid salt, and polyvinylpyrrolidone; lubricating agents such as talc, magnesium or calcium stearate, hydrogenated castor oil and solid polyethylene glycol; disintegrants such as povidone, croscarmellose sodium, and crospovidone; and surfactants such as polysorbate, cetyl alcohol and glycerol monostearate. Further, various pharmaceutical composition comprising a specific amount of active ingredient, together with or without additives such as said excipients, diluents or additives, may be prepared in accordance with any of the conventional procedures (*see Remington's Pharmaceutical Science*, Mack Publishing Company, Easton, Pa., 19th Edition, 1995).

For sterile injectable administration, the pharmaceutical composition of the present invention may be prepared by directly filling the inventive S-omeprazole strontium or a hydrate thereof and a pharmaceutically acceptable carrier in vials under a sterile condition, or by filling the amorphous powder obtained by dissolving the inventive S-omeprazole strontium or a hydrate thereof and a pharmaceutically acceptable carrier in sterile water and then freeze-drying in vials, which is dissolved in sterile water to be administered.

In a preferred embodiment, the pharmaceutical composition for oral administration of the present invention may contain S-omeprazole strontium of formula (I) or a hydrate thereof in an amount ranging from 0.1 to 95% by weight, preferably 1 to 70% by weight based on the total weight of the

composition.

A typical daily dose of S-omeprazole strontium of formula (I) or a hydrate thereof for a mammalian including human may range from about 0.5 to 500 mg/kg body weight, preferably 5 to 100 mg/kg body weight, and can be administered in a single dose or in divided doses.

The present invention will be described in further detail with reference to Examples. However, it should be understood that the present invention is not restricted by the specific Examples.

Example

The analysis conditions of HPLC employed in Examples are listed below, and the unit "% ee" as used herein means enantiomeric excess.

Condition A: For the measurement of the amount of omeprazole

- Column: Zorbax C8 XDB, 5㎛ (150㎜×4.6㎜)
- Detector: 281㎚
- Flow rate: 1.0 ㎖/minute
- Elution condition: Na_2HPO_4-NaH_2PO_4 buffer solution/CH_3CN=75/25 (v/v)

Condition B: For the measurement of the optical purity of S-omerprazole strontium

- Column: Chiral-AGP, 5㎛ (150㎜×4㎜)
- Detector: 280㎚
- Flow rate: 0.8 ㎖/minute
- Elution condition: NaH_2PO_4 buffer solution (pH 6.5)/CH_3CN=10/90 (v/v)

<Preparation of S-omerprazole strontium or hydrate thereof>

Examples 1 to 8: Preparation of crystalline tetrahydrate of S-omerprazole strontium (Crystalline Form A)

Example 1

S-Omeprazole (30.0g, 86.9mmol) having an optical purity of 95% ee was dissolved in 200㎖ of methanol, and strontium hydroxide octahydrate (13.8g, 51.9mmol) dissolved in 100㎖ of methanol was slowly added thereto, followed by stirring the mixture at room temperature for 3 hours. The precipitate formed was filtered, washed with 100㎖ of methanol and dried at 45℃ for 12 hours, to obtain 33.8 g of the title compound (yield: 92%) as an white crystalline powder.

M.P.: 201~203℃

Moisture content (Loss-on-Drying Test): 9.0% (calculated for tetrahydrate, 8.49%)

Strontium content (EDTA titration): 11.1% (calculated for anhydrate, 11.3%)

Omerprazole content (HPLC, condition A): 88.5% (calculated for anhydrate, 88.7%)

Optical purity (HPLC, condition B): 99.9% ee

Specific rotation, $[\alpha]_D^{20}$: -31.1° (c=1.0, acetone)

^{1}H-NMR (DMSO-d^6): δ 8.26(s, 1H), 7.38(d, 1H), 7.02(bs, 1H), 6.54(dd, 1H), 4.58(d, 2H, J=13.3), 4.46(d, 2H, J=13.4), 3.68(s, 3H), 3.66(s, 3H), 2.22(s, 3H), 2.10(s, 3H)

IR (KBr, cm^{-1}): 3422, 2991, 2831, 2364, 1638, 1611, 1569, 1561, 1476, 1444.4, 1390, 1365, 1271, 1204, 1156, 1077, 1027, 1000, 855, 844, 798, 637, 487

The result of X-ray powder diffraction analysis for the S-omeprazole strontium tetrahydrate showed that the S-omeprazole strontium tetrahydrate was crystal having the distinctively characteristic diffraction pattern as shown in FIG. 1. The main peaks having I/I_0 values of at least 3% are listed in Table 1.

Table 1

2θ (±2)	D	I/I_0 (%)	2θ (±2)	d	I/I_0 (%)
5.6	15.9	100	22.2	4.0	4.3
11.1	8.0	8.6	24.5	3.6	15.4
13.5	6.5	23.5	25.2	3.5	11.6
14.8	6.0	4.5	26.3	3.4	5.4
16.2	5.5	66.5	27.5	3.2	6.3
17.5	5.1	3.4	29.8	3.0	9.8
18.0	4.9	3.2	31.1	2.9	4.2
20.1	4.4	4.4	32.8	2.7	4.3
20.4	4.3	5.3	36.5	2.5	3.2
21.2	4.2	7.8			
2θ: angle of diffraction, d: distance within each crystal face, I/I_0 (%): relative intensity of peak					

Also, as can be seen from FIG. 2, the differential scanning calorimeter (DSC) curve obtained at 5℃/min of the crystalline S-omeprazole strontium tetrahydrate showed an endothermic peak of 178.9 J/g which starts at 100.04℃ and reaches its maximum at 118.33℃ and an exothermic peak of 451.3 J/g which starts at 203.06℃ and reaches its maximum at 210.68℃.

Example 2

S-Omeprazole (10.4g, 30.1mmol) having an optical purity of 90% ee was dissolved in 100mℓ of methanol, and strontium hydroxide octahydrate (4.6g, 17.3mmol) dissolved in 100mℓ of methanol was slowly added thereto, followed by stirring the resulting mixture at room temperature for 3 hours. The precipitate formed was filtered, washed with 50mℓ of methanol and dried at 45℃ for 12 hours, to obtain 10.7 g of the title compound (yield: 84%) as an white crystalline powder.

M.P.: 201~203℃

Moisture content (Loss-on-Drying Test): 8.9% (calculated for tetrahydrate, 8.49%)

Strontium content (EDTA titration): 11.2% (calculated for anhydrate, 11.3%)
Omerprazole content (HPLC, condition A): 88.4% (calculated for anhydrate, 88.7%)
Optical purity (HPLC, condition B): 99.9% ee

Example 3

S-Omeprazole (10.4g, 30.1mmol) having an optical purity of 80% ee was dissolved in 100㎖ of methanol, and strontium hydroxide octahydrate (4.6g, 17.3mmol) dissolved in 50㎖ of methanol was slowly added thereto, followed by stirring the resulting mixture at room temperature for 3 hours. The precipitate formed was filtered, washed with 50㎖ of methanol and dried at 45℃ for 12 hours, to obtain 9.3 g of the title compound (yield: 73%) as an white crystalline powder.

M.P.: 201~203℃
Moisture content (Loss-on-Drying Test): 8.7% (calculated for tetrahydrate, 8.49%)
Strontium content (EDTA titration): 11.2% (calculated for anhydrate, 11.3%)
Omerprazole content (HPLC, condition A): 88.5% (calculated for anhydrate, 88.7%)
Optical purity (HPLC, condition B): 99.7% ee

Example 4

Sodium hydroxide (3.8g, 95.0mmol) was dissolved in 150㎖ of water, and S-omeprazole (27.5g, 79.6mmol) having an optical purity of 90% ee was dissolved therein. Thereto, strontium chloride hexahydrate (12.7g, 47.8mmol) dissolved in 150㎖ of methanol was slowly added, and the resulting mixture was stirred at room temperature for 3 hours. The precipitate formed was filtered, washed with a mixture of water (20㎖) and methanol (80㎖) and dried at 45℃ for 12 hours, to obtain 29.7 g of the title compound (yield: 88%) as an white crystalline powder.

M.P.: 201~203℃
Moisture content (Loss-on-Drying Test): 8.9% (calculated for tetrahydrate, 8.49%)

Strontium content (EDTA titration): 11.35% (calculated for anhydrate, 11.3%)
Omerprazole content (HPLC, condition A): 88.6% (calculated for anhydrate, 88.7%)
Optical purity (HPLC, condition B): 99.8% ee

Example 5

Potassium hydroxide (5.3g, 94.5mmol) was dissolved in 150㎖ of water, and S-omeprazole (27.5g, 79.6mmol) having an optical purity of 95% ee was dissolved therein. Thereto, strontium chloride hexahydrate (12.7g, 47.8mmol) dissolved in 150㎖ of methanol was slowly added, and the resulting mixture was stirred at room temperature for 3 hours. The precipitate formed was filtered, washed with a mixture of water (20㎖) and methanol (80㎖) and dried at 45℃ for 12 hours, to obtain 28.7 g of the title compound (yield: 85%) as an white crystalline powder.

M.P.: 201~203℃
Moisture content (Loss-on-Drying Test): 9.0% (calculated for tetrahydrate, 8.49%)
Strontium content (EDTA titration): 11.3% (calculated for anhydrate, 11.3%)
Omerprazole content (HPLC, condition A): 88.5% (calculated for anhydrate, 88.7%)
Optical purity (HPLC, condition B): 99.8% ee

Example 6

Potassium hydroxide (5.3g, 94.5mmol) was dissolved in 150㎖ of water, and S-omeprazole (27.5g, 79.6mmol) having an optical purity of 95% ee was dissolved therein. 150㎖ of methanol and strontium acetate (12.7g, 47.8mmol) dissolved in 50㎖ of water were slowly added thereto, and the resulting mixture was stirred at room temperature for 3 hours. The precipitate formed was filtered, washed with a mixture of water (20㎖) and methanol (80㎖) and dried at 45℃ for 12 hours, to obtain 28.0 g of the title compound (yield: 83%) as an white crystalline powder.

M.P.: 201~203℃

Moisture content (Loss-on-Drying Test): 8.9% (calculated for tetrahydrate, 8.49%)
Strontium content (EDTA titration): 11.2% (calculated for anhydrate, 11.3%)
Omerprazole content (HPLC, condition A): 88.5% (calculated for anhydrate, 88.7%)
Optical purity (HPLC, condition B): 99.9% ee

Example 7

(S)-(-)-binol (25.0g, 87.3mmol) was dissolved in a mixture of 400㎖ of ethanol and 100㎖ of water at 60℃ and cooled to 50 to 55℃, to which 5.0㎖ of triethylamine (35.9mmol) and omeprazole (50.0g, 144.8mmol) were successively added. The resulting solution was slowly cooled to room temperature and stirred for 12 hours. The precipitate formed was filtered, washed with a mixture of 85㎖ of ethanol and 15㎖ of water and then 100㎖ of hexane and dried at 40℃, to obtain an inclusion complex of (S)-(-)-binol and S-omeprazole (optical purity: 97.0% ee).

80g of the inclusion complex of (S)-(-)-binol and S-omeprazole (optical purity: 97.0% ee) obtained above was dissolved in 400㎖ of methanol, and strontium hydroxide octahydrate (20g, 75.3mmol) was added thereto, followed by stirring the resulting mixture at room temperature for 3 hours. The precipitate formed was filtered, washed with 150㎖ of methanol and dried at 45℃ for 12 hours, to obtain 49.0 g of the title compound (yield: 91%) as an white crystalline powder.

M.P.: 201~203℃
Moisture content (Loss-on-Drying Test): 9.0% (calculated for tetrahydrate, 8.49%)
Strontium content (EDTA titration): 11.2% (calculated for anhydrate, 11.3%)
Omerprazole content (HPLC, condition A): 88.5% (calculated for anhydrate, 88.7%)
Optical purity (HPLC, condition B): 99.9% ee

Example 8

50g of the inclusion complex of (S)-(-)-binol and S-omeprazole (optical purity: 97.0% ee) obtained in Example 7 was dissolved in 500㎖ of

isopropyl acetate, and sodium hydroxide (3.8g, 95.0mmol) dissolved in 150 mℓ of water was thereto, followed by stirring the resulting mixture at room temperature for 3 hours. After separating isopropyl acetate, the aqueous layer was washed with 200mℓ of isopropyl acetate. To the basic aqueous layer including S-omeprazole, a strontium chloride hexahydrate (12.6g, 47.5 mmol) dissolved in 150mℓ of methanol was slowly added. The solution suspended was stirred for 3 hours. The precipitate formed was filtered, washed with a mixture of water (20mℓ) and methanol (80mℓ) and dried at 45℃ for 12 hours, to obtain 28.5 g of the title compound (yield: 85%) as an white crystalline powder.

M.P.: 201~203℃
Moisture content (Loss-on-Drying Test): 8.8% (calculated for tetrahydrate, 8.49%)
Strontium content (EDTA titration): 11.3% (calculated for anhydrate, 11.3%)
Omerprazole content (HPLC, condition A): 88.6% (calculated for anhydrate, 88.7%)
Optical purity (HPLC, condition B): 99.7% ee

Example 9: Preparation of partial or heterogenic crystalline anhydrate of S-omerprazole strontium (Crystalline Form B)

30.0g of crystalline S-omeprazole strontium tetrahydrate (Crystalline Form A) obtained in Example 1 was dried at 100℃ for 5 hours, to obtain 27.0 g of the title compound.

M.P.: decomposition at 196℃ or higher
Moisture content (Loss-on-Drying Test): 0.9%
Optical purity (HPLC, condition B): 99.9% ee

The result of XRD analysis for the S-omerprazole strontium obtained showed a major peak having an I/I_0 value of 100% at $2\theta \pm 0.2$ of 5.8 (FIG. 3), and DSC curve obtained at 5℃/min showed an exothermic peak which starts at 186.09℃ and reaches its maximum at 197.23℃ without a substantial endothermic peak, which was a partial or heterogenic crystalline anhydrate form.

Example 10: Preparation of partial or heterogenic crystalline hydrate of S-omeprazole strontium (Crystalline Form C)

20.0g of crystalline anhydrate of S-omerprazole strontium (Crystalline Form B) obtained in Example 9 was suspended in 150 ㎖ of water and stirred at room temperature for 12 hours. The precipitate formed was filtered and dried at 45℃ for 12 hours, to obtain 16.5 g of the title compound.

M.P.: phase transition at 105~107℃ and decomposition at 160℃ or higher
Moisture content (Loss-on-Drying Test): 8.5%
Optical purity (HPLC, condition B): 99.9% ee

The result of XRD analysis for the S-omerprazole strontium obtained showed a major peak having an I/I_0 value of 100% at $2\theta \pm 0.2$ of 25.2 (FIG. 5), and DSC curve obtained at 5℃/min showed an endothermic peak which starts at 37.11℃ and reaches its maximum at 68.09℃, as well as an exothermic peak which starts at 161.3℃ and reaches its maximum at 188.81℃ (FIG. 6), which was a partial and heterogenic crystalline hydrate form.

Example 11: Preparation of amorphous form of S-omerprazole strontium

25.0g of crystalline S-omeprazole strontium tetrahydrate (Crystalline Form A) obtained in Example 1 was dissolved in 250 ㎖ of acetone, and the resulting solution was subjected to solvent-evaporation under a reduced pressure, to obtain 21.0 g of the title compound.

M.P.: decomposition at 180℃ or higher
Moisture content (Loss-on-Drying Test): 6.0%
Optical purity (HPLC, condition B): 99.8% ee

The result of XRD analysis for the S-omerprazole strontium obtained showed an amorphous form having no distinctively characteristic peak as shown in FIG. 7.

Also, as can be seen from FIG. 8, DSC curve of the amorphous form

obtained at 5℃/min showed an endothermic peak which starts at 29.16℃ reaching maximum heat absorption point at 55.88℃, as well as an exothermic peak which starts at 182.85℃ reaching its peak at 207.78℃ in which phase transition occurred at 195.13℃.

<Preparation of S-omeprazole magnesium trihydrate>

Comparative Example 1

Magnesium trihydrate of S-omeprazole was prepared according to Example 7 of US Patent No. 6,369,085.

Specifically, potassium hydroxide (1.26g, 22.5mmol) was dissolved in 30㎖ of water, and S-omeprazole (5.18g, 15.0 mmol) having an optical purity of 95% ee was added thereto. Then, magnesium sulfate (1.81g, 15.0mmol) dissolved in 10㎖ of water was slowly added to the solution, followed by stirring the resulting mixture at room temperature for 3 hours. The precipitate formed was filtered, washed with 15㎖ of water, and was dried by blowing warm air at 45℃ for 12 hours, to obtain S-omeprazole magnesium trihydrate as a white crystalline powder in a yield of 95%.

Comparative Examples 2 and 3

The procedure of Comparative Example 1 was repeated except for using S-omeprazole having an optical purity of 90% ee and 80% ee, respectively.

Experimental Example 1: Optical purity test

The S-omeprazole strontium tetrahydrates obtained in Examples 1 to 3 and the S-omeprazole magnesium trihydrates obtained in Comparative Examples 1 to 3, respectively, were subjected HPLC analyses under the previously described condition B, to measure the optical purities thereof. The results are shown in Table 2.

Table 2

Effect of increasing optical purity		
Starting material (S-omeprazole)	Obtained salt of S-omeprazole	
	Magnesium trihydrate	Strontium tetrahydrate
80% ee	81.4% ee (Com. Ex. 1)	99.9% ee (Ex. 1)
90% ee	91.1% ee (Com. Ex. 2)	99.9% ee (Ex. 2)
95% ee	95.0% ee (Com. Ex. 3)	99.7% ee (Ex. 3)

As shown in Table 2, the optical purities of the inventive S-omeprazole strontium tetrahydrates were markedly higher than those of the starting materials and the S-omeprazole magnesium trihydrates.

Experimental Example 2: Water-solubility test

The S-omeprazole strontium or a hydrate thereof prepared according to the present invention and the S-omeprazole magnesium trihydrate were each dissolved in deionized water to saturation. The water-solubility of each of the saturated solutions was analyzed by HPLC under the previously described condition A and the amount of each salt hydrate dissolved was measured. The results are shown in Table 3.

Table 3

Salt	Solubility (mg/㎖, 25℃)	Saturation pH
Magnesium trihydrate	1.5	9.9
Strontium tetrahydrate (Crystalline Form A)	17.6	10.2
Strontium anhydrate (Crystalline Form B)	12.9	-
Strontium hydrate (Crystalline Form C)	8.1	-
Amorphous form of Strontium salt	11.6	

As shown in Table 3, the solubility of the inventive S-omeprazole strontium and hydrates thereof are at least 10 times higher than that of the known S-omeprazole magnesium trihydrate, which suggests that the inventive strontium salt and hydrates thereof are more suitable for injectable application.

Experimental Example 3: Hygroscopicity test

The S-omeprazole strontium tetrahydrate prepared according to the present invention was exposed in the naked state at 25 to 40℃ and 40 to 90% relative humidity for a period of over 15 days. The moisture contents of the inventive salt measured by loss-on-drying test at storage time 0, 3, 7 and 15 days are shown in Table 4.

Table 4

	Moisture content (wt%)			
	40% (25℃)	60% (25℃)	75% (40℃)	90% (35℃)
O day	9.0	9.0	9.0	9.0
3 days	8.9	9.0	8.9	9.2
7 days	8.7	9.2	9.0	9.3
15 days	8.8	9.1	8.9	9.2

As shown in Table 4, the inventive S-omeprazole strontium tetrahydrate was less hygroscopic under a highly humid condition, and its initial moisture content was maintained under a low humidity condition.

Experimental Example 4: Heat stability test

The S-omeprazole strontium tetrahydrate prepared according to the present invention was stored in the sealed state under a stressed condition of 60℃ and 75% relative humidity, and the remaining amounts of active S-omeprazole after 7, 14, 21 and 28 days were measured by HPLC condition A. The results are shown in Table 5.

Table 5

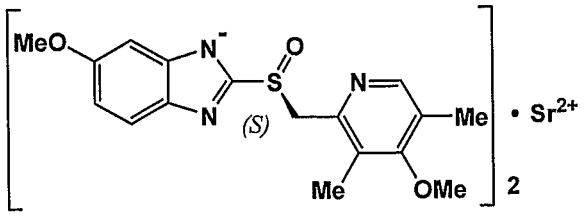
	Amount of titrated S-omeprazole (μg/mg)
Initial	997
7 days	997
14 days	998
21 days	997
28 days	997

As shown in Table 5, the inventive S-omeprazole strontium tetrahydrate is highly stable as witnessed by the result obtained under the accelerated aging condition.

While the invention has been described with respect to the specific embodiments, it should be recognized that various modifications and changes may be made by those skilled in the art to the invention which also fall within the scope of the invention as defined as the appended claims.

WHAT IS CLAIMED IS:

1. A S-omeprazole strontium of formula (I):



(I)

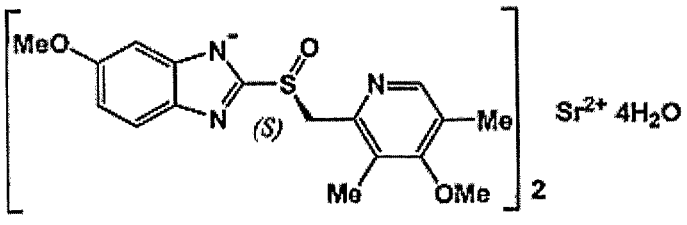
2. The S-omeprazole strontium of claim 1, which is a crystalline form whose X-ray powder diffraction spectrum shows a major peak having an I/I_o value of 100% at 2θ of 5.8±0.2.

3. The S-omeprazole strontium of claim 1, which is an amorphous form.

4. A hydrate of S-omeprazole strontium of claim 1.

5. The hydrate of S-omeprazole strontium of claim 4, which is a crystalline form whose X-ray powder diffraction spectrum shows major peaks having I/I_o values of at least 3% at 2θ±0.2 of 5.6, 11.1, 13.5, 14.8, 16.2, 17.5, 18.0, 20.1, 20.4, 21.2, 22.2, 24.5, 25.2, 26.3, 27.5, 29.8, 31.1, 32.8 and 36.5.

6. The hydrate of S-omeprazole strontium of claim 5, which is represented by formula (IV):

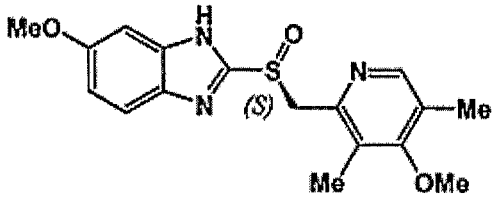


(IV)

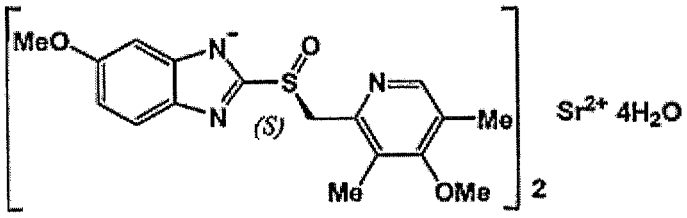
7. The hydrate of S-omeprazole strontium of claim 4, which is a crystalline form whose X-ray powder diffraction spectrum shows a major

peak having an I/I_o value of 100% at 2θ of 25.2±0.2.

8. A method for preparing the crystalline S-omeprazole strontium hydrate of formula (IV), which comprises adding strontium hydroxide to a neutral solution containing S-omeprazole of formula (III) and stirring the resulting mixture:



(III)



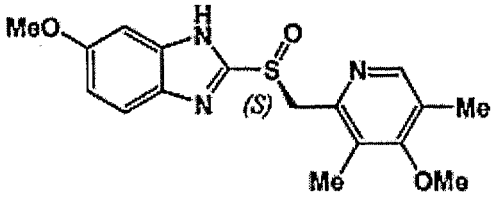
(IV)

9. The method of claim 8, wherein the strontium hydroxide is used in an amount ranging 0.5 to 0.75 molar equivalent based on S-omeprazole.

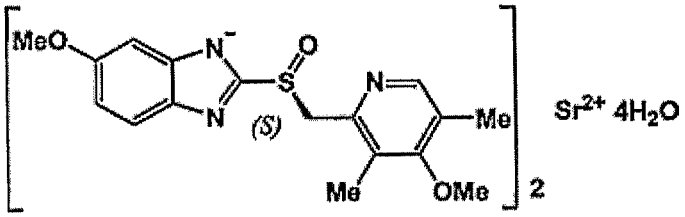
10. The method of claim 8, wherein the neutral solution is prepared by dissolving or suspending S-omeprazole in an organic solvent selected from the group consisting of methanol, ethanol, 1-propanol, 2-propanol, acetonitrile, tetrahydrofuran, acetone and a mixture thereof, or in a mixture of said organic solvent and water.

11. The method of claim 8, wherein the organic solvent is selected from methanol, acetone and a mixture thereof.

12. A method for preparing the crystalline S-omeprazole strontium hydrate of formula (IV), which comprises adding a reactive strontium salt to a basic solution of S-omeprazole of formula (III) containing a base, and stirring the resulting mixture:



(III)



(IV)

13. The method of claim 12, wherein the base is used in an amount ranging from 1 to 3 molar equivalents based on S-omeprazole.

14. The method of claim 12, wherein the reactive strontium salt is used in an amount ranging from 0.5 to 0.75 molar equivalent based on the base.

15. The method of claim 12, wherein the basic solution is prepared by dissolving or suspending S-omeprazole and the base in an organic solvent selected from the group consisting of methanol, ethanol, 1-propanol, 2-propanol, acetonitrile, tetrahydrofuran, acetone and a mixture thereof, or in a mixture of said organic solvent and water.

16. The method of claim 12, wherein the base is selected from the group consisting of lithium hydroxide, sodium hydroxide, potassium hydroxide, ammonia, methylamine, ethylamine, propylamine, dimethylamine, diethylamine, trimethylamine, triethylamine and a mixture thereof.

17. The method of claim 12, wherein the reactive strontium salt is selected from the group consisting of strontium chloride, strontium bromide, strontium sulfate, strontium nitrate, strontium perchlorate, strontium acetate, strontium carbonate, strontium oxalate and a mixture thereof.

18. A pharmaceutical composition for the prevention or treatment of a

gastric acid-related disorder, which comprises the S-omeprazole strontium or a hydrate thereof according to claim 1 or 4 as an active ingredient and a pharmaceutically acceptable salt.

19. The composition of claim 18, which is administered in the form of an oral formulation.

20. The composition of claim 19, wherein the amount of the S-omeprazole strontium or hydrate thereof is the range of 0.1 to 95% by weight based on the total composition.

21. The composition of claim 20, wherein the amount of the S-omeprazole strontium or hydrate thereof is the range of 1 to 70% by weight based on the total composition.

22. The composition of claim 18, which is administered in the form of a sterile injectable formulation.

23. The composition of claim 18, wherein the gastric acid-related disorder is gastroesophageal reflux disease, gastroenteritis or gastric ulcer.