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STABILIZED ENTERIC-COATED MICROGRANULES COMPRISING 2-[(4-METHOXY-3-METHYL)-2-PYRIDINYLMETHYLSULFINYL-5-(1H-PYRROL-1-YL)-1H-BENZIMIDAZOLE AND ORAL FORMULATIONS COMPRISING THE MICROGRANULES

TECHNICAL FIELD

The present invention relates to an enteric-coated microgranule comprising 2-[(4-methoxy-3-methyl)-2-pyridinyl]methylsulfinyl-5-(1H-pyrrol-1-yl)-1H-benzimidazole (hereinafter, referred to as IY-81149) as an active ingredient which has a potent inhibitory activity for gastric acid secretion by irreversibly inhibiting a proton pump that is related to the secretion of gastric acid, and oral formulations comprising it

The object of the present invention is to provide a stabilized enteric-coated microgranule comprising IY-81149, and oral formulations comprising it

BACKGROUND ART

The active ingredient of the enteric-coated microgranules according to the present invention, 2-[(4-methoxy-3-methyl)-2-pyridinyl] methylsulfinyl-5-(1H-pyrrol-1-yl)-1H-benzimidazole, is a novel compound developed by the present inventors, and its applications for approval as a product patent were filed in 27 countries including Korea, Japan, the United States, etc., some of which were granted patents. The compound has an excellent antiulcer effect by irreversibly inhibiting the proton pump, but is highly unstable under acidic conditions although it is stable under alkaline environment. That is, IY-81149 is very stable under an alkali condition of pH 7.6 or more, and yet it has a half time of 40 minutes or less under acidic conditions (about pH 4.0) and has a half time of 35 hours at neutral conditions (pH 7.0).

The general way for stabilizing the acid-unstable substances is to make an alkaline environment as well as to intercept the influx of moisture from the environment. However, the present inventors have found that the desired stabilizing effect can hardly be obtained by simply

mixing the acid-unstable active ingredient of the present invention with an alkali compound.

Therefore, the present inventors have extensively studied to establish a method by which IY-81149 can be stabilized. As a result, the present inventors have found that if IY-81149 is prepared in the form of enteric-coated microgranule having the particle size of 350 to 840 μm by mixing IY-81149 with an alkali compound as a stabilizer, coating the mixture with a film forming material to obtain a microgranule, and subsequently coating the microgranule with an enteric coating material, inactivation of IY-81149 can be prevented, and the long term stability can be maximized

Also, the present inventors have found through laboratory tests that a certain compound among the known organic or inorganic alkali compounds is highly appropriate for stabilizing IY-81149 by which an enteric-coated microgranule of optimally stabilized IY-81149 has been prepared.

DISCLOSURE OF THE INVENTION

The present invention provides stabilized enteric-coated microgranules having the particle size of 350 to 840 μm prepared by mixing the active ingredient, 2-[(4-methoxy-3-methyl)-2-pyridinyl]methylsulfinyl-5-(1H-pyrrol-1-yl)-1H-benzimidazole, alkali compound as a stabilizer, and a pharmaceutically acceptable additive, firstly coating the mixture with a film forming material to obtain microgranules, and secondly coating the microgranules with an enteric coating material, and oral formulations comprising the microgranules.

DETAILED DESCRIPTION OF THE INVENTION

The alkali compounds which can be used for enteric-coated microgranules according to the present invention are selected from the group consisting of magnesium hydroxide, sodium phosphate(dibasic), potassium phosphate(dibasic), sodium bicarbonate, sodium carbonate, potassium carbonate, potassium hydrogen carbonate, aluminum hydroxide, arginine, histidine and lysine, and the combination thereof. These stabilizers contribute to stability of IY-81149 by

maintaining the ambient pH of 7 to 13. However, the extent of their contribution to the stability is different from each other depending on their solubility, alkaline reaction efficiency, compatibility with the active ingredient, etc. For example, it has been identified that magnesium hydroxide exhibits a superior stabilizing effect upon the active ingredient of the present invention when compared with the other stabilizers (see, Test Examples 1 and 2).

The alkali compound as a stabilizer may be used in a molar amount of 0.2 to 7.0 times, preferably 0.5 to 6.5 times with respect to IY-81149. Although there are some differences according to the kind of stabilizer, this is because the stabilizing effect is trivial in a molar amount less than 0.2 times, and the increased hygroscopicity of the stabilizer may act as an obstacle for formulation in a molar amount more than 7.0 times.

The pharmaceutically acceptable additives used in the enteric-coated microgranules according to the present invention include conventional excipient, disintegrant, lubricant, binder, sweetener, flavor, etc.

The film forming material used in the first coating is water-soluble polymers that form water-soluble coating layer, and preferably selected from the group consisting of hydroxyethylcellulose(HEC), hydroxypropylcellulose(HPC), hydroxypropylmethylcellulose (HPMC), sodium alginate, and the combination thereof. The film forming material is used preferably in an amount of 0.5 to 30%, more preferably, 1.0 to 20% by weight with respect to the weight of the mixture comprising IY-81149. The film forming material used in the first coating is used in the form of being dissolved in some amount of purified water or ethanol. The operation of the first coating may be carried out by using a conventional granulator, CF-granulator or fluidized-bed granulator.

The first coated microgranule is then secondly coated with an enteric coating material to obtain acid resistance. The enteric coating material used in the second coating is preferably selected from the group consisting of hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, polyvinyl acetate phthalate, acrylate polymer(EudragitTM or KollicoatTM), hydroxypropyl methylcellulose acetate succinate, and combination thereof. The enteric coating material is

used preferably in an amount of 10 to 60%, more preferably, 10 to 40% by weight with respect to the total weight of the microgranule comprising IY-81149. The enteric coating material used in the second coating is used in the form of being dissolved in a purified water, ethanol, acetone, methylene chloride, and ethyl acetate, and the combination thereof. The operation of the second coating may be carried out by using a fluidized-bed granulator.

The enteric coating material used in the second coating consists of strong acidic compounds to play a role in preventing degradation by gastric acid of the microgranules comprising IY-81149 that is unstable under acidic conditions.

In the first coating by the film forming material and, in the second coating by the enteric coating material, a plasticizer is preferably used to enhance the efficacy of film forming and to prevent cleavage of the coating layer. The plasticizer is preferably selected from the group consisting of polyethylene glycol, propylene glycol, cetanol, glycerin fatty acid ester(MyvacetTM), dimethicone, diethylphthalate, triacetin, and triethyl citrate, and the combination thereof. The plasticizer is used in an amount of preferably 1.0 to 40%, more preferably 5 to 30 % by weight with respect to the weight of the first or the second coating material.

The microgranules according to the present invention may be formulated to oral formulations such as granule, capsule and tablet. The enteric-coated microgranules according to the present invention are formulated to granules by mixing the enteric-coated microgranules with an excipient, a lubricant, etc, and filling the mixture into an aluminium foil pack, to capsule by filling the mixture into a capsule shell, or to tablets by tableting the microgranules.

When the enteric-coated microgranules according to the present invention are administered to patients, the dosage is varied depending on necessity of patients, and seriousness of diseases which should be cured, and determination of dosage under a certain condition is known to those skilled in this art. The unit dose of the active ingredient in the microgranules according to the present invention is 5 to 20 mg, preferably 5 to 10 mg.

The present invention will be more specifically explained by the following examples

However, it should be understood that the examples are intended to illustrate but not to limit the scope of the present invention in any manner

Examples

Examples 1 ~ 10

Preparation of microgranules comprising IY-81149

Mg(OH)₂, Na₂HPO₄, NaHCO₃, arginine, etc, which are particularly suitable for stabilizing the active ingredient in the microgranules according to the present invention, IY-81149, are mixed with the active ingredient in a molar ratio of 1:2, microcrystalline cellulose as an excipient is added to this mixture, and the mixture is granulated by conventional granulator, CF-granulator or fluidized-bed granulator using a solution, in which the first film forming material and a plasticizer are dissolved in a suitable solvent, to obtain microgranules. These microgranules are secondly coated by a fluidized-bed granulator using another solution in which the second enteric coating material and a plasticizer are dissolved in a suitable solvent to obtain enteric-coated microgranules. Also, a control not to comprise a stabilizer for a stability test of IY-81149-comprising enteric-coated microgranules, is prepared in the same manner as the above described method

Example 1

IY-81149	10.0 mg
Magnesium hydroxide	3.2 mg
Microcrystalline cellulose	126.8 mg
Hydroxypropylmethyl cellulose 2910	7.5 mg
Polyethylene glycol 6000	1.5 mg
Hydroxypropylmethyl cellulose phthalate	40.0 mg
cetanol	4.0 mg
Myvacet TM	4.0 mg
Purified water	q.s.
Ethanol	q.s.
Acetone	q.s.

IY-81149 are mixed with magnesium hydroxide and microcrystalline cellulose. The obtained mixture is granulated by a fluidized-bed granulator using a solution in which

hydroxypropylmethylcellulose 2910 and polyethylene glycol 6000 are dissolved in the mixed solvent of purified water and ethanol. The obtained microgranules are secondly enteric-coated by the fluidized-bed granulator using another solution in which hydroxypropylmethylcellulose phthalate, cetanol and Myvacet™ are dissolved in the mixed solvent of ethanol and acetone, to prepare an enteric-coated microgranules.

Example 2

IY-81149	10.0 mg
Magnesium hydroxide	3.2 mg
Microcrystalline cellulose	126.8 mg
Hydroxypropylmethyl cellulose 2910	7.5 mg
Polyethylene glycol 6000	1.5 mg
Kollicoat™ MAE30DP(as a solid)	36.0 mg
Propylene glycol	6.0 mg
Purified water	q.s.
Ethanol	q.s.

IY-81149 are mixed with magnesium hydroxide and microcrystalline cellulose. The obtained mixture is granulated by a fluidized-bed granulator using a solution in which hydroxypropylmethylcellulose 2910 and polyethylene glycol 6000 are dissolved in the mixed solvent of purified water and ethanol. The obtained microgranules are secondly enteric-coated by the fluidized-bed granulator using another solution which is prepared by mixing the purified water and propylene glycol, and then mixing with Kollicoat™ MAE30DP, to prepare an enteric-coated microgranules.

Example 3

IY-81149	10.0 mg
Sodium phosphate(dibasic)	7.8 mg
Microcrystalline cellulose	122.2 mg
Hydroxypropyl cellulose	9.0 mg
Polyethylene glycol 6000	2.0 mg
Polyvinylacetate phthalate	38 mg
Diethyl phthalate	6.0 mg
Ethanol	q.s.
Methylene chloride	q.s.

IY-81149 are mixed with sodium phosphate(dibasic) and microcrystalline cellulose. The obtained mixture is granulated by a fluidized-bed granulator using a solution in which hydroxypropylcellulose and polyethylene glycol 6000 are dissolved in ethanol. The obtained microgranules are secondly enteric-coated by the fluidized-bed granulator using another solution in which polyvinylacetate phthalate and diethyl phthalate are dissolved in methylene chloride, to prepare an enteric-coated microgranules.

Example 4

IY-81149	10 0 mg
Sodium phosphate(dibasic)	7.8 mg
Microcrystalline cellulose	122 2 mg
Hydroxyethyl cellulose	9.0 mg
Triacetin	2 0 mg
Hydroxypropylmethylcellulose phthalate	40.0 mg
Cetanol	6.0 mg
Ethanol	q s
Acetone	q.s.
Ethyl acetate	q.s.

IY-81149 are mixed with sodium phosphate(dibasic) and microcrystalline cellulose. The obtained mixture is granulated by a fluidized-bed granulator using a solution in which hydroxyethylcellulose and triacetin are dissolved in ethanol. The obtained microgranules are secondly enteric-coated by the fluidized-bed granulator using another solution in which hydroxypropylmethylcellulose phthalate and cetanol are dissolved in the mixed solvent of acetone and ethyl acetate, to prepare an enteric-coated microgranules.

Example 5

IY-81149	10.0 mg
sodium bicarbonate	4 6 mg
Microcrystalline cellulose	125 4 mg
Sodium alginate	7 5 mg
Triethyl citrate	1.5 mg
Cellulose acetate phthalate	32.0 mg
Dimethicone	3.0 mg
Diethyl phthalate	9.0 mg
Purified water	q.s.

Acetone	q s.
Methylene chloride	q.s.

IY-81149 are mixed with sodium alginate and microcrystalline cellulose. The obtained mixture is granulated by a granulator using a solution in which sodium alginate and triethyl citrate are dissolved in purified water. The obtained microgranules are secondly enteric-coated by the fluidized-bed granulator using another solution cellulose acetate phthalate, dimethicone, diethyl phthalate are dissolved in the mixed solvent of acetone and methylene chloride, to prepare an enteric-coated microgranules.

Example 6

IY-81149	10 0 mg
Sodium bicarbonate	4 6 mg
Microcrystalline cellulose	125 4 mg
Hydroxypropylmethyl cellulose 2910	7 5 mg
Polyethylene glycol 6000	1 5 mg
Cellulose acetate phthalate	32.0 mg
Dimethicone	3.0 mg
Diethyl phthalate	9.0 mg
Purified water	q.s
Ethanol	q s
Acetone	q.s
Methylene chloride	q s

IY-81149 are mixed with sodium bicarbonate and microcrystalline cellulose. The obtained mixture is granulated by a fluidized-bed granulator using a solution in which hydroxypropylmethyl cellulose 2910 and polyethylene glycol 6000 are dissolved in the mixed solvent of purified water and ethanol. And the obtained microgranules are secondly enteric-coated by the fluidized-bed granulator using another solution in which cellulose acetate phthalate, dimethicone and diethyl phthalate are dissolved in the mixed solvent of acetone and methylene chloride, to prepare an enteric-coated microgranules.

Example 7

IY-81149	10.0 mg
Sodium carbonate	5.8 mg

Microcrystalline cellulose	124.2 mg
Hydroxypropyl cellulose	9.0 mg
Polyethylene glycol 4000	2.0 mg
Kollicoat™ MAE30DP(as a solid)	36.0 mg
Propylene glycol	6.0 mg
Purified water	q.s.
Ethanol	q.s.

IY-81149 are mixed with sodium carbonate and microcrystalline cellulose. The obtained mixture is granulated by a fluidized-bed granulator using a solution in which hydroxypropylcellulose and polyethylene glycol 4000 are dissolved in ethanol. The obtained microgranules are secondly enteric-coated by the fluidized-bed granulator using another solution which is prepared by mixing the purified water and propylene glycol, and then mixing with Kollicoat™ MAE30DP, to prepare an enteric-coated microgranules.

Example 8

IY-81149	10.0 mg
Sodium carbonate	5.8 mg
Microcrystalline cellulose	124.2 mg
Hydroxypropyl cellulose	9.0 mg
Polyethylene glycol 4000	2.0 mg
Polyvinylacetate phthalate	38.0 mg
Diethyl phthalate	8.0 mg
Ethanol	q.s.
Methylene chloride	q.s.

IY-81149 are mixed with sodium carbonate and microcrystalline cellulose. The obtained mixture is granulated by a fluidized-bed granulator using a solution in which hydroxypropyl cellulose and polyethylene glycol 4000 are dissolved in ethanol. The obtained microgranules are secondly enteric-coated by the fluidized-bed granulator using another solution in which polyvinylacetate phthalate and diethyl phthalate are dissolved in methylene chloride, to prepare an enteric-coated microgranules.

Example 9

IY-81149	10.0 mg
Arginine	9.6 mg
Microcrystalline cellulose	120.4 mg
Hydroxyethyl cellulose	9.0 mg
Triethyl citrate	2.0 mg
Hydroxypropylmethylcellulose acetate succinate	40.0 mg
Diethyl phthalate	8.0 mg
Ethanol	q.s.
Acetone	q.s.
Ethyl acetate	q.s.

IY-81149 are mixed with arginine and microcrystalline cellulose. The obtained mixture is granulated by CF-Granulator using a solution in which hydroxyethyl cellulose and triethyl citrate are dissolved in ethanol and obtained the microgranules are secondly enteric-coated by the fluidized-bed granulator using another solution in which hydroxypropylmethylcellulose acetate succinate and diethyl phthalate are dissolved in mixed solvent of acetone and ethyl acetate, to prepare an enteric-coated microgranules.

Example 10

IY-81149	10.0 mg
Arginine	9.6 mg
Microcrystalline cellulose	120.4 mg
Sodium alginate	7.5 mg
Triethyl citrate	1.5 mg
Hydroxypropylmethylcellulose acetate succinate	40.0 mg
Diethyl phthalate	8.0 mg
Purified water	q.s.
Acetone	q.s.
Ethyl acetate	q.s.

IY-81149 are mixed with arginine and microcrystalline cellulose. The obtained mixture is granulated by a fluidized-bed granulator using a solution in which sodium alginate and triethyl citrate are dissolved in purified water. The obtained microgranules are secondly enteric-coated by the fluidized-bed granulator using another solution in which hydroxypropylmethylcellulose

acetate succinate and diethyl phthalate are dissolved in mixed solvent of acetone and ethyl acetate, to prepare an enteric-coated microgranules

Comparative Example 1

IY-81149	10.0 mg
Microcrystalline cellulose	130.0 mg
Hydroxypropylmethyl cellulose 2910	7.5 mg
Polyethylene glycol 6000	1.5 mg
Hydroxypropylmethylcellulose phthalate	40.0 mg
Cetanol	4.0 mg
Myvacet™	4.0 mg
Purified water	q.s.
Ethanol	q.s.
Acetone	q.s.

IY-81149 are mixed with microcrystalline cellulose without any stabilizer. The obtained mixture is granulated by a fluidized-bed granulator using a solution in which hydroxypropylmethyl cellulose 2910 and polyethylene glycol 6000 are dissolved in the mixed solvent of purified water and ethanol. The obtained microgranules are secondly enteric-coated by the fluidized-bed granulator using another solution in which hydroxypropylmethylcellulose phthalate, cetanol and Myvacet™ are dissolved in a mixed solvent of ethanol and acetone, to prepare an enteric-coated microgranules.

Test Example 1

Stability of the active ingredient depending on the stabilizer

In order to determine the stabilizing effects of organic or inorganic alkali compounds, the active ingredient of the present invention, IY-81149, and omeprazole, which is one of most well known benzimidazole derivatives, were mixed, respectively with the alkali compound in a molar ratio of 1:1, and then stored for 15 days under an accelerative condition (40°C, relative humidity of 75%). Then, the content of the active ingredient that was not decomposed was analyzed by using a liquid chromatography. The sample containing only the active ingredient without a stabilizer was used as a control. The analyzing conditions were represented in the following, and the results are shown in Table 1.

< Conditions for Liquid Chromatography >

- Column μ -Bondapack C18 (3.9 X 300mm) or the equivalent
- Mobile Phase. phosphate buffer/acetonitrile=6/4, v/v (pH8.3)
- Detector: Absorption photometer in ultraviolet part (wavelength: 237nm)
- Flow Rate: 1.0ml/min
- Injection Amount. 20 μ l

Table 1

Stability of the active ingredient depending on the stabilizer

Stabilizer	Mole Ratio	Water-Solubility (g/ml)	Content of the Active Ingredient (%) (IY-81149)		Content of the Active Ingredient (%) (Omeprazole)	
			Initial	After 15days	Initial	After 15days
not used	-	-	100.1	12.6	99.3	26.7
Mg(OH) ₂	1:1	1/80,000	99.8	93.5	100.2	86.1
Na ₂ HPO ₄	1:1	1/8	99.2	82.1	99.8	94.0
K ₂ HPO ₄	1:1	1/0.67	100.0	74.2	99.4	70.7
NaHCO ₃	1:1	1/10	98.9	78.0	99.7	87.5
Na ₂ CO ₃	1:1	1/3.5	99.4	79.9	100.1	75.3
K ₂ CO ₃	1:1	1/1	100.5	63.4	100.0	63.9
KHCO ₃	1:1	1/2.8	100.3	65.3	99.9	59.4
Al(OH) ₃	1:1	1/10,000	99.6	50.7	99.6	67.6
Arginine	1:1	1/6.67	99.2	75.5	99.1	76.0
Histidine	1:1	1/23.9	100.6	66.2	99.7	67.1
Lysine	1:1	1/less than 1	100.6	58.8	99.2	60.3

The results of the above Table 1 provide very important information which can be referred to in selecting the alkali compounds as a stabilizer for the active ingredient of the present invention. That is, the data show that the tested stabilizers show stabilizing effects with respect to the active ingredient of the present invention in the order of $\text{Mg}(\text{OH})_2 > \text{Na}_2\text{HPO}_4 > \text{Na}_2\text{CO}_3 > \text{NaHCO}_3 > \text{arginine} > \text{K}_2\text{HPO}_4 > \text{histidine} > \text{KHCO}_3 > \text{K}_2\text{CO}_3 > \text{lysine} > \text{Al}(\text{OH})_3$ when compared with the control group. On the other hand, in a case of the known omeprazole, the tested stabilizers show stabilizing effects in the order of $\text{Na}_2\text{HPO}_4 > \text{NaHCO}_3 > \text{Mg}(\text{OH})_2 > \text{arginine} > \text{Na}_2\text{CO}_3 > \text{K}_2\text{HPO}_4 > \text{Al}(\text{OH})_3 > \text{histidine} > \text{K}_2\text{CO}_3 > \text{lysine} > \text{KHCO}_3$. Therefore, such results suggest that the same alkali compound may exhibit a different stabilizing effect depending on the active ingredient to be stabilized.

Further, the results represented in Table 1 suggest that the water-solubility (i.e., hygroscopicity) and alkalizing ability of the stabilizers have some close relationship with the stabilizing ability thereof. Therefore, it can be seen that one of the essential aspects which should be considered when a stabilizer for a certain compound is selected, is the water-solubility of the stabilizer.

Test Example 2

Determination of suitable amount of the stabilizer

After the stabilizer is selected based on the results of Table 1, it is necessary to measure the stabilizing effects according to the amount of the stabilizer. That is, a suitable amount to be used should be determined. Therefore, in order to determine a suitable amount of the stabilizer, the present inventors mixed IY-81149 with the respective stabilizers in molar ratios of 1:0.2, 1:0.5, 1:1.0, 1:2.0, 1:5.0, 1:7.0, respectively, and then stored the mixtures for 15 days under an accelerative condition (40°C, relative humidity of 75%). Then, the content of IY-81149 was analyzed in the same manner as Test Example 1. The results are shown in the following Table 2.

Table 2

Stability of the active ingredient depending on the amount of the stabilizer

Stabilizer	Content of IY-81149(%) after 15days under the accelerative condition					
	Mole ratio of 1.0.2	Mole ratio of 1.0.5	Mole ratio of 1.1	Mole ratio of 1.2	Mole ratio of 1.5	Mole ratio of 1.7
Mg(OH) ₂	65.7	87.2	93.5	97.0	93.3	90.0
Na ₂ HPO ₄	56.0	76.8	82.1	88.4	80.2	73.3
K ₂ HPO ₄	78.4	67.4	74.2	73.5	64.7	52.6
NaHCO ₃	58.5	72.1	78.0	80.8	77.6	72.5
Na ₂ CO ₃	51.2	68.0	79.9	84.2	70.0	66.2
K ₂ CO ₃	37.9	56.7	63.4	64.0	54.5	47.1
KHCO ₃	40.8	58.5	65.3	68.4	62.7	53.3
Al(OH) ₃	27.6	38.3	50.7	53.1	53.5	52.9
Arginine	51.0	66.9	75.5	77.3	69.4	68.4
Histidine	38.2	55.4	66.2	68.5	67.1	61.5
Lysine	34.6	51.7	58.8	47.1	42.7	43.8

From the results of Table 2, it can be seen that the suitable amount of the stabilizer based on its water-solubility ranges in a molar amount of 0.2 to 7.0 times with respect to IY-81149, and specifically in the most cases, the stabilizing effect is much better when the molar ratios are 1:1 to 1.7. When the stabilizer was in a molar amount less than 0.2 times, the desired stabilizing effect cannot be obtained and when the stabilizer was in a molar amount more than 7.0 times, the increased hygroscopicity of the stabilizer may act as an obstacle for the formulation.

Test Example 3

Distribution of particle sizes of the microgranules comprising IY-81149

Distribution of particle sizes was measured for the microgranules according to Examples 1 to 10 and Comparative Example 1. Measurement of distribution of particle sizes was conducted by sieving 20.0g of the microgranules through sieves of Mesh No 12 (1410µm), No 20

(840 μ m) and No 42 (350 μ m), which are overlapped upon a container with a cover, with shaking the container horizontally for 3 minutes while sometimes slightly hitting the container. Then, the weights of remainders on each sieve and the container were measured. The inner diameter of the sieves used in this test was 75 mm. The results are shown in the following Table 3.

Table 3

Distribution of particle sizes of the microgranules comprising IY-81149 (%)

Particle size	Comparative Example 1	Example No									
		1	2	3	4	5	6	7	8	9	10
1410 μ m~840 μ m	2.1	3.5	1.6	4.1	3.0	2.7	1.3	2.4	4.5	1.7	2.3
840 μ m~350 μ m	86.7	88.0	89.0	86.8	86.3	87.2	89.8	90.9	87.4	88.3	88.5
less than 350 μ m	11.2	8.5	9.4	9.1	10.7	10.1	8.9	6.7	8.1	10.0	9.2

As shown in Table 3, all the microgranules passed Mesh No.12 (1410 μ m), and most microgranules are distributed between Mesh No. 20 (840 μ m) and Mesh No. 42 (350 μ m). Therefore, the distribution of particle sizes of the microgranules according to the present invention is regular.

Test Example 4

Stability Test for the microgranules comprising IY-81149

Stability tests were carried out for the microgranules according to Examples 1 to 10 and Comparative Example 1. The stability test was conducted by storing the microgranules for 3 months under an accelerative condition (40 $^{\circ}$ C, relative humidity of 75%) and analyzing the content of IY-81149 in the same manner as Test Example 1. The results are shown in the following Table 4.

Table 4

Stability of the microgranules comprising IY-81149

		Comparative Example 1	Example No									
			1	2	3	4	5	6	7	8	9	10
Content (%) of IY- 81149	Initial	99.8	100 5	100 .1	99. 5	99. 2	99 7	100 1	99 9	99. 5	99. 3	100 2
	After 3 months	60.1	99 1	96. 5	95. 8	94. 0	88. 1	88 8	88 5	83 1	86. 4	83 0

As shown in Table 4, the microgranules comprising IY-81149 of Examples 1 to 10 maintained an excellent stability even after 3-month accelerative period when compared with the microgranules of Comparative Example 1 which do not contain a stabilizer. From this test, it is proved that stability of the microgranules comprising IY-81149 according to the present invention is maintained during the storage period.

Examples 11 ~ 14

Preparation of granules comprising the microgranules comprising IY-81149

Microgranules according to Examples 1 to 4, which are particularly well stabilized for IY-81149, are mixed with lubricant, sweetener and flavor, and the obtained mixture is filled into an aluminum foil pack, to obtain granule.

Example 11

Enteric-coated microgranules prepared in Example 1(10.0mg as IY-81149)	197.0 mg
Magnesium stearate	5 0 mg
Aspartame	2 0 mg
Orange flavoring powder	3 0 mg

Enteric-coated microgranules prepared in Example 1 are mixed with magnesium stearate as a lubricant, aspartame as a sweetener, and orange flavoring powder as a flavor, and the obtained mixture is filled into an aluminum foil pack, to obtain granule.

Example 12

Enteric-coated microgranules prepared in 2(10.0mg as IY-81149)	Example	191.0 mg
Magnesium stearate		5.0 mg
Stevioside		2.0 mg
Orange flavoring powder		3.0 mg

Enteric-coated microgranules prepared in Example 12 are mixed with magnesium stearate as a lubricant, stevioside as a sweetener, and orange flavoring powder as a flavor, and the obtained mixture is filled into an aluminum foil package to obtain granule.

Example 13

Enteric-coated microgranules prepared in 3(10.0mg as IY-81149)	Example	197.0 mg
Magnesium stearate		5.0 mg
Aspartame		2.0 mg
Orange flavoring powder		3.0 mg

Enteric-coated microgranules prepared in Example 13 are mixed with magnesium stearate as a lubricant, aspartame as a sweetener, and orange flavoring powder as a flavor, and the obtained mixture is filled into an aluminum foil package to obtain granule.

Example 14

Enteric-coated microgranules prepared in 4(10.0mg as IY-81149)	Example	197.0 mg
Magnesium stearate		5.0 mg
Aspartame		2.0 mg
Orange flavoring powder		3.0 mg

Enteric-coated microgranules prepared in Example 14 are mixed with magnesium stearate as a lubricant, aspartame as a sweetener, and orange flavoring powder as a flavor, and the obtained mixture is filled into an aluminum foil package to obtain granule.

Comparative Example 2

Enteric-coated microgranules prepared in 1970 mg
Comparative Example 1(100mg as IY-81149)

Magnesium stearate 50 mg
Aspartame 20 mg
Orange flavoring powder 3.0 mg

Enteric-coated microgranules prepared in Comparative Example 1 are mixed with magnesium stearate as a lubricant, aspartame as a sweetener, and orange flavoring powder as a flavor, and the obtained mixture is filled into an aluminum foil pack, to obtain granule

Test Example 5

Stability Test for the granules comprising the microgranules comprising IY-81149

Stability tests were carried out for the granules according to Examples 11 to 14 and Comparative Example 2 in the same manner as Test Example 4. The results are shown in the following Table 5

Table 5

Stability of the granules using microgranules comprising IY-81149

		Comparative Example 2	Example No			
			11	12	13	14
Content (%) of IY- 81149	Initial	99.9	100.3	99.8	100.1	99.5
	After 3 months	66.4	98.4	95.7	94.3	94.7

As shown in Table 5, the granules comprising IY-81149 according to Examples 11 to 14, respectively, maintained an excellent stability even after 3-month accelerative period compared with the granules of Comparative Example 2 which do not contain a stabilizer. From this test, it is proved that stability of granules comprising IY-81149 according to the present invention is maintained during the storage period.

Examples 15 ~ 18

Preparation of a capsule using the microgranules comprising IY-81149

Microgranules according to Examples 1 to 4, which are particularly well stabilized for IY-81149, are mixed with a lubricant, a sweetener and a flavor, and the obtained mixture is filled into a capsule shell, to obtain a capsule.

Example 15

Enteric-coated microgranules prepared in Example 1(10 0mg as IY-81149)	197.0 mg
Lactose	68 0 mg
Magnesium stearate	5 0 mg
Hard capsule shell	62.0 mg

Enteric-coated microgranules prepared in Example 1 are mixed with lactose as an excipient and magnesium stearate as a lubricant, and the obtained mixture is filled into a hard capsule shell, to obtain a capsule.

Example 16

Enteric-coated microgranules prepared in Example 2(10 0mg as IY-81149)	191 0 mg
Mannitol	74.0 mg
Magnesium stearate	5.0 mg
Hard capsule shell	62 0 mg

Enteric-coated microgranules prepared in Example 2 are mixed with mannitol as an excipient and magnesium stearate as a lubricant, and the obtained mixture is filled into a hard capsule shell, to obtain a capsule.

Example 17

Enteric-coated microgranules prepared in Example 3(10 0mg as IY-81149)	197 0 mg
Microcrystalline cellulose	68.0 mg

Magnesium stearate	5.0 mg
Hard capsule shell	62.0 mg

Enteric-coated microgranules prepared in Example 3 are mixed with microcrystalline cellulose as an excipient and magnesium stearate as a lubricant, and the obtained mixture is filled into a hard capsule shell, to obtain capsule.

Example 18

Enteric-coated microgranules prepared in Example 4(10.0mg as IY-81149)	197.0 mg
Granules of starch and lactose	68.0 mg
Magnesium stearate	5.0 mg
Hard capsule shell	62.0 mg

Enteric-coated microgranules prepared in Example 4 are mixed with granules of starch and lactose as an excipient and magnesium stearate as a lubricant, and the obtained mixture is filled into a hard capsule shell, to obtain capsule

Comparative Example 3

Enteric-coated microgranules prepared in Comparative Example 1(10.0mg as IY-81149)	197.0 mg
Lactose	68.0 mg
Magnesium stearate	5.0 mg
Hard capsule shell	62.0 mg

Enteric-coated microgranules prepared in Comparative Example 1 are mixed with lactose as an excipient and magnesium stearate as a lubricant, and the obtained mixture is filled into a hard capsule shell, to obtain capsule.

Test Example 6

Stability Test for capsules comprising the microgranules comprising IY-81149

Stability tests were carried out for the capsules according to Examples 15 to 18 and Comparative Example 3 in the same manner as Test Example 4. The results are shown in the

following Table 6

Table 6

Stability of the capsules comprising microgranules comprising IY-81149

		Comparative Example 3	Example No			
			15	16	17	18
Content (%) of IY- 81149	Initial	98.9	99.5	100.3	99.2	99.8
	After 3 months	59.2	97.1	96.5	93.6	95.2

As shown in Table 6, the capsules comprising IY-81149 according to Examples 15 to 18, respectively, maintained an excellent stability even after 3-month accelerative period when compared with the capsules of Comparative Example 3 which do not contain a stabilizer. From this test, it is proved that stability of capsules comprising IY-81149 according to the present invention is maintained during the storage period.

Examples 19 ~ 22

Preparation of a tablet comprising the microgranules comprising IY-81149

Microgranules according to Examples 1 to 4, which are particularly well stabilized for IY-81149, are mixed with excipient, lubricant and binder, and the obtained mixture is tableted to obtain a tablet.

Example 19

Enteric-coated microgranules prepared in Example 1 (10.0 mg as IY-81149)	197.0 mg
Microcrystalline cellulose	118.0 mg
Low-substituted hydroxypropylcellulose	4.0 mg
Magnesium stearate	5.0 mg

Enteric-coated microgranules prepared in Example 1 are mixed with microcrystalline cellulose as an excipient, low-substituted hydroxypropylcellulose as a binder and magnesium stearate as a lubricant, and the obtained mixture is tableted to obtain a tablet

Example 20

Enteric-coated microgranules prepared in Example 2 (10.0mg as IY-81149)	191.0 mg
Granules of starch and lactose	124.0 mg
Low-substituted hydroxypropylcellulose	4.0 mg
Magnesium stearate	5.0 mg

Enteric-coated microgranules prepared in Example 2 are mixed with granules of starch and lactose as an excipient, low-substituted hydroxypropylcellulose as a binder and magnesium stearate as a lubricant, and the obtained mixture is tableted to obtain a tablet.

Example 21

Enteric-coated microgranules prepared in Example 3 (10.0mg as IY-81149)	197.0 mg
Microcrystalline cellulose	118.0 mg
Povidone	4.0 mg
Magnesium stearate	5.0 mg

Enteric-coated microgranules prepared in Example 3 are mixed with microcrystalline cellulose as an excipient, povidone as a binder and magnesium stearate as a lubricant, and the obtained mixture is tableted to obtain a tablet.

Example 22

Enteric-coated microgranules prepared in Example 4 (10.0mg as IY-81149)	197.0 mg
Lactose	118.0 mg
Low-substituted hydroxypropylcellulose	4.0 mg
Magnesium stearate	5.0 mg

Enteric-coated microgranules prepared in Example 4 are mixed with lactose as an excipient, low-

substituted hydroxypropylcellulose as a binder and magnesium stearate as a lubricant, and the obtained mixture is tableted to obtain a tablet.

Comparative Example 4

Enteric-coated microgranules prepared in Example 1 (10.0mg as IY-81149)	197.0 mg
Microcrystalline cellulose	118.0 mg
Low-substituted hydroxypropylcellulose	4.0 mg
Magnesium stearate	5.0 mg

Enteric-coated microgranules prepared in Comparative Example 1 are mixed with microcrystalline cellulose as an excipient, low-substituted hydroxypropylcellulose as a binder and magnesium stearate as a lubricant, and the obtained mixture is tableted to obtain a tablet.

Test Example 7

Stability Test for tablets comprising the microgranules comprising IY-81149

Stability tests were carried out for the tablets according to Examples 19 to 22 and Comparative Example 4 in the same manner as Test Example 4. The results are shown in the following Table 7

Table 7

Stability of the tablets comprising microgranules comprising IY-81149

		Comparative Example 4	Example No.			
			19	20	21	22
Content (%) of IY-81149	Initial	99.2	99.7	100.1	99.6	99.7
	After 3 months	63.5	97.9	95.7	93.4	95.2

As shown in Table 7, the tablets comprising IY-81149 according to Examples 19 to 22,

respectively, maintained an excellent stability even after 3-month accelerative period when compared with the tablets of Comparative Example 4 which do not contain a stabilizer. From this test, it is proved that stability of tablets comprising IY-81149 according to the present invention is maintained during the storage period.

Test Example 8

Acid resistance Test for the microgranules comprising IY-81149

IY-81149, the active ingredient, is highly unstable under acidic conditions like other benzimidazole derivatives. Therefore, stability of a microgranules for oral administration of IY-81149 should be maintained under strong acidic condition in stomach as well as during the storage period, and thus, IY-81149 should be reached to the upper part of the small intestine that is an absorbing site without degradation or loss of pharmacological effects. Therefore, the inventors tested acid resistance of the microgranules according to Examples 1 to 10 and Comparative Example 1.

Acid resistance test was carried out according to the first method of dissolution test set forth in General Tests of Korean Pharmacopoeia (Rotating Basket Method, 37°C, 50rpm). That is, the microgranules of Examples 1 to 10 (comprising 100mg as IY-81149) were put in the sample baskets, respectively, and the baskets were put into a rotating shaft and surrounded by Mesh No 200 to prevent the microgranules from going out. The baskets were then added to 900 ml of artificial gastric fluids (pH 1.2), and tested by Rotating Basket Method for 2 hours. The microgranules remaining in the baskets were collected respectively, and the contents of the active ingredient in the microgranules were analyzed in the same manner as Test Example 1. Further, the contents of the active ingredient remaining in the microgranules stored for 3 months under an accelerative condition (40°C, relative humidity of 75%), were analyzed in the same manner as Test Example 1. The results are shown in the following Table 8.

Table 8

Acid resistance of the microgranules according to Examples 1-10 and Comparative Example 1

		Comparative Example 1	Example No									
			1	2	3	4	5	6	7	8	9	10
Content (%) of IY- 81149	Initial	99.8	98.9	99.2	99.9	98.1	101.1	99.5	99.6	100.2	98.9	99.3
	After 3 months	67.3	98.1	95.6	92.4	90.7	84.8	85.2	82.1	83.0	87.0	86.1

As shown in Table 8, all the microgranules of Examples 1 to 10 are suitable for acid resistance test just after the preparation. All the microgranules of Examples 1 to 10 which were stored for 3 months also exhibited much more stability compared with the microgranules of Comparative Example 1.

Therefore, the enteric-coated microgranules comprising IY-81149 according to the present invention, whose stability is maintained under strong gastric acid conditions at the time of oral administration and during the storage period, are much more effective for the treatments of gastric ulcer and duodenal ulcer.

Test Example 9

Acid Resistance Test for the microgranules comprising IY-81149

Acid Resistance Test was carried out for the granules according to Examples 11 to 14 and Comparative Example 2 in the same manner as Test Example 8. The results are shown in the following Table 9.

Table 9

Acid resistance of the granules according to Examples 11-14 and Comparative Example 2

		Comparative Example 2	Example No			
			11	12	13	14
Content (%) of IY- 81149	Initial	99.1	99.8	99.6	98.8	99.5
	After 3 months	62.9	98.1	96.6	92.8	91.2

As shown in Table 9, all the granules of Examples 11 to 14 are suitable for acid resistance test just after the preparation. All the granules of Examples 11 to 14 which were stored for 3 months also exhibited much more stability compared with the granules of Comparative Example 2.

Therefore, the granules comprising the enteric-coated microgranules comprising IY-81149 according to the present invention, whose stability is maintained under strong gastric acid conditions at the time of oral administration and during the storage period, are much more effective for the treatments of gastric ulcer and duodenal ulcer.

Test Example 10

Acid Resistance Test for the microgranules comprising IY-81149

Acid Resistance Test was carried out for the capsules according to Examples 15 to 18 and Comparative Example 3 in the same manner as Test Example 8. The results are shown in the following Table 10.

Table 10

Acid resistance of the capsules according to Examples 15-18 and Comparative Example 3

		Comparative Example 3	Example No.			
			15	16	17	18
Content (%) of IY- 81149	Initial	98.6	99.2	99.4	99.0	98.8

	After 3 month s	65.2	97.3	94.7	90.9	91.7
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As shown in Table 10, all the capsules of Examples 15 to 18 are suitable for acid resistance test just after the preparation. All the capsules of Examples 15 to 18 which were stored for 3 months also exhibited much more stability compared with the capsules of Comparative Example 3.

Therefore, the capsules comprising the enteric-coated microgranules comprising IY-81149 according to the present invention, whose stability is maintained under strong gastric acid conditions at the time of oral administration and during the storage period, are much more effective for the treatments of gastric ulcer and duodenal ulcer.

Test Example 11

Acid Resistance Test for the tablets comprising IY-81149

Acid Resistance Test was carried out for the tablets according to Examples 19 to 22 and Comparative Example 4 in the same manner as Test Example 8. The results are shown in the following Table 11.

Table 11

Acid resistance of the granules according to Examples 19-22 and Comparative Example 4

		Comparative Example 4	Example No			
			19	20	21	22
Content (%) of IY- 81149	Initial	98.1	96.9	99.1	97.5	98.1
	After 3 month s	60.7	95.7	95.5	93.7	92.4

As shown in Table 11, all the tablets of Examples 19 to 22 are suitable for acid resistance

test just after the preparation All the tablets of Examples 19 to 22 which were stored for 3 months also exhibited much more stability compared with the granules of Comparative Example 4

Therefore, the tablets comprising the enteric-coated microgranules comprising IY-81149 according to the present invention, whose stability is maintained under strong gastric acid conditions at the time of oral administration and during the storage period, are much more effective for the treatments of gastric ulcer and duodenal ulcer

WHAT IS CLAIMED IS:

- 1 Stabilized enteric-coated microgranules having the particle size of 350 to 840 μm prepared by mixing 2-[(4-methoxy-3-methyl)-2-pyridinyl]methylsulfinyl-5-(1H-pyrrol-1-yl)-1H-benzimidazole as an active ingredient, alkali compound as a stabilizer, and a pharmaceutically acceptable additive, firstly coating the mixture with a film forming material to obtain microgranules, and secondly coating the microgranules with an enteric coating material.
- 2 The stabilized enteric-coated microgranules of claim 1 wherein the alkali compound is selected from the group consisting of magnesium hydroxide, sodium phosphate(dibasic), potassium phosphate(dibasic), sodium bicarbonate, sodium carbonate, potassium carbonate, potassium hydrogen carbonate, aluminum hydroxide, arginine, histidine and lysine, and the combination thereof.
- 3 The stabilized enteric-coated microgranules of claim 1 wherein the alkali compound is used in a molar amount of 0.2 to 7.0 times with respect to 2-[(4-methoxy-3-methyl)-2-pyridinyl]methylsulfinyl-5-(1H-pyrrol-1-yl)-1H-benzimidazole.
- 4 The stabilized enteric-coated microgranules of claim 3 wherein the alkali compound is used in a molar amount of 0.5 to 6.5 times with respect to 2-[(4-methoxy-3-methyl)-2-pyridinyl]methylsulfinyl-5-(1H-pyrrol-1-yl)-1H-benzimidazole.
- 5 The stabilized enteric-coated microgranules of claim 1 wherein the film forming material used in the first coating is selected from the group consisting of hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, sodium alginate, and the combination thereof.
- 6 The stabilized enteric-coated microgranules of claim 5 wherein the film forming material is used in an amount of 0.5 to 30% by weight with respect to the weight of the mixture comprising 2-[(4-methoxy-3-methyl)-2-pyridinyl]methylsulfinyl-5-(1H-pyrrol-1-yl)-1H-benzimidazole.

7 The stabilized enteric-coated microgranules of claim 6 wherein the film forming material is used in an amount of 1 to 20% by weight with respect to the weight of the mixture comprising 2-[(4-methoxy-3-methyl)-2-pyridinyl]methylsulfinyl-5-(1H-pyrrol-1-yl)-1H-benzimidazole

8 The stabilized enteric-coated microgranules of claim 1 wherein the enteric coating material used in the second coating is selected from the group consisting of hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, polyvinyl acetate phthalate, acrylate polymer(Eudragit™ or Kollicoat™), hydroxypropyl methylcellulose acetate succinate, and the combination thereof

9 The stabilized enteric-coated microgranules of claim 8 wherein the enteric coating material is used in an amount of 10 to 60%, by weight with respect to the total weight of the microgranule comprising 2-[(4-methoxy-3-methyl)-2-pyridinyl]methylsulfinyl-5-(1H-pyrrol-1-yl)-1H-benzimidazole.

10 The stabilized enteric-coated microgranules of claim 9 wherein the enteric coating material is used in an amount of 10 to 40% by weight with respect to the total weight of the microgranule comprising 2-[(4-methoxy-3-methyl)-2-pyridinyl]methylsulfinyl-5-(1H-pyrrol-1-yl)-1H-benzimidazole

11. The stabilized enteric-coated microgranules of claim 1 wherein the pharmaceutically acceptable additive include excipient, disintegrant, lubricant, binder, sweetener or flavor, or the combination thereof

12 Oral formulations comprising the stabilized enteric-coated microgranules according to any one of claims 1 to 11.