200200477-8
24 JAN 2002

TABLET FOR ORAL ADMINISTRATION COMPRISING 2-[(4-METHOXY-3-METHYL)-2-PYRIDINYL]METHYLSULFINYL-5-(1H-PYRROL-1-YL)-1H-BENZIMIDAZOLE

TECHNICAL FIELD

The present invention relates to a tablet comprising 2-[(4-methoxy-3-methyl)-2-pyridinyl]methylsulfinyl-5-(1H-pyrrol-1-yl)-1H-benzimidazole (hereinafter, referred to IY-81149). More specifically, the present invention relates to IY-81149 as an active ingredient which has potent inhibitory activity for gastric acid secretion by irreversibly inhibiting a proton pump that is related to the secretion of gastric acid. The object of the present invention is to provide stabilized tablet for oral administration comprising IY-81149.

BACKGROUND ART

The active ingredient, 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 are presently pending or granted in 27 countries including Korea, Japan, the United States, etc. The compound has an excellent antiulcerative effect by irreversibly inhibiting the proton pump, but is highly unstable under acidic conditions although it is stable under an alkaline environment. That is, IY-81149 is very stable under alkali conditions 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 tableted with an alkali compound as a stabilizer, coated by an film forming material first, and subsequently coated by an enteric coating material second, 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 enteric-coated tablet of optimally stabilized IY-81149 has been prepared.

DISCLOSURE OF THE INVENTION

The present invention provides a tablet for oral administration 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, tableting

the mixture to make a naked tablet, firstly coating the naked tablet with a film forming material, and secondly coating the tablet with an enteric coating material.

DETAILED DESCRIPTION OF THE INVENTION

The alkali compounds which can be used in a stabilized tablet for oral administration according to the present invention are selected from the group consisting of magnesium hydroxide, sodium phosphate(dibasic), potassium phosphate(dibasic), sodium bicarbonate, sodium carbonate, anhydrous, potassium carbonate, potassium hydrogen carbonate, aluminum hydroxide, arginine, lysine, and the combination thereof. These stabilizers contribute to the stability of IY-81149 by maintaining the ambient pH of 7 to 13. However, the extent of the contribution to the stability of each stabilizer is different from each other depending on its 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 compared with the other stabilizers (see, Test Examples 1 and 2).

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

The pharmaceutically acceptable additives used in the stabilized tablet for oral administration according to the present invention include conventional excipient, disintegrant, lubricant, binder, sweetener, flavor, etc.

The film forming material used in the first coating of the tablet according to the present invention 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 0.1 to 30%, more preferably, 2.0 to 6.0% by weight with respect to the naked tablet 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 pan coater or hi-coater.

The first coating is to prevent the second coating material from directly contacting with the naked tablet. Direct contact may result in degradation of IY-81149 and loss of the content.

The first coated tablet is then secondly coated with an enteric coating material to obtain an antiacidic enteric-coated tablet. 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(Eudragit™ or

Kollicoat™), hydroxypropyl methylcellulose acetate succinate, and combination thereof. The enteric coating material is used preferably in an amount of 0.1 to 40%, more preferably 5.0 to 20% by weight with respect to the naked tablet comprising IY-81149. The enteric coating material used in the second coating is used in the form of being dissolved in some amounts of 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 conventional pan coater or hi-coater.

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 tablet 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(Myvacet™), 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 10 to 30 % by weight with respect to the first or the second coating material.

When the tablet comprising IY-81149 according to the present invention is administrated 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 tablet 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

$Mg(OH)_2$, Na_2HPO_4, $NaHCO_3$, arginine, etc, which are particularly suitable for stabilizing the active ingredient of the present invention, IY-81149, are mixed with the active ingredient in a molar ratio of 1: 2, and microcrystalline cellulose as an excipient, and magnesium stearate as a lubricant are added to this mixture, and the mixture is tableted. An obtained naked tablet is firstly coated with a film forming material by using a conventional pan coater, and then secondly coated with an enteric coating material. Also, a control not to comprise a stabilizer for a stability test of IY-81149 comprising enteric-coated tablet, 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	135.3 mg
Magnesium stearate	1.5 mg
Hydroxypropylmethyl cellulose 2910	5.0 mg
Polyethylene glycol 6000	1.0 mg
Hydroxypropylmethyl cellulse phthalate	20.0 mg
Cetanol	2.0 mg
Myvacet™	2.0 mg
Purified water	q.s.
Ethanol	q.s.
Acetone	q.s.

IY-81149 is mixed with magnesium hydroxide, microcrystalline cellulose and magnesium stearate. The mixture is tableted, and the obtained tablet is firstly coated with a solution in which hydroxypropylmethylcellulose 2910 and polyethylene glycol 6000 are dissolved in the mixed solvent of purified water and ethanol, and secondly coated with a solution in which hydroxypropylmethylcellulose phthalate, cetanol and Myvacet™ are dissolved in the mixed solvent of ethanol and acetone to prepare a tablet.

Example 2

IY-81149	10.0 mg
Magnesium hydroxide	3.2 mg
Microcrystalline cellulose	135.3 mg
Magnesium stearate	1.5 mg
Hydroxypropylmethyl cellulose 2910	5.0 mg
Polyethylene glycol 6000	1.0 mg
Kollicoat™ MAE30DP	36mL (12.0 mg as a solid)
Propylene glycol	1.0 mg
Purified water	q.s.
Ethanol	q.s.

IY-81149 is mixed with magnesium hydroxide, microcrystalline cellulose and magnesium stearate. The mixture is tableted, and the obtained tablet is firstly coated with a solution in which hydroxypropylmethylcellulose 2910 and polyethylene glycol 6000 are dissolved in the mixed solvent of purified water and ethanol, and secondly coated with a solution which is prepared by mixing the purified water and propylene glycol, and then mixing with Kollicoat™ MAE30DP to prepare a tablet.

Example 3

IY-81149	10.0 mg
Sodium phosphate(dibasic)	7.8 mg
Microcrystalline cellulose	130.7 mg
Magnesium stearate	1.5 mg
Hydroxypropyl cellulose	6.0 mg
Polyethylene glycol 6000	1.0 mg
Polyvinylacetate phthalate	15 mg
Diethyl phthalate	5.0mg
Ethanol	q.s.
Methylene chloride	q.s.

IY-81149 are mixed with sodium phosphate(dibasic), microcrystalline cellulose and magnesium stearate. The mixture is tableted, and the obtained tablet is firstly coated with a solution in which hydroxypropylcellulose and polyethylene glycol 6000 are dissolved in ethanol, and secondly coated with a solution in which polyvinylacetate phthalate and diethyl phthalate are dissolved in methylene chloride to prepare a tablet.

Example 4

IY-81149	10.0 mg
Sodium phosphate(dibasic)	7.8 mg
Microcrystalline cellulose	130.7 mg
Magnesium stearate	1.5 mg
Hydroxyethyl cellulose	6.0 mg
Triacetin	1.0 mg
Hydroxypropylmethylcellulose phthalate	20.0 mg
Cetanol	3.0mg
Ethanol	q.s.
Acetone	q.s.
Ethyl acetate	q.s.

IY-81149 is mixed with sodium phosphate (dibasic), microcrystalline cellulose and magnesium stearate. The mixture is tableted, and the obtained tablet is firstly coated with a solution in which hydroxyethylcellulose and triacetin are dissolved in ethanol, and secondly coated with a solution in which hydroxypropylmethylcellulose phthalate and cetanol are dissolved in the mixed solvent of acetone and ethyl acetate to prepare a tablet.

Example 5

IY-81149	10.0 mg
Sodium bicarbonate	4.6 mg
Microcrystalline cellulose	133.9 mg
Magnesium stearate	1.5 mg
Sodium alginate	5.0 mg
Triethyl citrate	1.0 mg
Cellulose acetate phthalate	12.0 mg
Dimethicone	1.5 mg
Diethyl phthalate	4.5 mg
Purified water	q.s.
Acetone	q.s.
Methylene chloride	q.s.

IY-81149 is mixed with sodium bicarbonate, microcrystalline cellulose and magnesium stearate. The mixture is tableted, and the obtained tablet is firstly coated with a solution in which sodium alginate and triethyl citrate are dissolved in purified water, and secondly coated with a solution in which cellulose acetate phthalate, dimethicone, diethyl phthalate are dissolved in the mixed solvent of acetone and methylene chloride to prepare a tablet.

Example 6

IY-81149	10.0 mg
Sodium bicarbonate	4.6 mg
Microcrystalline cellulose	133.9 mg
Magnesium stearate	1.5 mg
Hydroxypropylmethyl cellulose 2910	5.0 mg
Polyethylene glycol 6000	1.0 mg
Cellulose acetate phthalate	12.0 mg
Dimethicone	1.5 mg
Diethyl phthalate	4.5 mg
Purified water	q.s.
Ethanol	q.s.
Acetone	q.s.
Methylene chloride	q.s.

IY-81149 is mixed with sodium bicarbonate, microcrystalline cellulose and magnesium stearate. The mixture is tableted, and the obtained tablet is firstly coated with a solution in which hydroxypropylmethyl cellulose 2910 and polyethylene glycol 6000 are dissolved in the mixed solvent of purified water and ethanol, and secondly coated with a solution in which cellulose acetate phthalate, dimethicone and diethyl phthalate are dissolved in the mixed solvent of acetone and methylene chloride to prepare a tablet.

Example 7

IY-81149	10.0 mg
Sodium carbonate, anhydrous	5.8 mg
Microcrystalline cellulose	132.7 mg
Magnesium stearate	1.5 mg
Hydroxypropyl cellulose	6.0 mg
Polyethylene glycol 4000	1.0 mg
Kollicoat™ MAE30DP	36mL (12.0 mg as a solid)
Propylene glycol	1.0 mg
Purified water	q.s.
Ethanol	q.s.

IY-81149 is mixed with sodium carbonate, anhydrous, microcrystalline cellulose and magnesium stearate. The mixture is tableted, and the obtained tablet is firstly coated with a solution in which hydroxypropylcellulose and polyethylene glycol 4000 are dissolved in ethanol, and secondly coated with a solution which is prepared by mixing the purified water and propylene glycol, and then mixing with Kollicoat™ MAE30DP to prepare a tablet.

Example 8

IY-81149	10.0 mg
Sodium carbonate, anhydrous	5.8 mg
Microcrystalline cellulose	132.7 mg
Magnesium stearate	1.5 mg
Hydroxypropyl cellulose	6.0 mg
Polyethylene glycol 4000	1.0 mg
Polyvinylacetate phthalate	15.0 mg
Diethyl phthalate	5.0 mg
Ethanol	q.s.
Methylene chloride	q.s.

IY-81149 is mixed with sodium carbonate, anhydrous, microcrystalline

cellulose and magnesium stearate. The mixture is tableted, and the obtained tablet is firstly coated with a solution in which hydroxypropyl cellulose and polyethylene glycol 4000 are dissolved in ethanol, and secondly coated with a solution in which polyvinylacetate phthalate and diethyl phthalate are dissolved in methylene chloride to prepare a tablet.

Example 9

IY-81149	10.0 mg
Arginine	9.6 mg
Microcrystalline cellulose	128.9 mg
Magnesium stearate	1.5 mg
Hydroxyethyl cellulose	6.0 mg
Triethyl citrate	1.0 mg
Hydroxypropylmethylcellulose acetate succinate	20.0 mg
Diethyl phthalate	6.0 mg
Ethanol	q.s.
Acetone	q.s.
Ethyl acetate	q.s.

IY-81149 is mixed with arginine, microcrystalline cellulose and magnesium stearate. The mixture is tableted, and the obtained tablet is firstly coated with a solution in which hydroxyethyl cellulose and triethyl citrate are dissolved in ethanol, and secondly coated with a solution in which hydroxypropylmethylcellulose acetate succinate and dithyl phthalate are dissolved in mixed solvent of acetone and ethyl acetate to prepare a tablet.

Example 10

IY-81149	10.0 mg
Arginine	9.6 mg
Microcrystalline cellulose	128.9 mg
Magnesium stearate	1.5 mg
Sodium alginate	5.0 mg
Triethyl citrate	1.0 mg
Hydroxypropylmethylcellulose acetate succinate	20.0 mg
Diethyl phthalate	6.0 mg
Purified water	q.s.
Acetone	q.s.
Ethyl acetate	q.s.

IY-81149 is mixed with arginine, microcrystalline cellulose and magnesium stearate. The mixture is tableted, and the obtained tablet is firstly coated with a solution in which sodium alginate and triethyl citrate are dissolved in purified water, and secondly coated with a solution in which hydroxypropylmethylcellulose acetate succinate and diethyl phthalate are dissolved in mixed solvent of acetone and ethyl acetate to prepare a tablet.

Comparative Example 1

IY-81149	10.0 mg
Microcrystalline cellulose	138.5 mg
Magnesium stearate	1.5 mg
Hydroxypropylmethyl cellulose 2910	5.0 mg
Polyethylene glycol 6000	1.0 mg
Hydroxypropylmethylcellulose phthalte	20.0 mg
Cetanol	2.0 mg
Myvacet™	2.0 mg
Purified water	q.s.
Ethanol	q.s.
Acetone	q.s.

IY-81149 is mixed with microcrystalline cellulose and magnesium

stearate without a stabilizer. The mixture is tableted, and the obtained tablet is firstly coated with a solution in which hydroxypropylmethyl cellulose 2910 and polyethylene glycol 6000 are dissolved in the mixed solvent of purified water and ethanol, and secondly coated with a solution in which hydroxypropylmethylcellulose phthalate, cetanol and Myvacet™ are dissolved in mixed solvent of ethanol and acetone to prepare a comparative tablet.

The prescriptions according to Examples 1 to 10 and Comparative Example 1 are summarized in Table 1.

Table 1

The prescriptions according to Examples 1 to 10 and Comparative Example 1(unit: mg)

	Comparative Example 1	Example 1	Example 2	Example 3	Example 4
Active ingredient (IY-81149)	10.0	10.0	10.0	10.0	10.0
Stabilizer	-	$Mg(OH)_2$ 3.2	$Mg(OH)_2$ 3.2	Na_2HPO_4 7.8	Na_2HPO_4 7.8
Excipient (Microcrystalline cellulose)	138.5	135.3	135.3	130.7	130.7
Lubricant (Magnesium stearate)	1.5	1.5	1.5	1.5	1.5
Weight of naked tablet	150.0	150.0	150.0	150.0	150.0
First coating substance	HPMC2910[1] 5.0	HPMC2910[1] 5.0	HPMC2910[1] 5.0	HPC[3] 6.0	HEC[2] 6.0
Plasticizer for first coating	PEG6000[5] 1.0	PEG6000[5] 1.0	PEG6000[5] 1.0	PEG6000[5] 1.0	triacetin
Solvent for first coating	Water+ethanol	Water+ethanol	Water+ethanol	ethanol	ethanol
Weight of firstly coated tablet	156.0	156.0	156.0	157.0	157.0
First coating substance	HPMCP[8] 20.0	HPMCP[8] 20.0	Kollicoat™ 12.0	PVAP[10] 15.0	HPMCP[8] 20.0
Plasticizer for second coating	cetanol 2.0 Myvacet™ 2.0	cetanol 2.0 Myvacet™ 2.0	PG[13] 1.0	DEP[14] 5.0	cetanol 3.0
Solvent for second coating	acetone+ethanol	acetone+ethanol	water	MC[15]	acetone+EA[16]
Weight of secondly coated tablet	180.0	180.0	169.0	177.0	180.0

Table 1(Continued)

The prescriptions according to Examples 1 to 10 and Comparative Example 1(unit: mg)

Example 5	Example 6	Example 7	Example 8	Example 9	Example 10
10.0	10.0	10.0	10.0	10.0	10.0
$NaHCO_3$	$NaHCO_3$	Na_2CO_3	Na_2CO_3	Arginine	Arginine
4.6	4.6	5.8	5.8	9.6	9.6
133.9	133.9	132.7	132.7	128.9	128.9
1.5	1.5	1.5	1.5	1.5	1.5
150.0	150.0	150.0	150.0	150.0	150.0
SA[4]	HPMC2910[1]	HPC[3]	HPC[3]	HEC[2]	SA[4]
5.0	5.0	6.0	6.0	6.0	5.0
TEC[7]	PEG6000[5]	PEG4000[6]	PEG4000[6]	TEC[7]	TEC[7]
1.0	1.0	1.0	1.0		
Water	Water+ethanol	ethanol	ethanol	ethanol	Water
156.0	156.0	157.0	157.0	157.0	156.0
CAP[11]	CAP[11]	Kollicoat™	PVAP[10]	HPMCAS[12]	HPMCAS[12]
12.0	12.0	12.0	15.0	20.0	20.0
Dimethicone 1.5	dimethicone 1.5	PG[13]	DEP[14]	DEP[14]	DEP[14]
DEP[14] 4.5	DEP[14] 4.5	1.0	5.0	6.0	6.0
Acetone	acetone	water	MC[15]	acetone	acetone
+MC[15]	+MC[15]	170.0	177.0	+EA[16]	+EA[16]
174.0	174.0			183.0	182.0

1) HPMC2910 = hydroxypropylmethylcellulose 2910, 2) HEC = hydroxyethylcellulose, 3) HPC = hydroxypropylcellulose, 4) SA = sodium alginate, 5) PEG6000 = polyethylene glycol 6000, 6) PEG4000 = polyethylene glycol 4000, 7) TEC = triethyl citrate, 8) HPMCP = hydroxypropylmethylcellulose phthalate, 9) Kollicoat = Trade mark of acrylate polymer(Kollicoat MAE30DP, BASF), 10) PVAP = polyvinylacetate phthalate, 11) CAP = cellulose acetate phthalate, 12) HPMCAS = hydroxypropylmethylcellulose acetate succinate, 13) PG = propylene glycol, 14) DEP = diethyl phthalate, 15) MC = methylene chloride, 16) EA =ethyl acetate

Test Example 1

Stability Test 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 that is one of the most well known benzimidazole derivatives, were mixed with the alkali compound in a molar ratio of 1:1 and then stored for 15 days under an accelerative condition (40℃, relative humidity of 75%). Then, the content of the active ingredient that was not decomposed was analyzed using a liquid chromatography. The sample containing only the active ingredient without a stabilizer (tablet according to Comparative Example 1) was used as a control. The analyzing conditions were represented in the following, and the results are shown in Table 2.

<Conditions for Liquid Chromatography>

- Column: μ-Bondapack C_{18} (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: 20μℓ

Table 2

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_2HPO_4	1:1	1/8	99.2	82.1	99.8	94.0
K_2HPO_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_2CO_3	1:1	1/3.5	99.4	79.9	100.1	75.3
K_2CO_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 2 provide very important information which can be referred in selecting 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 $Mg(OH)_2$〉 Na_2HPO_4〉 Na_2CO_3〉 $NaHCO_3$〉 arginine〉K_2HPO_4〉histidine〉$KHCO_3$〉K_2CO_3〉lysine〉$Al(OH)_3$ when compared with the control group. On the other hand, in the case of the known omeprazole, the tested stabilizers show stabilizing effects in the order of

Na_2HPO_4> $NaHCO_3$> $Mg(OH)_2$> arginine> Na_2CO_3> K_2HPO_4> $Al(OH)_3$> histidine> K_2CO_3> lysine> $KHCO_3$. 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 2 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 the 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℃, relative humidity of 75%). Then, the content of IY-81149 was analyzed according to the same manner as Test Example 1. The results are shown in the following Table 3.

Table 3

Stability of the active ingredient depending on amounts 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_2HPO_4	56.0	76.8	82.1	88.4	80.2	73.3
K_2HPO_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_2CO_3	51.2	68.0	79.9	84.2	70.0	66.2
K_2CO_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 3, it can be seen that the suitable amount of the stabilizer based on its water-solubility ranges in a molar amount from 0.2 to 7.0 times with respect to IY-81149, and specifically in the most cases, the stabilizing effect is far better when the molar ratios are 1:1 to 1:7. When the stabilizer was in an amount of less than 0.2 times molar amount, the desired stabilizing effect cannot be obtained, and when the stabilizer was in a molar amount more than 7.0 times molar amount, the increased hygroscopicity of the stabilizer may act as an obstacle for the formulation.

Example 3

Stability Test for the tablets comprising IY-81149

Stability tests were carried out for the tablets according to Examples 1 to 10 and Comparative Example 1. The stability tests were conducted by storing the tablets for 3 months under an accelerative condition (40℃, 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 IY-81149 in the tablets according to Examples 1-10

		Comparative Example 1	Example No.									
			1	2	3	4	5	6	7	8	9	10
Content (%) of IY-81149	Initial	99.6	100.0	100.2	99.9	99.8	99.5	99.8	99.6	99.4	99.8	100.1
	After 3 months	64.9	98.8	97.3	95.8	93.2	87.5	88.9	83.5	85.1	89.8	87.6

As shown in Table 4, stabilities of the tablets comprising IY-81149 of Examples 1 to 10 are maintained after 3-month accelerative period compared with the tablets of Comparative Example 1 which do not contain a stabilizer.

Example 4

Antiacidity Test for the tablets comprising IY-81149

IY-81149, the active ingredient, is highly unstable under acidic conditions like other benzimidazole derivatives. Therefore, stability of an

tablet for oral administration of IY-81149 should be maintained under strong acidic condition in stomach as well as during storage period, and, so, 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. Thus, the inventors tested antiacidity of the tablets according to Examples 1 to 10 and Comparative Example 1.

Antiacidity Test was carried out according to the second method of dissolution test set forth in General Tests of Korean Pharmacopoeia (Paddle Method, 37℃, 100rpm). That is, the tablets of Examples 1 to 10 (comprising 10.0mg as IY-81149) were put into 900 ml of artificial gastric fluids (pH 1.2), respectively, and tested by Paddle Method for 2 hours, and the contents of the active ingredient remaining in the tablets were analyzed in the same manner as Test Example 1. Further, the contents of the active ingredient remaining in the tablets stored for 3 months under an accelerative condition (40℃, relative humidity of 75%), were analyzed in the same manner as Test Example 1. The results are shown in the following Table 5.

Table 5

Antiacidity of the tablets 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	99.6	99.5	99.3	98.9	98.6	100.1	99.8	100.2	99.7	99.6	99.5
	After 3 months	625	97.2	97.0	90.6	91.2	81.7	82.5	79.9	80.0	88.2	89.8

As shown in Table 5, all of the tablets of Examples 1 to 10 are suitable for antiacidity test just after the preparation. All of the tablets stored for 3 months of Examples 1 to 10 also exhibited far better stability compared with the tablets of Comparative Example 1.

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

WHAT IS CLAIMED IS:

1. An stabilized tablet for oral administration 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 to make a naked tablet, tableting the mixture, firstly coating the naked tablet with a film forming material, and secondly coating the tablet with an enteric coating material.

2. The stabilized tablet 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(anhydrous), potassium carbonate(anhydrous), potassium hydrogen carbonate, aluminum hydroxide, arginine, lysine and the combination thereof.

3. The stabilized tablet of claim 1 wherein the alkali compound is used from 0.2 to 7.0 times in a molar amount with respect to 2-[(4-methoxy-3-methyl)-2-pyridinyl]methylsulfinyl-5-(1H-pyrrol-1-yl)-1H-benzimidazole.

4. The stabilized tablet of claim 3 wherein the alkali compound is used 0.5 to 6.5 times in molar amount with respect to 2-[(4-methoxy-3-methyl)-2-pyridinyl]methylsulfinyl-5-(1H-pyrrol-1-yl)-1H-benzimidazole.

5. The stabilized tablet of claim 1 wherein the film forming material used in the first coating is selected from the group consisting of hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose,

* C L M S *

sodium alginate, and the combination thereof.

6. The stabilized tablet of claim 5 wherein the film forming material is used in an amount of 0.1 to 30% by weight with respect to the naked tablet.

7. The stabilized tablet of claim 6 wherein the film forming material is used in an amount of 2.0 to 6.0% by weight with respect to the naked tablet.

8. The stabilized tablet 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 tablet of claim 8 wherein the enteric coating material is used in an amount of 0.1 to 40%, by weight with respect to the naked tablet.

10. The stabilized tablet of claim 9 wherein the enteric coating material is used in an amount of 5.0 to 20% by weight with respect to the naked tablet.

11. The stabilized tablet of claim 1 wherein the pharmaceutically acceptable additive includes excipient, disintegrant, lubricant, binder, sweetener and flavor.

* C L M S *