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(IN). **MALIK, Rajiv** [IN/AT]; Haus 13/4, Unterer  
Schreiberweg, A-1190 Wien (AT).

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(74) Common Representative: **RANBAXY LABORATO-  
RIES LIMITED**; c/o DESHMUKH, Jay, R., 600 College  
Road East, Suite 2100, Princeton, NJ 08540 (US).

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(71) Applicant (*for all designated States except US*): **RAN-  
BAXY LABORATORIES LIMITED** [IN/IN]; 19, Nehru  
Place, New Delhi, Delhi 110 019 (IN).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **SINGH, Romi,  
Barat** [IN/IN]; A-14, Badshah Bagh, Varanasi, Uttar  
Pradesh 221002 (IN). **KUMAR, Pananchukunnath,  
Manoj** [IN/IN]; 25 Laxmi Vihar Apartments, Block  
H-3, Vikas Puri, New Delhi, Delhi 110018 (IN). **NA-  
GAPRASAD, Vishnubhotla** [IN/IN]; 102, Surya Niwas  
Apartments, Balaji Nagar, Kukatpally, Hyderabad, Andhra  
Pradesh 500072 (IN). **SETHI, Sanjeev, Kumar** [IN/IN];  
House No. 365, Sector - 8, Faridabad, Haryana 121006

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(54) Title: PHARMACEUTICAL COMPOSITIONS OF BENZIMIDAZOLE AND PROCESSES FOR THEIR PREPARATION

(57) Abstract: The technical field of the present invention relates to stable pharmaceutical compositions of acid-labile benzimidazole derivative using increased amounts of low-viscosity hydroxypropylcellulose, and processes for the preparation of these compositions. The pharmaceutical composition includes one or more cores. The cores include an acid-labile benzimidazole derivative and at least 10% w/w of low-viscosity hydroxypropylcellulose by weight of the benzimidazole derivative.



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## PHARMACEUTICAL COMPOSITIONS OF BENZIMIDAZOLE AND PROCESSES FOR THEIR PREPARATION

### Technical Field of the Invention

The technical field of the present invention relates to stable pharmaceutical  
5 compositions of acid-labile benzimidazole derivative using increased amounts of low-  
viscosity hydroxypropylcellulose, and processes for the preparation of these compositions.

### Background of the Invention

Benzimidazole derivatives, such as esomeprazole, omeprazole, lansoprazole,  
laminoprazole, pariprazole, rabeprazole and pantoprazole, etc. are known proton pump  
10 inhibitors with powerful inhibitory action against the secretion of gastric acid. They are  
indicated for the treatment of various digestive ulcers, are well known in the art, and are  
described, for example, in EP 0005129 A (having U.S. equivalent U.S. Patent No.  
4,255,431).

It has been found that these benzimidazole derivatives are easily destroyed in acid  
15 medium and thus are difficult to formulate for oral administration. Upon oral  
administration, the pharmaceutical composition comes in contact with the gastric fluid in  
the stomach, which is highly acidic, leading to breakdown and loss of activity of the  
benzimidazole derivative.

Pharmaceutical compositions comprising acid-labile agents are protected from  
20 acidic gastric juices by an enteric coating until it reaches the desired site of action, e.g., the  
small intestine. Most of the enteric coatings are either themselves acidic materials, or  
contain acidic materials, which may react with the benzimidazole derivative and cause  
degradation. Hence, conventional enteric coatings are not suitable for this purpose.

Several approaches have been employed by researches to stabilize acid-labile  
25 benzimidazole derivatives in pharmaceutical compositions. For example, U.S. Patent No.  
4,786,505 addresses this problem by formulating the benzimidazole derivative and an  
alkaline reacting compound into pellets with an inert sub-coating and then an enteric  
coating. The alkaline reacting compound presumably increases stability by maintaining  
the benzimidazole in an alkaline environment and the inert sub-coating prevents contact  
30 between the benzimidazole derivative and the enteric coating.

U.S. Patent Application No. 2002/0039597 discloses a pharmaceutical preparation of a benzimidazole type compound that is characterized within the application as being chemically stable. The preparation is stabilized by incorporating in the core at least one substance selected from sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, amino alkyl methacrylate copolymer E, arginine aspartate, hydroxypropylcellulose and crospovidone.

### Summary of the Invention

In one general aspect there is provided a pharmaceutical composition that includes one or more cores. The cores include an acid-labile benzimidazole derivative and at least 10% w/w of low-viscosity hydroxypropylcellulose by weight of the benzimidazole derivative.

Embodiments of the pharmaceutical composition may include one or more of the following features. For example, the pharmaceutical composition may be a solid dosage form selected from the group that includes powder, tablet, granule, pellet, spheroid and capsule.

The low-viscosity hydroxypropylcellulose may vary from about 10% to about 100% by weight of the weight of the benzimidazole derivative. The low-viscosity hydroxypropylcellulose may be a hydroxypropylcellulose having a viscosity less than about 1000 cps.

The benzimidazole derivative may be one or more selected from the group that includes esomeprazole, omeprazole, lansoprazole, leminoprazole, pariprazole, rabeprazole, pantoprazole, and their pharmaceutically acceptable salts with metals. The benzimidazole derivative may be one or both of pantoprazole sodium and rabeprazole sodium.

The pharmaceutical composition may further include one or more pharmaceutically acceptable inert excipients. The one or more pharmaceutically acceptable inert excipients may be selected from the group that includes alkaline reacting compounds, antioxidants, binders, diluents, disintegrants, surfactants, plasticizers, coloring agents and flavoring agents.

The alkaline reacting compound may be one or more of sodium, potassium, calcium, magnesium, and aluminum salts of phosphoric acid, carbonic acid, citric acid or other weak inorganic or organic acids, aluminum hydroxides, calcium hydroxides and

magnesium hydroxides, magnesium oxide,  $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$ ,  $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$ ,  $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$ , organic pH buffering substances, and trihydroxymethylaminomethane. In particular, the alkaline reacting compound may be sodium carbonate.

5           The pharmaceutical composition may further include one or both of a sub-coat layer and an enteric coat layer around the core. The sub coat layer may be one or more film-forming agents. The film-forming agent may be selected from the group that includes carageenan, ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, polyethylene glycol, polyvinyl alcohol and xanthan gum. In  
10           particular, the film-forming agent may be hydroxypropyl methylcellulose.

          The enteric coat layer may be one or more enteric polymers. The enteric polymer may be one or more of cellulose acetate phthalate, hydroxypropyl methylcellulose acetate phthalate, polyvinyl acetate phthalate, hydroxy propyl phthalate, hydroxypropyl  
15           methylcellulose phthalate hydroxypropyl methylcellulose acetate succinate; and methacrylic acid copolymers. In particular, the enteric polymer may be methacrylic acid copolymer.

          In another general aspect there is provided a process for the preparation of a pharmaceutical composition that contains one or more cores. The process includes  
20           forming a core containing an acid-labile benzimidazole derivative and at least 10% w/w of low-viscosity hydroxypropylcellulose by weight of the benzimidazole derivative.

          Embodiments of the process may include one or more of the following features or those described above. For example, the acid-labile benzimidazole may be blended with the low-viscosity hydroxypropylcellulose with or without one or more pharmaceutically  
25           acceptable inert excipients and then formed into the core. The process may further include forming tablets from the cores.

          The blend may be granulated and the granulation may be carried out by wet granulation or dry granulation technique. The blend may be further processed into a suitable sized core by the process of extrusion-spheronization.

30           The process may further include coating the core with one or both of a sub coat layer and an enteric coat layer. Either or both of the sub coat layer and the enteric coat layer may be applied as a solution or dispersion of film-forming agent or enteric polymer

in a suitable solvent. The solvent may be selected from the group that includes methylene chloride, isopropyl alcohol, acetone, methanol, ethanol and water. Either or both of the sub coat layer and the enteric coat layer may be applied using a hot melt technique.

5 In another general aspect there is provided a method of treating a patient for a condition for which a benzimidazole derivative is needed. The method includes administering a pharmaceutical composition of benzimidazole derivative that includes one or more cores containing an acid labile benzimidazole derivatives and at least 10% w/w of low-viscosity hydroxypropylcellulose by weight of the benzimidazole.

10 Embodiments of the method of treating may include one or more of the following features or those described above. For example, the benzimidazole derivative may be selected from the group that includes esomeprazole, omeprazole, lansoprazole, leminoprazole, pariprazole, rabeprazole, pantoprazole; and their pharmaceutically acceptable salts. The acceptable salt may be one or more of sodium, potassium, calcium, and magnesium. The benzimidazole derivative may be one or both of pantoprazole  
15 sodium and rabeprazole sodium.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

#### Detailed Description of the Invention

20 As may be evident from the discussion of the background above, stabilization of benzimidazole derivatives in pharmaceutical compositions has been a key area of research ever since the discovery of these benzimidazoles as potent proton pump inhibitors. We have now discovered that degradation of benzimidazole derivatives, particularly pantoprazole and rabeprazole, in pharmaceutical compositions can be inhibited by the  
25 incorporation of a conventionally used binder, low-viscosity hydroxypropylcellulose, in amounts greater than used in the past as a binder in admixture with benzimidazole derivative.

The term "benzimidazole derivative" as used herein includes benzimidazole derivatives that are used as proton pump inhibitors. Examples include esomeprazole,  
30 omeprazole, lansoprazole, leminoprazole, pariprazole, rabeprazole, pantoprazole; and pharmaceutically acceptable salts thereof. Pharmaceutically acceptable salts include metal

salts of sodium, potassium, calcium, magnesium and the like. In particular pantoprazole sodium or rabeprazole sodium may be used.

Low-viscosity hydroxypropylcellulose is conventionally used as a binder, although in low amounts. However, the pharmaceutical compositions of the present invention

5 comprise increased or high amounts of low-viscosity hydroxypropylcellulose, at least in amounts greater than as a conventional binder. We have surprisingly discovered that the chemical degradation, as well as the discoloration, of highly acid-labile benzimidazole derivatives, particularly pantoprazole and rabeprazole, may be inhibited or at least reduced to a reasonable extent with the use of higher amounts of low-viscosity

10 hydroxypropylcellulose. The amount of low-viscosity hydroxypropylcellulose should be at least about 10% by weight of the weight of benzimidazole derivative, and in particular from about 10% to about 100% of the weight of the benzimidazole derivative.

As detailed below, pharmaceutical compositions comprising pantoprazole and higher amounts of low-viscosity hydroxypropylcellulose were prepared and evaluated for

15 stability at 400°C and 75% relative humidity over a period of 3 months. The results of the stability evaluation, listed in Table 1 below are highly convincing for recommending the use of low-viscosity hydroxypropylcellulose as a stabilizer. The results in Table 1 further reveal the synergistic improvement in stability upon incorporation of alkaline reacting compounds.

20 Hydroxypropylcellulose is a non-ionic water-soluble cellulose ether that is formed by reaction with propylene oxide. It has a longstanding history of safe and effective use in the pharmaceutical industry. Hydroxypropylcellulose is commercially available from Aqualon and Nippon Soda Co. under the brand names Klucel® and HPC® and provides a remarkable set of physical properties for tablet binding, modified release, and film coating.

25 Based on the requirement and the role it has to play in the pharmaceutical composition, hydroxypropylcellulose of a desired viscosity range may be selected. Broadly, the viscosity ranges and corresponding hydroxylpropylcelluloses are classified as low, medium and high viscosity hydroxypropylcelluloses. Examples of low-viscosity hydroxypropylcellulose include Klucel EF, Klucel LF, Klucel JF and Klucel GF, whose

30 2% by weight aqueous solutions have viscosities less than about 1000 cPs. Other examples are HPC-SL, HPC-L, and HPC-M whose 2% by weight aqueous solutions have viscosities of 3-6, 6-10, and 150-400 cPs, respectively. In particular HPC-L may be used.

The term "pharmaceutical composition" as used herein includes solid dosage forms such as powder, tablet, granule, pellet, spheroid, capsule, and the like. The pharmaceutical composition may include one or more of a core, a sub coat layer, an enteric coat layer, and one or more pharmaceutically acceptable inert excipients.

5           The term "core" as used herein includes conventionally used cores for oral administration such as tablets, granules, pellets, spheroids, capsules and the like. The core may comprise acid-labile benzimidazole derivative and low-viscosity hydroxypropylcellulose with or without other pharmaceutically acceptable inert excipients.

10           The sub coat layer may comprise a film-forming agent with or without other pharmaceutically acceptable inert excipients. Specific examples of film forming agents include carageenan, hydroxypropyl methylcellulose, hydroxypropylcellulose, methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, polyethylene glycol, polyvinyl alcohol, xanthan gum and the like. In particular,  
15           hydroxypropylmethyl cellulose may be used as the film forming agent in concentrations from about 40% to about 90% by weight of the total solid content in the coating composition. Sub coating is carried out until a weight build-up is attained of about 7.5% to about 20% w/w over the core, in particular about 10% to about 20% w/w.

            The enteric coat layer may comprise an enteric polymer with or without other  
20           pharmaceutically acceptable inert excipients. Specific examples of enteric polymers include cellulose acetate phthalate, hydroxypropyl methylcellulose acetate phthalate, polyvinyl acetate phthalate, hydroxy propyl phthalate, hydroxypropyl methylcellulose phthalate (HPMC phthalate), hydroxypropyl methylcellulose acetate succinate; methacrylic acid copolymers such as Eudragit® L 100-55, Eudragit® L30 D-55, Eudragit®  
25           L 100, Eudragit® S 100; and mixtures thereof. In particular, methacrylic acid copolymers (type C), for example, Eudragit® L30 D-55 & Eudragit® L 100 may be used as the enteric polymer in concentrations from about 40% to about 95% by weight of the total solid content in the coating composition. Enteric coating is carried out until attaining a weight build up of about 7.5% to about 15 % w/w over the sub coated core, in particular about  
30           10% to about 12.5% w/w.

            The term "pharmaceutically acceptable inert excipients" as used herein includes all physiologically inert excipients used in the pharmaceutical art of dispensing. Examples

include alkaline reacting compounds, antioxidants, binders, diluents, disintegrants, surfactants, plasticizers, lubricants/glidants, coloring agents, flavoring agents, and the like.

Examples of alkaline reacting compound include sodium, potassium, calcium, magnesium, and aluminum salts of phosphoric acid, carbonic acid, citric acid or other  
5 suitable weak inorganic or organic acids, such as sodium carbonate; substances normally used in antacid preparations such as aluminum, calcium and magnesium hydroxides; magnesium oxide or composite substances such as  $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$ ,  $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$ ,  $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$  or similar compounds; organic pH buffering substances such as trihydroxymethylaminomethane and the like.

10 Examples of suitable antioxidants include lipophilic antioxidants, inorganic antioxidants and the like. In particular butylated hydroxy anisole (BHA) and butylated hydroxy toluene (BHT) alone or in combination may be used.

Specific examples of binders include methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, gelatin, gum arabic, ethyl cellulose,  
15 polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, and the like.

Specific examples of diluents include calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, cellulose-microcrystalline, cellulose powdered, dextrates, dextrans, dextrose excipients, fructose, kaolin, lactitol, lactose,  
20 mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, sugar confectioners, and the like.

Specific examples of disintegrants include low-substituted hydroxypropylcellulose (L-HPC), sodium starch glycollate, carboxymethyl cellulose, calcium carboxymethyl cellulose, sodium carboxymethyl cellulose, croscarmellose sodium A-type (Ac-di-sol),  
25 starch, crystalline cellulose, hydroxypropyl starch, partly pregelatinized starch, and the like.

Examples of surfactants include both non-ionic and ionic (cationic, anionic and zwitterionic) surfactants suitable for use in pharmaceutical compositions. These include polyethoxylated fatty acids and their derivatives, for example polyethylene glycol 400  
30 distearate, polyethylene glycol – 20 dioleate, polyethylene glycol 4 – 150 mono dilaurate, polyethylene glycol – 20 glyceryl stearate; alcohol – oil transesterification products, for example polyethylene glycol – 6 corn oil; polyglycerized fatty acids, for example



polyglyceryl – 6 pentaoleate; propylene glycol fatty acid esters, for example propylene glycol monocaprylate; mono and diglycerides for example glyceryl ricinoleate; sterol and sterol derivatives; sorbitan fatty acid esters and its derivatives, for example polyethylene glycol – 20 sorbitan monooleate, sorbitan monolaurate; polyethylene glycol alkyl ether or phenols, for example polyethylene glycol – 20 cetyl ether, polyethylene glycol – 10 – 100 nonyl phenol; sugar esters, for example sucrose monopalmitate; polyoxyethylene – polyoxypropylene block copolymers known as “poloxamer”; ionic surfactants, for example sodium caproate, sodium glycocholate, soy lecithin, sodium stearyl fumarate, propylene glycol alginate, octyl sulfosuccinate disodium, palmitoyl carnitine; and the like

10            Specific examples of lubricants/glidants include colloidal silicon dioxide, stearic acid, magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, talc, hydrogenated castor oil, sucrose esters of fatty acid, microcrystalline wax, yellow beeswax, white beeswax, and the like

15            Specific examples of plasticizers include acetylated triacetin, triethylcitrate, tributylcitrate, glyceroltributyrate, monoglyceride, rape oil, olive oil, sesame oil, acetyltributylcitrate, acetyltriethylcitrate, glycerin sorbitol, diethyloxalate, diethyl phthalate, diethylmalate, diethylfumarate, dibutylsuccinate, diethylmalonate, dioctylphthalate, dibutylsebacate, and the like.

20            Coloring agents and flavoring agents include any FDA approved color or flavor for oral use.

Stable pharmaceutical compositions of acid-labile benzimidazole derivative may be prepared by processes known in the prior art including, for example, by comminuting, mixing, granulation, melting, sizing, filling, drying, molding, immersing, coating, compressing, extrusion-spheronization etc.

25            In a first embodiment, a core that includes an acid-labile benzimidazole derivative is prepared by a process that includes the steps of blending benzimidazole derivative and low-viscosity hydroxypropylcellulose with or without one or more pharmaceutically acceptable inert excipients; wet granulating the blend with a granulating fluid or solution/dispersion of one or more pharmaceutically acceptable inert excipients in the granulating fluid; drying and sizing the granules; optionally blending with one or more pharmaceutically acceptable inert excipient; and forming a suitable sized core.

30

In a second embodiment, a core that includes an acid-labile benzimidazole derivative is prepared by a process that includes the steps of blending benzimidazole derivative and low-viscosity hydroxypropylcellulose with or without one or more pharmaceutically acceptable inert excipients; dry granulating the blend by roller compactor or slugging; sizing the granules; optionally blending with one or more pharmaceutically acceptable inert excipients; and forming a suitable sized core.

In a third embodiment, a core that includes an acid-labile benzimidazole derivative is prepared by a process that includes the steps of blending benzimidazole derivative and low-viscosity hydroxypropylcellulose with or without one or more pharmaceutically acceptable inert excipients; and forming a suitable sized core.

In a fourth embodiment, a core that includes an acid-labile benzimidazole derivative is prepared by a process that includes the steps of blending benzimidazole derivative and low-viscosity hydroxypropylcellulose with or without one or more pharmaceutically acceptable inert excipients; forming a wet mass using a granulating fluid or solution/dispersion of one or more pharmaceutically acceptable inert excipients in the granulating fluid; passing the wet mass through an extruder equipped with a screen; spheronizing the extrudate in a spheronizer; drying and sizing the spheroids; and forming a suitable sized core.

The sub coat layer and enteric coat layer may be applied over the core prepared by any of the methods above in the form of a solution or dispersion of a film forming agent or an enteric polymer, with or without other pharmaceutically acceptable inert excipients. These coatings may be applied using any conventional coating technique known in the art, including spray coating in a conventional coating pan or fluidized bed processor, or dip coating. Alternatively, either of both of the coatings can be applied using a hot melt technique.

Specific examples of solvents used as a granulating fluid and for preparing the solution/dispersion of coating substances include methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, water and the like.

The invention is further illustrated by the following examples, which are not intended and should not be construed to limit the scope of the invention.

**Examples 1-7****Core tablets**

<b>Ingredient</b>	<b>Amount/tablet (mg)</b>						
	<b>Ex 1</b>	<b>Ex 2</b>	<b>Ex 3</b>	<b>Ex 4</b>	<b>Ex 5</b>	<b>Ex 6</b>	<b>Ex 7</b>
<b>Intragranular</b>							
<b>Pantoprazole sodium equivalent to pantoprazole</b>	40.0	40.0	40.0	40.0	40.0	40.0	40.0
<b>Mannitol</b>	31.2	21.2	-	41.2	37.2	31.2	31.2
<b>Microcrystalline cellulose</b>	-	10.0	31.2	-	10.0	10.0	10.0
<b>Crospovidone</b>	50.0	50.0	50.0	50.0	25.0	-	-
<b>Sodium starch glycollate</b>	-	-	-	-	-	50.0	-
<b>Low viscosity hydroxypropylcellulose</b>	15.5	15.5	15.5	15.5	15.5	15.5	15.5
<b>Sodium Carbonate</b>	10.0	10.0	10.0		10.0	10.0	10.0
<b>L-HPC</b>	-	-	-	-	-	-	50.0
<b>Extragranular</b>							
<b>Microcrystalline cellulose</b>	-	-	-	-	4.0	-	-
<b>Crospovidone</b>	-	-	-	-	25.0	-	-
<b>Calcium Stearate</b>	3.2	3.2	3.2	3.2	3.1	3.2	3.2

**Procedure:**

A portion of the mannitol, a portion of the microcrystalline cellulose, a portion of  
 5 the disintegrant (crospovidone or sodium starch glycollate or L-HPC, etc., respectively)  
 and a portion of the low viscosity hydroxypropylcellulose were mixed with pantoprazole  
 sodium in a high shear blender. This premix was granulated using purified water and the  
 bulk then was dried. The dried granules were sized and mixed with extra granular  
 excipients, which may include the remaining parts of mannitol, microcrystalline cellulose,  
 10 disintegrant and low-viscosity hydroxypropylcellulose. The blend so obtained then was  
 lubricated with calcium stearate and compressed into suitable sized tablets.

The core tablets containing alkaline stabilizer were prepared by incorporating  
 sodium carbonate intra granularly and/or extra granularly.

**Sub coat Layer**

	<b>Ingredient</b>	<b>Weight (%)</b>
	Hydroxypropyl methylcellulose	82.58
	Povidone	3.33
5	Titanium dioxide	1.47
	Ferric oxide yellow	0.05
	Propylene glycol	2.79

**Procedure:**

- 10      1.      Propylene glycol and povidone were dissolved in purified water to form a clear solution.
2.      Appropriately sieved titanium dioxide and ferric oxide yellow were dispersed in purified water under constant stirring and passed through a colloid mill to form a dispersion.
3.      The dispersion of step 2 was added to the solution of step 1.
- 15      4.      Hydroxypropyl methylcellulose was added to the dispersion of step 3 under stirring for 30 minutes to give a uniform dispersion of 10 – 20 % w/w.
5.      The core tablets prepared in the Example 1-7 above then were coated with the dispersion of step 4 until the desired weight build up was attained.

**Enteric coat layer**

20	<b>Ingredient</b>	<b>Weight (%)</b>
	Eudragit L 30D	84.84
	Triethyl citrate	9.07
	Sodium lauryl sulphate	1.49
	Titanium dioxide	4.47
25	Ferric oxide yellow	0.14

**Procedure:**

1. Appropriately sieved titanium dioxide and ferric oxide yellow were dispersed in purified water under constant stirring and passed through a colloid mill.
- 5 2. Sodium lauryl sulphate and triethyl citrate were added to the dispersion of step 1 under continuous stirring.
3. Eudragit L 30 D was dispersed in purified water under continuous stirring, to achieve a final dispersion of 10 – 25 % w/w.
- 10 4. The dispersion of step 2 was added to the dispersion of step 3 slowly, under continuous stirring, followed by continued stirring for at least one hour.
5. The sub coated tablets prepared above then were coated with the dispersion of step 4 until the desired weight build up was attained.

The coated tablets were stored at 40<sup>0</sup>C and 75% relative humidity for 3 months and then the impurities were measured. The results are provided below in Table 1. The results in Table 1 demonstrate that the degradation of benzimidazole derivatives, particularly pantoprazole and rabeprazole, in pharmaceutical compositions can be inhibited by the incorporation of low-viscosity hydroxypropylcellulose at amounts greater than used in the past as a binder in admixture with benzimidazole derivative and therefore support the use of low-viscosity hydroxypropylcellulose as a stabilizer.

20 **Table 1.** Stability data generated after storage of coated tablets at 40<sup>0</sup>C, 75% relative humidity for three months

Impurity		Percentage (%) Impurity			
		Ex 2	Ex 4	Ex 6	Ex 7
Pantoprazole sulphone	Initial	0.065	0.067	0.021	0.055
	After 3 months	0.052	0.060	0.041	0.064
Total Unknown	Initial	0.118	0.104	0.289	0.283
	After 3 months	0.242	0.410	0.448	0.205

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention.

We Claim:

- 1 1. A pharmaceutical composition comprising one or more cores, the cores  
2 comprising:  
3 an acid-labile benzimidazole derivative; and  
4 at least 10% w/w of low-viscosity hydroxypropylcellulose by weight of the  
5 benzimidazole derivative.
- 1 2. The pharmaceutical composition according to claim 1 wherein the low-viscosity  
2 hydroxypropylcellulose may vary from about 10% to about 100% by weight of the weight  
3 of the benzimidazole derivative.
- 1 3. The pharmaceutical composition according to claim 1 wherein the low-viscosity  
2 hydroxypropylcellulose comprises a hydroxypropylcellulose having a viscosity less than  
3 about 1000 cps.
- 1 4. The pharmaceutical composition according to claim 1 wherein the benzimidazole  
2 derivative comprises one or more selected from the group consisting of esomeprazole,  
3 omeprazole, lansoprazole, leminoprazole, pariprazole, rabeprazole, pantoprazole, and their  
4 pharmaceutically acceptable salts with metals.
- 1 5. The pharmaceutical composition according to claim 4 wherein the benzimidazole  
2 derivative comprises one or both of pantoprazole sodium and rabeprazole sodium.
- 1 6. The pharmaceutical composition according to claim 1 wherein the composition  
2 further comprises one or more pharmaceutically acceptable inert excipients.
- 1 7. The pharmaceutical composition according to claim 6 wherein the one or more  
2 pharmaceutically acceptable inert excipients are selected from the group consisting of  
3 alkaline reacting compounds, antioxidants, binders, diluents, disintegrants, surfactants,  
4 plasticizers, coloring agents and flavoring agents.
- 1 8. The pharmaceutical composition according to claim 1 wherein pharmaceutical  
2 composition comprises a solid dosage form selected from the group consisting of powder,  
3 tablet, granule, pellet, spheroid and capsule.
- 1 9. The pharmaceutical composition according to claim 1 further comprising one or  
2 both of a sub-coat layer and an enteric coat layer around the core.

- 1 10. The pharmaceutical composition according to claim 9 wherein the sub coat layer  
2 comprises one or more film-forming agents.
- 1 11. The pharmaceutical composition according to claim 10 wherein the film-forming  
2 agent is selected from the group consisting of carageenan, ethylcellulose, hydroxypropyl  
3 methylcellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose,  
4 hydroxymethylcellulose, hydroxyethylcellulose, polyethylene glycol, polyvinyl alcohol  
5 and xanthan gum.
- 1 12. The pharmaceutical composition according to claim 10 wherein the film-forming  
2 agent comprises hydroxypropyl methylcellulose.
- 1 13. The pharmaceutical composition according to claim 9 wherein the enteric coat  
2 layer comprises one or more enteric polymers.
- 1 14. The pharmaceutical composition according to claim 13 wherein the enteric  
2 polymer comprises one or more of cellulose acetate phthalate, hydroxypropyl  
3 methylcellulose acetate phthalate, polyvinyl acetate phthalate, hydroxy propyl phthalate,  
4 hydroxypropyl methylcellulose phthalate hydroxypropyl methylcellulose acetate  
5 succinate; and methacrylic acid copolymers.
- 1 15. The pharmaceutical composition according to claim 13 wherein the enteric  
2 polymer comprises methacrylic acid copolymer.
- 1 16. The pharmaceutical composition according to claim 7 wherein the alkaline reacting  
2 compound comprises one or more of sodium, potassium, calcium, magnesium, and  
3 aluminum salts of phosphoric acid, carbonic acid, citric acid or other weak inorganic or  
4 organic acids, aluminum hydroxides, calcium hydroxides and magnesium hydroxides,  
5 magnesium oxide,  $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$ ,  $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$ ,  
6  $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$ , organic pH buffering substances, and  
7 trihydroxymethylaminomethane.
- 1 17. The pharmaceutical composition according to claim 16 wherein the alkaline  
2 reacting compound comprises sodium carbonate.
- 1 18. A process for the preparation of a pharmaceutical composition comprising one or  
2 more cores, the process comprising forming a core containing an acid-labile  
3 benzimidazole derivative and at least 10% w/w of low-viscosity hydroxypropylcellulose  
4 by weight of the benzimidazole derivative.



- 1 19. The process according to claim 18, wherein the acid-labile benzimidazole is  
2 blended with the low-viscosity hydroxypropylcellulose with or without one or more  
3 pharmaceutically acceptable inert excipients and then formed into the core.
- 1 20. The process according to claim 18, further comprising coating the core with one or  
2 both of a sub coat layer and an enteric coat layer.
- 1 21. The process according to claim 19 wherein the blend is granulated.
- 1 22. The process according to claim 21 wherein the granulation is carried out by wet  
2 granulation or dry granulation technique.
- 1 23. The process according to claim 21 wherein the blend is further processed into a  
2 suitable sized core by the process of extrusion-spheronization.
- 1 24. The process according to claim 20 wherein either or both of the sub coat layer and  
2 the enteric coat layer are applied as a solution or dispersion of film-forming agent or  
3 enteric polymer in a suitable solvent.
- 1 25. The process according to claim 24 wherein solvent is selected from the group  
2 consisting of methylene chloride, isopropyl alcohol, acetone, methanol, ethanol and water.
- 1 26. The process according to claim 20 wherein either or both of the sub coat layer and  
2 the enteric coat layer are applied using a hot melt technique.
- 1 27. The process according to claim 18 further comprising forming the cores into  
2 tablets.
- 1 28. A method of treating a patient for a condition for which a benzimidazole derivative  
2 is needed, the method comprising administering a pharmaceutical composition of  
3 benzimidazole derivative comprising one or more cores containing an acid labile  
4 benzimidazole derivatives and at least 10% w/w of low-viscosity hydroxypropylcellulose  
5 by weight of the benzimidazole.
- 1 29. The method according to claim 28 wherein the benzimidazole derivative is selected  
2 from the group consisting of esomeprazole, omeprazole, lansoprazole, leminoprazole,  
3 pariprazole, rabeprazole, pantoprazole; and their pharmaceutically acceptable salts.
- 1 30. The method according to claim 29, wherein the acceptable salt comprises one or  
2 more of sodium, potassium, calcium, and magnesium.

- 1 31. The method according to claim 28 wherein the benzimidazole derivative comprises
- 2 one or both of pantoprazole sodium and rabeprazole sodium.

# INTERNATIONAL SEARCH REPORT

PCT/IB2004/002784

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K9/20 A61K9/30 A61K31/4439

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	EP 0 995 447 A (TAKEDA CHEMICAL INDUSTRIES LTD) 26 April 2000 (2000-04-26) page 16 - page 17; example 6	1-31
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Hedegaard, A

## INTERNATIONAL SEARCH REPORT

PCT/IB2004/002784

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