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(54) **STABLE BENZIMIDAZOLE FORMULATION**

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(57) **ABSTRACT**

A benzimidazole formulation which lacks an intermediate layer and yet which is stable both during storage and during the passage through the stomach, and which has low levels of residual volatile excipients, including but not limited to residual alkalinizing agents and/or residual solvents.

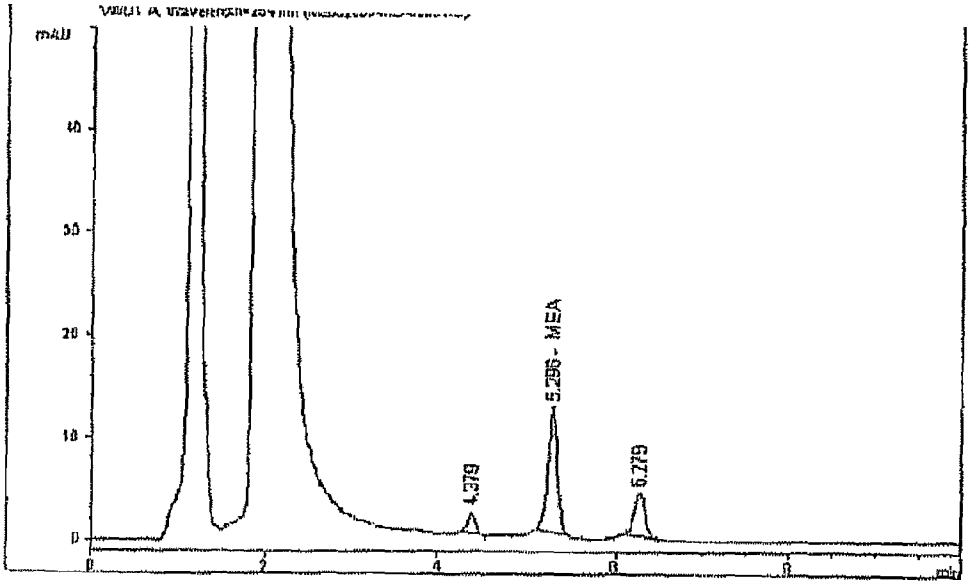

Figure 1

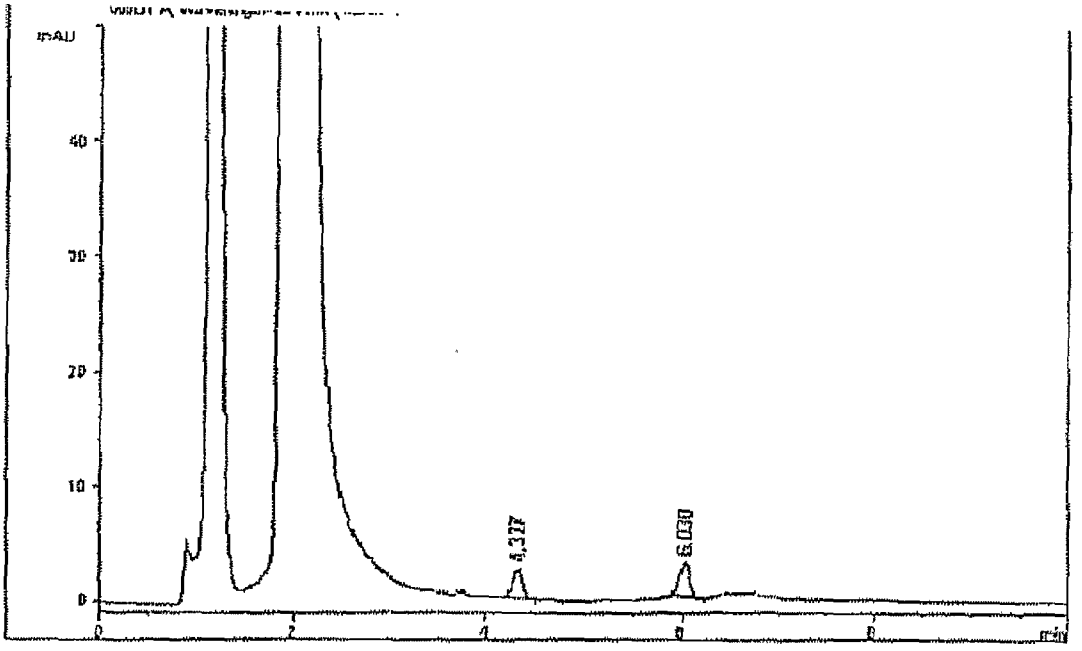

Figure 2

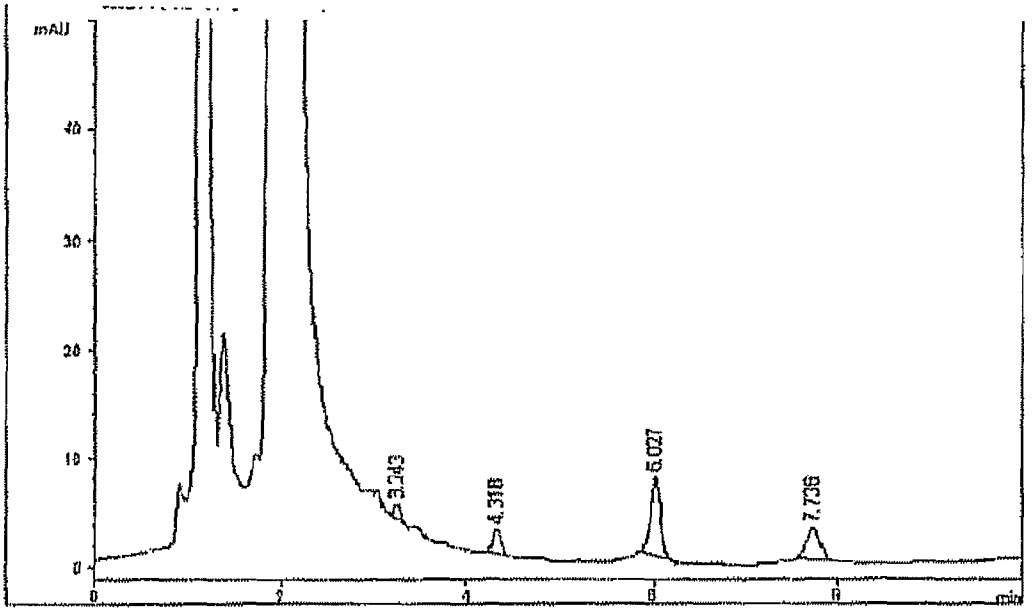

Figure 3

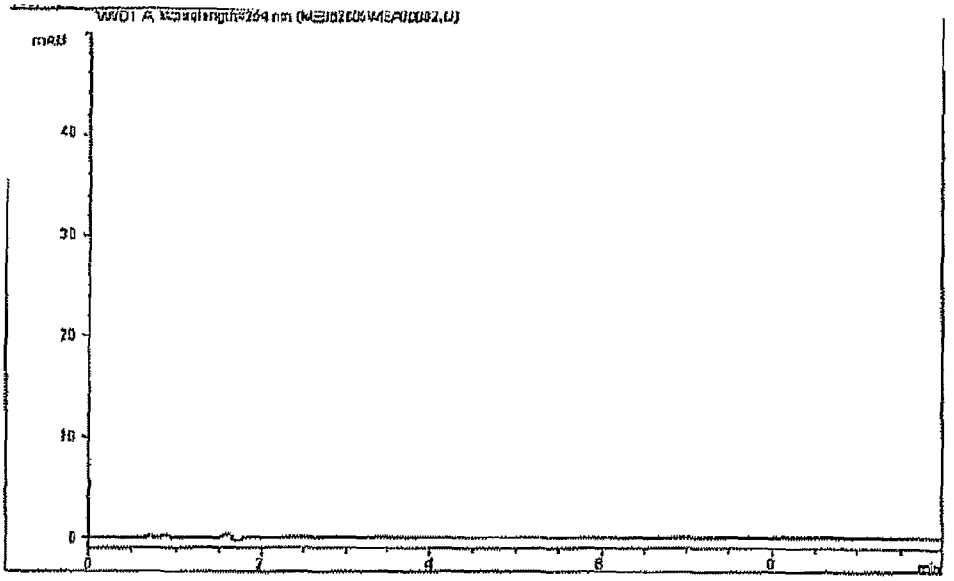

Figure 4

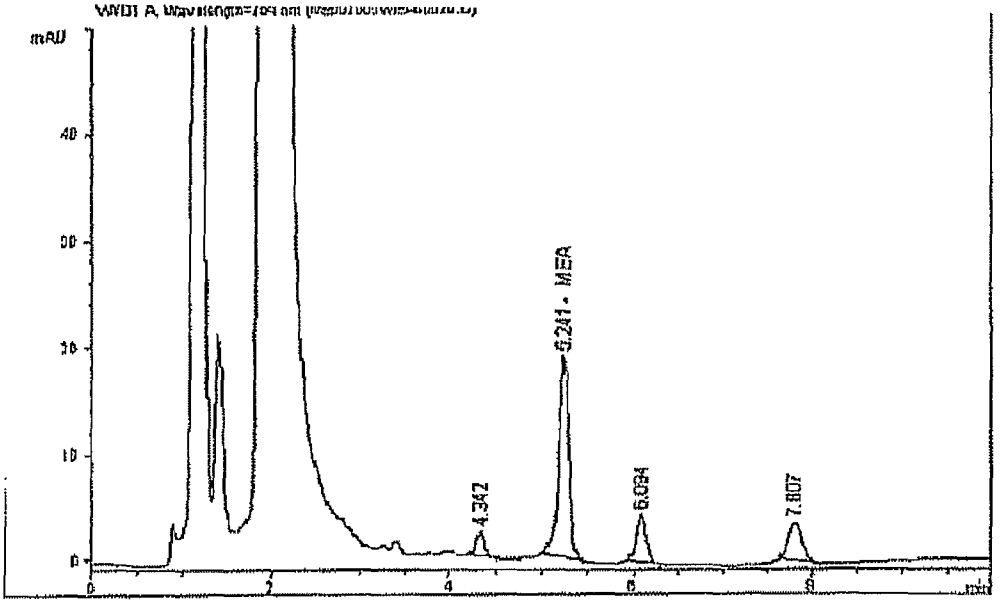

Figure 5

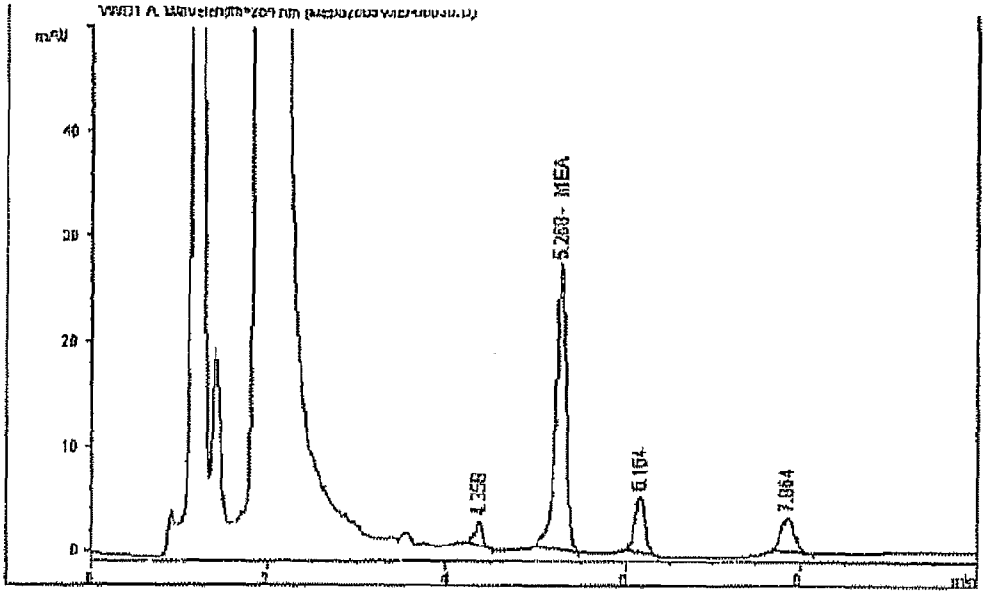

Figure 6

STABLE BENZIMIDAZOLE FORMULATION

FIELD OF THE INVENTION

[0001] The present invention relates to a novel stable formulation for an acid labile benzimidazole, and methods of preparation and administration thereof, and in particular, for a stable formulation of a benzimidazole which is suitable for oral administration, and has low levels of residual volatile excipients such as solvents.

BACKGROUND OF THE INVENTION

[0002] Omeprazole, Pantoprazole, Lansoprazole and other derivatives of benzimidazole, which are active proton pump inhibitors and used conventionally for decreasing gastric secretion are known to be susceptible to degradation and transformation in acid media. Omeprazole, 5-methoxy-2(((4-methoxy-3,5-dimethyl-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole, is disclosed and described in European Patent No. 5129 and European Patent No. 124495, as well as in numerous other patents and published patent applications.

[0003] The susceptibility of these active proton pump inhibitor substances to degradation and transformation in acid media increases the difficulty of preparing a pharmaceutical form designed for oral administration. If the active substance comes into contact with the stomach content, which is a highly acidic medium, these chemical substances become degraded. Thus, these benzimidazole derivatives should be protected both during storage and during their passage through the acidic environment of the stomach.

[0004] The stability of Omeprazole has been extensively studied (see for example A. Pilbrant and C. Cederberg, *Scan. J. Gastroenterol.*, 20: 113-120, 1985). Omeprazole degrades with a half-life of less than 10 minutes in an environment with pH values below 4.0. At pH 6.5, the half life of Omeprazole is 18 hours and at pH 11 about 300 days. Therefore, the environment of Omeprazole should be kept at a sufficiently high pH value in order to maintain the stability of the compound, in a formulation which is suitable as a product for oral administration, for example by locating Omeprazole within a core which also contains alkaline constituents. This leads to an alkaline reaction aimed at improving stability of the active substance during manufacture thereof and during storage of the pharmaceutical formulation.

[0005] In addition, such a formulation must protect Omeprazole from the acidic environment of the stomach, since if Omeprazole is given orally without any protective coating, it will degrade in the acid environment of the stomach. European Patent No. 237,200 discloses one solution, which is to directly coat the solid core containing Omeprazole, or another benzimidazole derivative, with an enteric coating layer.

[0006] However, this apparent solution to the instability of Omeprazole caused further complications, in that the alkaline core containing Omeprazole was found to react with the enteric coating, thereby causing the enteric coating to degrade. A solution to these further complications is disclosed in United Kingdom Patent Application No. 2,189,698, in which Omeprazole is contained within a solid active core, which is coated first with a subcoating layer and then with an enteric coating layer. The enteric coating layer protects the Omeprazole during the passage through the stomach, while the subcoating layer protects the enteric coating layer from reacting negatively with the alkaline core containing Omeprazole.

[0007] The background art describes other attempts to provide formulations which are suitable for oral administration of acid-labile substances. For example, PCT Application No. WO 97/12581 discloses a composition adapted for oral administration containing Omeprazole which specifically does not include alkaline-reacting compounds. Instead, the composition features a core composed of a nuclei and Omeprazole compressed together, an intermediate layer and an enteric layer.

[0008] European Patent Application No. 519,144 discloses a formulation for Omeprazole, which features a neutral (sugar) core. Omeprazole is sprayed onto the sugar core, after which an intermediate coating layer and an enteric coating layer are sprayed onto the core.

[0009] PCT Application No. WO 98/00114 discloses a modification to other background art formulations for Omeprazole, in which the intermediate subcoating layer is partially neutralized with an alkaline compound. However, this modified formulation still features the subcoating layer, which is a disadvantage in that it complicates the manufacturing process and increases the expense and difficulty of manufacture. Thus, the formulation disclosed in PCT Application No. WO 98/00114, like those disclosed in European Patent Application No. 519,144 and other background art references, has the disadvantage of requiring the intermediate layer.

[0010] PCT Application No. WO 83/00435 discloses a solid dosage form, such as a capsule or tablet, containing a pharmacologically active agent coated with an anionic polymer, which is insoluble in gastric juice and in intestinal juice below pH 7. The preferred anionic polymer is a partly methyl esterified methacrylic acid polymer in which the ratio of free carboxylic groups to ester groups is about 1:2. In contrast to the present invention, Omeprazole is not disclosed as one of the active agents.

[0011] French Application No. 2,692,146 discloses stable compositions of microgranules of gastro-protected Omeprazole. The composition features a center of Omeprazole diluted in mannitol. This center is coated with an intermediate layer featuring mannitol. An enteric coating is then added over this intermediate layer. PCT Application No. WO 97/12581 discloses a formulation in which an intermediate layer between the core and an enteric coating contains silicium dioxide.

[0012] PCT Application No. WO 96/37195 discloses a formulation which lacks a subcoating layer, but which features a core containing titanium dioxide. Both the core containing Omeprazole and the enteric coating layer placed on top of the core include titanium dioxide as an ingredient. Unfortunately, titanium dioxide is only able to mask the discoloration caused by the reaction between Omeprazole and the enteric coating layer, but cannot prevent such an undesirable reaction. Thus, the disclosed formulation does not prevent the undesirable reaction between the benzimidazole derivative and the enteric coating, which is known in the art.

[0013] German Patent Application No. 196 26 045 A1 discloses a method for stabilising Omeprazole by coating small tablets or pellets, containing large amounts of mannitol, with a subcoating of Eudragit L. The subcoating of Eudragit L is neutralized, after which a final enteric coat of non-neutralized Eudragit L is applied.

[0014] A formulation of a benzimidazole derivative, such as Omeprazole, which lacks an intermediate coating layer and yet which is stable both during storage and during the passage

through the stomach, is described in U.S. patent application Ser. No. 10/018,992. This formulation involves neutralization of the enteric coating with an alkaline compound, such as ammonium hydroxide. The formulation is simple to manufacture and exposes the sensitive benzimidazole derivative to fewer production steps, thereby decreasing degradation of the active compound during production.

[0015] However, neutralization of enteric coatings with an alkalinizing agent usually results in a certain amount of the alkalinizing agent remaining in the final product. Furthermore, benzimidazole formulations are frequently prepared using volatile organic solvents, a residual amount of which is also found in the final product. Since there is no therapeutic benefit from residual alkalinizing agents and residual solvents, and these may, in fact, have a harmful effect, it is desirable to keep the levels of such residual solvents as low as possible for toxicity/safety reasons.

SUMMARY OF THE INVENTION

[0016] The background art does not teach or suggest a benzimidazole formulation, particularly for Omeprazole, which lacks an intermediate layer and yet which is stable both during storage and during the passage through the stomach, and which has low levels of residual alkalinizing agents and residual solvents.

[0017] The present invention overcomes these drawbacks of the background art by providing a benzimidazole formulation which lacks an intermediate layer and yet which is stable both during storage and during the passage through the stomach, and which has low levels of residual volatile excipients, including but not limited to residual alkalinizing agents and/or residual solvents.

[0018] According to some embodiments of the present invention, there is provided a stable composition for a benzimidazole derivative, the composition comprising a substrate, comprising the benzimidazole derivative; and a single coating layer consisting essentially of at least one neutralized enteric polymer, the enteric polymer having been neutralized by an alkalizing agent. The alkalizing agent is selected from the group consisting of amino alcohols, alkylene diamines, ammonia solution, arginine and lysine. Optionally and preferably there is a single coating layer layered directly over the substrate, without an intermediate layer between the substrate and the enteric coating. The composition comprises less than about 500 parts per million of residual alkalizing agent relative to the total weight of the composition.

[0019] According to some embodiments of the present invention, there is provided a stable composition for a benzimidazole derivative, the composition comprising a substrate comprising the benzimidazole derivative and a single coating layer consisting of one or more enteric polymers treated by at least one volatile alkalizing agent prior to applying over the substrate. The composition comprises less than 500 parts per million of residual volatile alkalizing agents relative to the composition weight, and a pH of the coating layer is in the range of from about 4.5 to about 6.5 as measured in 30 ml of distilled water at 20-25° C.

[0020] Optionally and preferably, the pH is in the range of from about 5 to about 6; more preferably the pH is about 5.

[0021] Optionally and preferably, the alkalizing agent comprises at least one of basic sodium, potassium, methanolamine, ammonium solution (such as ammonium hydroxide), amino alcohols (such as methanolamine, monoethanol amine, or propanolamine, or combinations thereof), arginine, lysine, and alkylene diamines (such as methylene diamine, ethylene diamine, or propylene diamine, or combinations thereof).

[0022] Optionally and preferably, the enteric polymer is dissolved in an organic solvent prior to application. Optionally and preferably, such a composition comprises less than about 1000 parts per million of residual organic solvent.

[0023] Non-limiting examples of organic solvents include acetone, ethanol, isopropanol or a mixture thereof.

[0024] Non-limiting examples of enteric polymers include cellulose acetate phthalate (CAP); hydroxypropyl methylcellulose phthalate (HPMCP); polyvinyl acetate phthalate; cellulose acetate trimellitate; poly((methacrylic acid, methyl methacrylate)1:1) (Eudragit L100™), poly((methacrylic acid, ethyl acrylate)1:1) (Eudragit L30D-55) or Eudragit L100-55™, (poly(methacrylic acid, methyl methacrylate)1:2) Eudragit™ S hydroxypropyl methylcellulose acetate succinate (HPMCAS), sodium alginate, and alginic acid or mixtures thereof.

[0025] Optionally and preferably, the substrate is an active core for containing the benzimidazole derivative, such as, for example, a pellet, a bead or a tablet.

[0026] Optionally and preferably, the active core is a tablet formed by compression.

[0027] According to some embodiments of the present invention, the substrate features a neutral core; and an active coating containing the benzimidazole derivative, wherein the active coating is layered over the neutral core; such that the composition is in a form of a pellet.

[0028] Optionally and preferably, the substrate features a core containing the benzimidazole derivative with a suitable binding agent, the core being prepared by spheronisation and pelletization; such that the composition is in a form of a pellet.

[0029] The benzimidazole is optionally one or more of Omeprazole, Pantoprazole, Lansoprazole, Leminoprazole, Perprazole, Rabeprazole, or pharmaceutically acceptable salts thereof, or combinations thereof.

[0030] Optionally, the substrate further comprises a filler, such as, for example, one or more of microcrystalline cellulose, sodium carboxymethycellulose, ethylcellulose, cellulose acetate, starch, lactose, glucose, fructose, sucrose, dicalcium phosphate, sorbitol, mannitol, mantitol, lactitol, xylitol, isomalt, erythritol, and hydrogenated starch hydrolysates, or a mixture thereof.

[0031] Optionally, the substrate further comprises a disintegrant, such as, for example, one or more of low-substituted carboxymethyl cellulose sodium, cross-linked polyvinyl pyrrolidone, sodium starch glycolate, cross-linked sodium carboxymethyl cellulose, pregelatinized starch, microcrystalline starch, water insoluble starch, calcium carboxymethyl cellulose, and low substituted hydroxypropyl cellulose magnesium aluminum silicate, or a mixture thereof.

[0032] Optionally, the substrate further comprises a lubricant, such as, for example, one or more of sodium stearyl fumarate, polyethylene glycol, silica colloidal anhydrous and magnesium stearate, or a mixture thereof.

[0033] Optionally, the substrate further comprises an alkalinizing agent, such as, for example, one or more of sodium stearate, meglumine, disodium phosphate, and ammonia, or a mixture thereof.

[0034] Optionally, the coating layer further comprises a plasticizer, such as, for example, one or more of a citric acid ester and a phthalic acid ester.

[0035] Optionally, the coating layer further comprises a surfactant, such as, for example, one or more of polysorbate 80 and sodium lauryl sulfate.

[0036] Optionally, the coating layer further comprises a glidant, such as, for example one or more of talc and titanium dioxide.

[0037] Optionally, the coating layer further comprises at least one of a coloring agent and a polishing agent.

[0038] According to some embodiments there is provided a method for preparing a stable composition for a benzimidazole derivative, the method comprising neutralizing one or more enteric polymers with at least one volatile alkalizing agent; and layering the enteric polymer(s) over a substrate comprising the benzimidazole derivative to form a coating layer, the composition comprising the substrate and the coating layer, such that the composition comprises less than 1000 parts per million of residual volatile alkalizing agents relative to composition weight.

[0039] Optionally, the alkalizing agent comprises one or more of amino alcohols, alkylene diamines, arginine, lysine, and ammonia solution.

[0040] According to some embodiments, there is provide a method for preparing a stable composition for a benzimidazole derivative, the method comprising dissolving one or more enteric polymers in an organic solvent; neutralizing the enteric polymer(s) with at least one volatile alkalizing agent; and layering the enteric polymer(s) over a substrate comprising the benzimidazole derivative to form a coating layer, the composition comprising the substrate and the coating layer, such that the composition comprises less than 1000 parts per million of residual solvent relative to composition weight.

BRIEF DESCRIPTION OF THE DRAWINGS

[0041] The invention is herein described, by way of example only, with reference to the accompanying drawings. With specific reference now to the drawings in detail, it is stressed that the particulars shown are by way of example and for purposes of illustrative discussion of the preferred embodiments of the present invention only, and are presented in the cause of providing what is believed to be the most useful and readily understood description of the principles and conceptual aspects of the invention. In this regard, no attempt is made to show structural details of the invention in more detail than is necessary for a fundamental understanding of the invention, the description taken with the drawings making apparent to those skilled in the art how the several forms of the invention may be embodied in practice.

[0042] In the drawings:

[0043] FIGS. **1-6** relate to the suitability of test method for determination of residual monoethanolamine.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0044] The formulation of the present invention contains a benzimidazole derivative, such as Omeprazole, and is able to maintain the stability of this active ingredient without a separating layer between the active compound and an enteric coating layer. Instead, the enteric coating layer is prepared as an aqueous dispersion or in organic solvent and neutralized with an alkalinizing agent, before being applied as a solution directly to the benzimidazole derivative substrate.

[0045] Preferably, the aqueous dispersion has a pH in the range of at least 6.5, and more preferably in the range of from about 7 to about 10.

[0046] After being applied to the substrate, the aqueous dispersion dries to form a coating layer, preferably having a pH in the range of from about 4.5 to about 6.5, and more preferably from about 5 to about 6, as measured in 30 ml of distilled water at 22° C.

[0047] The resulting formulation comprises less than about 500 parts per million of residual alkalizing agent relative to the total weight of the composition.

[0048] Preferably, the composition comprises less than about 1000 parts per million of residual organic solvent and more preferably less than about 500 ppm.

[0049] The resultant formulation maintains the stability of the benzimidazole derivative during storage and at the same time protects the product during passage through the acidic environment of the stomach. The problem of interaction between the enteric coat and the alkaline core is thus completely eliminated as the enteric coat at this stage does not release the free protons that are responsible for its acidic properties. At the same time, the formulation has low levels of residual alkalinizing agent and residual organic solvent in the final product.

[0050] The preparation of the benzimidazole-containing compositions of the present invention is described first with reference to the following general description and then with reference to the following non-limiting examples of the preparation and application of the compositions of the present invention.

[0051] The formulation of the present invention includes a substrate which features the benzimidazole derivative. A coating suspension, which has a pH value of at least 6.5 and more preferably of from about 7 to about 10, is prepared with the enteric coating material. Preferably, a pH value in the desired range is obtained by adding an alkalinizing agent to an enteric coating material

[0052] More preferably, the alkalinizing agent is selected from the group consisting of basic sodium, potassium, methanolamine or ammonium hydroxide, amino alcohols and alkylene diamines, arginine, and lysine. This enteric coating solution is then layered directly over the substrate to form the composition of the present invention.

[0053] The term "substrate" refers to substantially any structure which features the benzimidazole derivative, such as Omeprazole. For example, this structure could be an active core containing the benzimidazole derivative. The active core may comprise, for example, a pellet, a bead, or a tablet. This active core could be prepared in a number of different ways which are known in the art. For example, the active core could be formed by compressing the benzimidazole derivative with an alkaline substance. As another example, the active core could be prepared by mixing the benzimidazole derivative with an alkaline substance, spheronizing the mixture and then forming cores through pelletisation. As yet another example, the active core is optionally and preferably prepared by embedding the active ingredient in a poloxamer and compressing the embedded material into tablets. The active core is also optionally formed by granulating the active ingredient with an alkaline substance and compressing the granulation into tablets.

[0054] Alternatively and optionally, the structure could include a neutral core, such as a sugar bead which does not contain the benzimidazole derivative, over which the benzimidazole derivative is coated. The coating includes Omeprazole or other benzimidazole derivative with a suitable adhesive polymer. The pellet may optionally be prepared by spheronization and pelletization of the benzimidazole derivative and a suitable binding agent.

[0055] The benzimidazole derivative of the present invention may comprise, for example, Omeprazole, Pantoprazole, Lansoprazole, Leminoprazole, Perprazole, or Rabeprazole,

or pharmaceutically acceptable salts thereof. Preferably, the benzimidazole derivative is omeprazole.

[0056] Optionally, the substrate may further comprise a filler. Examples of suitable fillers include microcrystalline cellulose, sodium carboxymethycellulose, ethylcellulose, cellulose acetate, starch, lactose, glucose, fructose, sucrose, dicalcium phosphate, sorbitol, manitol, mantitol, lactitol, xylitol, isomalt, erythritol, and hydrogenated starch hydrolysates, or a mixture thereof.

[0057] Further optionally, the substrate may comprise a disintegrant, such as, for example, low-substituted carboxymethyl cellulose sodium, cross-linked polyvinyl pyrrolidone, sodium starch glycolate, cross-linked sodium carboxymethyl cellulose, pregelatinized starch, microcrystalline starch, water insoluble starch, calcium carboxymethyl cellulose, and low substituted hydroxypropyl cellulose magnesium aluminum silicate, or a mixture thereof.

[0058] Also optionally, the substrate may further comprise a lubricant, such as, for example, sodium stearyl fumarate, polyethylene glycol, silica colloidal anhydrous and magnesium stearate, or a mixture thereof.

[0059] The substrate may optionally further comprises an alkalinizing agent, such as, for example, sodium stearate, meglumine, disodium phosphate, magnesium carbonate, and ammonia, or a mixture thereof.

[0060] Substantially any type of neutralized suitable enteric coating material could be used in order to coat the benzimidazole substrate, including but not limited to, cellulose acetate phthalate (CAP); hydroxypropyl methylcellulose phthalate (HPMCP); polyvinyl acetate phthalate; cellulose acetate trimellitate; poly((methacrylic acid, methyl methacrylate)1:1) (Eudragit L100™), poly((methacrylic acid, ethyl acrylate)1:1) (Eudragit L30D-55) or Eudragit L100-55™, (poly(methacrylic acid, methyl methacrylate)1:2) Eudragit™, hypromellose acetate succinate (HPMCAS), sodium alginate, and alginic acid or mixtures thereof.

[0061] As used herein, the term "neutralized enteric coating material" refers to enteric coating material which has been at least partially neutralized by reaction with an alkalizing agent. Suitable alkalizing agents for neutralizing the enteric polymer include, but are not limited, to amino alcohols such as methanolamine, monoethanol amine, propanolamine and alkylene diamines such as methylene diamine, ethylene diamine, propylene diamine, and ammonia solution such as ammonium hydroxide, basic ammonium salts, arginine, lysine and any other pharmaceutically acceptable amino compound bases, or a combination thereof.

[0062] Preferably, the enteric coating material is at least about 60% neutralized, more preferably the enteric coating material is at least about 80% neutralized, and most preferably the enteric coating material is at least about 95% neutralized.

[0063] The enteric coating is optionally prepared in an organic solvent, such as, for example, acetone, ethanol or isopropanol, or a combination thereof; such as a mixture of ethanol and water (30/70 or 40/60); or a mixture of isopropyl alcohol and ethanol.

[0064] The enteric coating optionally contains at least one of a plasticizer (such, as for example, a citric acid ester or a phthalic acid ester), a surfactant (such as, for example, polysorbate 80 or sodium lauryl sulfate), a glidant (such as, for example, talc or titanium dioxide), a coloring agent and a polishing agent.

[0065] The method for applying the enteric coating material to the substrate can vary. Substantially any coating method can be used, such as pan coating or fluidized bed coating, with the solution of the enteric coat chosen.

[0066] A preferred embodiment of the formulation of the present invention is presented in Example 1 below. Residual akalinizing agent in the coating was analyzed as described in Examples 2 and 3, respectively.

[0067] The following specific examples illustrate various aspects of the compositions of the present invention, and are not intended to be limiting in any way. Specific reference is made to Omeprazole for the purposes of description only and without intending to be limiting.

Examples

Example 1

Delayed Release Tablets, 20 mg OTC Formulation

[0068]

Ingredients	Pharmaceutical function	Amount mg/tablet	Percent/ tablet
Active constituent			
Omeprazole USP	Active	20.00	6.51
Core			
Lactose monohydrate NF	Filler	203.00	66.12
Sodium starch glycolate NF	disintegrant	10.00	3.25
Sodium stearate NF	alkalinizing agent	10.00	3.25
Sodium stearyl fumarate NF	lubricant	7.00	2.28
Coating			
Hypromellose acetate succinate NF	enteric coating polymer	32.00	10.42
Triethyl citrate NF	plasticizer	4.50	1.47
Sodium lauryl sulfate NF	wetting agent	0.50	0.16
Talc USP	Glidant	8.14	2.65
Strong ammonium solution NF	alkalinizing agent	NA*	—
Monoethanolamine NF	alkalinizing agent	1.00	0.33
Sepisperse AP 3527	coloring agent	10.80	3.52
Carnauba wax NF	polishing agent	0.06	0.02
Purified water	Solvent	NA*	—
Total weight		307.00	Ca 100

*strong ammonium solution is used as a volatile alkalizing agent which is evaporated during the coating process.

[0069] Preparation of the substrate: Omeprazole was thoroughly mixed with lactose, sodium starch glycolate, sodium stearate and sodium stearyl fumarate. The mixture was then compressed into tablets weighing 250 mg each. The tablets were then transferred into a conventional coating pan and coated with the enteric coating, prepared as described below.

Preparation of Enteric Coating

[0070] Coating A: triethyl citrate was dissolved in water, sodium lauryl sulfate was then added to this solution, HPMCAS and talc were dispersed in this solution, such that the concentration of HPMCAS was about 7% weight per volume. Monoethanolamine was added to this dispersion. Ammonia in a 25% solution was added to adjust the pH value in a range of from about 7 to about pH 9. The pigment was then added to the enteric coating dispersion.

[0071] Coating B: Triethyl citrate was dissolved in a mixture of isopropyl alcohol and alcohol, sodium lauryl sulfate was then added to this solution, HPMCAS and talc were dispersed in this solution, such that the concentration of

HPMCAS was about 6% weight per volume. Ammonia in a 25% solution was added to adjust the pH value in a range of from about 7 to about pH 9. The pigment was then added to the enteric coating dispersion. The tablet cores were then transferred into a conventional coating pan and coated with the enteric coating layer.

[0072] Coating C: Triethyl citrate was dissolved in water to form an aqueous solution; sodium lauryl sulfate was then added to this aqueous solution. HPMCAS, colloidal silicon dioxide and talc were dispersed in this solution, such that the concentration of HPMCAS was about 7% weight per volume. Ammonia in a 25% solution was added to adjust the pH value of the coating dispersion in a range of from about 7 to about pH 9.

[0073] Coating D: Triethyl citrate was dissolved in water to form an aqueous solution; sodium lauryl sulfate was then added to this aqueous solution. HPMCAS, talc, and monoethanolamine were dispersed in this solution. Ammonia in a 25% solution was added to adjust the pH value of the coating dispersion in a range of from about 7 to about pH 9.

Example 2

Omeprazole Delayed Release Tablets 20 mg—Determination of Ammonia

[0074] Samples were stored at room temperature prior to analysis.

[0075] The samples were analyzed according to Standard Methods for Examination of Water and Waste Water, Ed. 19, 1995, Method 4500-NH_3 F (phenate method). The samples were prepared in triplicate by adding 30 ml HPLC grade water to one tablet, shaking overnight on an inverting shaker, followed by centrifugation at 4000 rpm for 15 minutes. This solution was filtered through 2 layers of glass fiber cartridge (GFC) filters and analyzed according to the above mentioned method. Quantitation was performed using a calibration curve prepared from solutions of NH_4Cl in water in the concentration range of 0.05 μg/mL to 1.0 μg/mL NH_3. The uncoated tablets served as a control sample for the analysis of the coated tablets.

[0076] Results are presented in Table 1.

TABLE 1

Lab no.	Batch No. (based on Example 1)	NH_3 mg/tablet
3789	BO415 (coated)	0.011; 0.07; 0.011 Mean 0.010
3980	BO425 (coated)	0.09; 0.010; 0.010 Mean 0.010
3981	BO515 (coated)	0.010; 0.012; 0.011 Mean 0.011

Example 3

Omeprazole Delayed Release Tablet 20 mg—Determination of Residual Monoethanolamine

[0077] Samples were stored at room temperature prior to analysis.

Materials	
Dansyl chloride	Across 1158500
Sodium hydrogen carbonate	Merck 106329
Acetone	J. T. Baker 9002
Acetonitrile	J. T. Baker 9017

-continued

Materials	
Sodium hydroxide	J. T. Baker 3722
Water HPLC grade	Milli-Q in-house
Monoethanolamine	Analyst sample 5015
Hydrochloric acid	Riedel de Haen 30721

Equipment	
Test tubes PP 50 ml	
Laboratory glassware Class A	
GFC filter paper 12.5 cm	Whatman 1822-125
Shaker	Heidolf
Centrifuge capable of maintaining 4000 rpm	

HPLC instrument and conditions	
Apparatus:	Agilent 1100 with variable wavelength detector and autosampler and Chemstation Rev A 10.01 software
Column:	Symmetry C 18 4.6 × 150 mm, 3.5 μ
Injection volume:	10 μL
Flow rate:	1.0 mL/min
Detection:	254 nm
Column temperature:	ambient
Run time:	10 minutes
Retention time of MEA derivative:	~5.3 minutes

Solutions

[0078] Hydrochloric acid 4 N was prepared by mixing 83.3 mL of concentrated hydrochloric acid (specific gravity 1.19, 37%) with 200 mL water in a 250 mL volumetric flask. The volume was made up with water.

[0079] Dilute hydrochloric acid was prepared by adding 1.2 mL hydrochloric acid (specific gravity 1.19, 37%) to a 1 L volumetric flask containing about 500 mL water, diluting to volume with water and mixing well.

[0080] Mobile phase was prepared by mixing 600 mL of water with 400 mL acetonitrile, mixing well and sonicating to degas.

[0081] 0.2% dansyl chloride was prepared by weighing accurately about 100 mg dansyl chloride in a 50 mL volumetric flask and diluting with acetone.

[0082] 0.1 M sodium hydrogen carbonate was prepared by weighing about 840 mg of sodium hydrogen carbonate into a 100 mL volumetric flask, diluting with water to give a pH of 9.0.

[0083] Monoethenolamine standard stock solution (1000 μg/mL) was prepared in duplicate by weighing accurately about 100 mg of monoethanolamine into a 100 ml volumetric flask, dissolving and diluting with water.

[0084] Monoethanolamine intermediate standard stock solution (100 μg/mL) was prepared by adding 5.0 mL standard stock solution to a 50 mL volumetric flask with dilute hydrochloric acid.

[0085] Monoethanolamine working standard solution (10 μg/mL) was prepared from intermediate standard stock solution by adding 5.0 mL to a 50 mL volumetric flask with dilute hydrochloric acid.

Sample Preparation

[0086] Samples were prepared in duplicate. One tablet was placed per 50 mL conical test tube and 50 mL of water added. Test tubes were placed on an inverting shaker at speed 6 for 2-3 hours, until disintegration of the tablets, then acidified by adding 200 μL of 4 N HCl. Test tubes were centrifuged for 15 minutes at 4000 rpm and filtered through Whatman GFC.

Derivatization Reaction

[0087] The procedure was performed on water as control and on all standards and samples, directly in autosampler vials.

[0088] 100 μL of water, standard or sample solution was mixed with 200 μL 0.2% dansyl chloride solution. 400 μL 0.1 M sodium hydrogen carbonate and 400 μL acetone were added. The vials were closed, mixed and heated for 20 minutes in a water bath at 60° C. The contents of the vials were cooled to room temperature and injected into the HPLC system.

[0089] Results are presented in Table 2.

TABLE 2

Lab no.	Sample name	Monoethanolamine mg/tablet
3789	BO415	0.77 (% RSD = 6.0)
3980	BO425	0.730; 0.681 Mean 0.71
3981	BO515	0.822; 0.755 Mean 0.79
5273	BO615	0.908; 0.780 Mean 0.84

Example 4

Suitability of Test Method for Determination of Residual Monoethanolamine

[0090] In order to evaluate the suitability of the method as described above, the method was evaluated for specificity, linearity, precision (system and method) and recovery.

[0091] In order to demonstrate the specificity, the following samples and solutions were analyzed: a sample blank (water); a standard containing 10 μg/mL monoethanolamine that had undergone the derivatization procedure; omeprazole tablets, prepared without the use of monoethanolamine, prepared according to the test method; and water.

Specificity

[0092] As shown in FIGS. **1** to **6**, no interfering peaks at the retention time of monoethanolamine were recorded in the chromatograms of the blank sample, water, or the tablet without monoethanolamine.

Linearity

[0093] The linearity of the method was demonstrated in the range of from 1 to 50 μg/mL monoethanolamine, corresponding to 0.05 to 2.5 mg/tablet. Results are presented in Table 3.

TABLE 3

Concentration (μg/mL)	Peak area mAU*s	% difference
0/96	7.4978E±00	43.7
1.92	1.5817E±01	10.9
4.81	4.4112E±01	−2.5
9.62	9.2365E±01	−6.0
19.24	2.0443 ± 02	−0.4
48.10	5.2640 ± 02	0.3

TABLE 3-continued

Concentration (μg/mL)	Peak area mAU*s	% difference
correlation	0.99982	
square correlation	0.99963	
slope	1.1074E+01	
intercept	−7.8104E+00	−7.6

Precision

[0094] The precision of the method was evaluated by replicate injections of a standard containing a nominal 10 μg/mL monoethanolamine derivatized according to the test method (system precision) and by preparing a sample of omeprazole tablets in 6 independent replicates according to the test method (method precision).

[0095] The system precision results as presented in Table 4 show that good precision was obtained for the peak areas as well as for the retention times.

TABLE 4

Replicate	Retention time (min)	Peak areas mAU*s
1	5.291	9.0628E+01
2	5.286	8.9055E+01
3	5.283	9.1252E+01
4	5.283	8.8879E+01
5	5.262	8.9296E+01
6	5.225	9.0930E+01
Mean	5.272	9.0007E+01
% RSD	0.5	1.2

[0096] Method precision was performed using 6 preparations of omeprazole tablets (analyst sample 3789). Results were calculated against a standard containing 9.62 μg/mL monothenaolamine with an average peak area of 9.5519E+01 mAU*s, using the following formula:

$$\text{mg/tablet} = \frac{\text{area } smp \times Cst \times 50}{\text{area } st \times 1000}$$

[0097] area smp=monoethanolamine peak area in sample chromatogram

[0098] area st=average peak area of standard "10 μg/mL"

[0099] cst=standard concentration in μg/mL

[0100] 50=sample extraction volume (mL)

[0101] 1000=conversion factor of μg to mg

[0102] A representative chromatogram is presented in FIG. **5**.

[0103] Method precision data and results are presented in Table 5.

TABLE 5

Analyst no. and replicate	Sample name	MEA peak area mAU*s	Concentration of MEA in sample solution (μg/mL)	MEA in tablets mg/tablet
3789-1	coated	1.4518E+0.2	14.6	0.731
3789-2	BO4 15	1.6711E+0.2	16.8	0.842
3789-3		1.4151E+0.2	14.3	0.713
3789-4		1.5385E+0.2	15.5	0.775
3789-5		1.5710E+0.2	15.8	0.791
3789-6		1.5804E+0.2	15.9	0.796
MEAN				0.774
% RSD				6.0

Recovery

[0104] The recovery of the method was demonstrated by spiking control (no monoethanolamine) and monoethanolamine-containing omeprazole tablets with three levels of monoethanolamine.

[0105] Omeprazole tablets containing monoethanolamine (sample 3789, batch BO415) were spiked at the 0.1% w/w level in triplicate. Omeprazole control tablets (no MEA) were spiked at three levels with 0.15, 0.3 and 0.9 mg/tablet, corresponding to 0.05, 0.1 and 0.3% w/w. The test was performed by transferring the tablets to 50 mL test tubes, adding suitable volumes of a solution of 1000 μg/mL MEA, followed by 50 ml of water and preparation according to the method described above.

[0106] Results as presented in Tables 6 and 7 show good recovery results, within generally accepted limits for residue analysis. Recovery results were calculated against a standard containing 9.62 μg/mL MEA with an average peak area of 9.5519E+01 mAU*s. The recovery results in the tablets containing MEA were calculated as follows:

$$\%\ \text{recovery} = \frac{\text{mg/tablet found} \times 100}{\text{average mg/tablet (unspiked)} + \text{mg/tablet added}}$$

[0107] A representative chromatogram of omeprazole tablets (analyst sample 3789 Batch BO415) spiked with MEA is presented in FIG. **6**.

TABLE 6

Analyst No. and replicate	Sample name	MEA peak area (mAu*s)	Spiking level in mg/tablet	Concentration of MEA in sample solution (μg/mL)	MEA in tablets	% recovery
5274-1	omeprazole	0.0000E+00		0.0	0.000	
5274-2	20 mg	0.0000E+00		0.0	0.000	
5274-3	uncoated 100605	0.0000E+00		0.0	0.000	
Mean					0.000	
5274-1	omeprazole	2.4417E+0.1	0.144	2.46	0.123	85.5
5274-2	20 mg	2.4339E+01		2.45	0.123	85.2
5274-3	uncoated 100605	2.4966E+01		2.51	0.126	87.4
Mean					0.124	86.0
% RSD					1.4	1.4
5274-1+0.1%	omeprazole	4.9693E+01	0.289	5.00	0.252	87.2
5274-2+0.1%	20 mg	5.1115E+01		5.15	0.259	89.7
5274-3+0.1%	uncoated 100605	5.1356E+01		5.17	0.260	90.1
Mean					0.257	89.0
% RSD					1.8	1.8
5274-1+0.3%	Omeprazole	1.845E+02	0.962	18.59	0.948	98.5
5274-2+0.3%	20 mg	1.8919E+02		19.05	0.972	101.0
5274-3+0.3%	uncoated 100605	1.8982E+02		19.12	0.975	101.4
Mean					0.965	100.3
% RSD					1.5	1.5

TABLE 7

Analyst No. and replicate	Sample name	MEA peak area mAU*s	Spiking level mg/tablet	Concentration of MEA in sample solution μg/mL	MEA in tablet mg/tablet	% recovery
3789-1	coated	1.4518E+02		14.6	0.731	
3789-2	BO415	1.6711E+02		16.8	0.842	
3789-3		1.4151E+02		14.3	0.713	
Mean					0.762	
% RSD					9.2	
3789-1+0.1%	coated	2.1507E+0.2	0.289	21.7	1.083	107.6
3789-2+0.1%	B0415	2.1576E+0.2		21.7	1.086	107.9
3789-3+0.1%		2.3641E+0.2		23.8	1.1190	118.2
Mean					1.120	111.2
% RSD					5.5	5.5

Standard and Sample Solution Stability

[0108] During the method development, stock solution stability was demonstrated for 48 hours at room temperature. In addition, it was found that the MEA derivative is stable in autosampler vials at room temperature for at least 48 hours, because the response of the MEA derivative did not change upon reinjection.

Example 5

Omeprazole Delayed Release Tablets 20 mg—Determination of Final pH of Enteric Coating

[0109] Enteric coated omeprazole tablets were prepared according to the composition of Example 1 (Batch #B0425). The enteric coating was prepared in aqueous dispersion, and the pH value of the coating dispersion was adjusted to the range from about 7 to about pH 9 by a combination of monoethanolamine and concentrated ammonia solution. The ammonia solution evaporated during the coating process.

[0110] The pH of the coating layer following evaporation of the ammonia solution was measured in the following test solutions:

[0111] 1. Purified water (pH 5.9 at 22° C.), obtained from MILI Q system; and

[0112] 2. 1% buffer solution of Intestinal Fluid NF (pH 6.9 at 22° C.) using potassium dihydrogenphosphate (lot #B36148 purchased from Baker), and sodium hydroxide (lot #B452998549 from Merck), with no pancreatin added.

[0113] For each test solution, three coated tablets were split and the core was removed by washing using purified water. The resulting film coats were then transferred into a vial containing 30 ml test solution, and stirred for 2 hours with a magnetic stirrer at 1000 rpm. The pH of the medium was determined.

[0114] It was found that in purified water, the coating films partially disintegrated and partially dissolved. The pH value of the medium was found to be 5.4.

[0115] In intestinal fluid, the coating films were fully disintegrated and fully dissolved (except for talc and the coloring powder of Sepisperse). The pH value of the medium was found to be 5.3. Hence, it is shown that the polymer retains its acidic properties and thus provides an acidic reaction.

[0116] Since the pH of the coating solution was initially basic, it can be concluded that the change in pH occurs due to evaporation of ammonia solution, causing the polymer, hydroxypropyl methylcellulose acetate succinate (HPMCAS) to revert to its acid form, having enteric properties. The acidic form of HPMCAS can be soluble in water only through ionization of all free acidic groups in an aqueous medium with pH values above 5.5. This is in fact the reason that the polymer is characterized as an enteric polymer. While the native pH value of pure HPMCAS aqueous dispersion is about 4.5, the pH value of about 5.3 found using the composition of the present invention may be due to the presence of residual monoethanolamine, which is used a second alkalizing agent for neutralization of HPMCAS.

[0117] The present study shows that when the entering coating polymer is placed in purified water as test medium, a partial dissolution of the polymer first takes place, which continues for as long as the pH of the medium remains basic. Once the pH of the medium reaches an acidic value of about 5.4, dissolution of the polymer stops and the polymer disintegrates. In diluted neutral buffer solution-1% simulated intestinal fluid, on the other hand, an acidic pH was achieved only after full polymer dissolution.

[0118] The temporarily neutralized HPMCAS coating prepared using a high concentration of ammonia during the coating process provides an enteric film coat surrounding the omeprazole-containing cores which can withstand pH values of up to about 5. This can provide the active material with an appropriate protection while passing through the stomach even if the pH values of gastric fluid are elevated.

[0119] It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination.

[0120] Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad scope of the appended claims. All publications, patents and patent applications mentioned in this specification are herein incorporated in their entirety by reference into the specification, to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference. In addition, citation or identification of any reference in this application shall not be construed as an admission that such reference is available as prior art to the present invention.

1. A stable composition for a benzimidazole derivative, the composition comprising:

a substrate, said substrate comprising the benzimidazole derivative; and

a single coating layer consisting essentially of at least one neutralized enteric polymer, wherein said enteric polymer is neutralized to a pH of at least 6.5 by at least two alkalizing agents prior to applying to said substrate, wherein said at least two alkalizing agents are is selected from the group consisting of amino alcohols, alkylene diamines, ammonia solution, arginine and lysine, said single coating layer layered directly over said substrate, without an intermediate layer between said substrate and said enteric coating,

wherein said composition comprises less than about 500 parts per million of residual alkalizing agent relative to the total weight of the composition.

2. A stable composition for a benzimidazole derivative, the composition comprising:

a substrate, said substrate comprising the benzimidazole derivative and

a single coating layer consisting of one or more enteric polymers treated by at least one volatile alkalizing agent prior to applying over the substrate to give a pH of at least 6.5;

wherein said composition comprises less than 500 parts per million of residual volatile alkalizing agents relative to composition weight,

and wherein a pH of said coating layer after being applied to said substrate is in the range of from about 4.5 to about 6.5 as measured in 30 ml of distilled water at 20-25° C.

3. The composition of claim **2**, wherein said pH of said coating layer after being applied to said substrate is in the range of from about 5 to about 6.

4. The composition of claim **3**, wherein said pH is about 5.

5. The composition of claim **1**, wherein said alkalizing agent is selected from the group consisting of basic sodium,

potassium, methanolamine, ammonium solution, amino alcohols, arginine, lysine, and alkylene diamines.

6. The composition of claim **5**, wherein said amino alcohol is selected from the group consisting of methanolamine, monoethanol amine, and propanolamine.

7. The composition of claim **5**, wherein said alkylene diamine is selected from the group consisting of methylene diamine, ethylene diamine, and propylene diamine.

8. The composition of claim **5**, wherein said ammonium solution comprises ammonium hydroxide.

9. The composition of claim **1**, wherein said enteric polymer is dissolved in an organic solvent prior to application.

10. The composition of claim **9**, comprising less than about 1000 parts per million of residual organic solvent.

11. The composition of claim **9**, wherein said organic solvent is selected from the group consisting of acetone, ethanol, isopropanol and a mixture thereof.

12. The composition of claim **1**, wherein said enteric polymer is selected from the group consisting of cellulose acetate phthalate (CAP); hydroxypropyl methylcellulose phthalate (HPMCP); polyvinyl acetate phthalate; cellulose acetate trimellitate; poly((methacrylic acid, methyl methacrylate)1:1) (Eudragit L100™), poly((methacrylic acid, ethyl acrylate)1:1) (Eudragit L30D-55) or Eudragit L100-55™, (poly(methacrylic acid, methyl methacrylate)1:2) Eudragit™ S hydroxypropyl methylcellulose acetate succinate (HPMCAS), sodium alginate, and alginic acid or mixtures thereof.

13. The composition of claim **1**, wherein said substrate is an active core for containing the benzimidazole derivative.

14. The composition of claim **13**, wherein said active core is selected from the group consisting of a pellet, a bead and a tablet.

15. The composition of claim **14**, wherein said active core is a tablet formed by compression.

16. The composition of claim **1**, wherein said substrate features:

(i) a neutral core; and

(ii) an active coating containing the benzimidazole derivative, said active coating being layered over said neutral core;

such that the composition is in a form of a pellet

17. The composition of claim **1**, wherein said substrate features a core containing the benzimidazole derivative with a suitable binding agent, said core being prepared by spheronisation and pelletization; such that the composition is in a form of a pellet.

18. The composition of claim **1**, wherein the benzimidazole derivative is selected from the group consisting of Omeprazole, Pantoprazole, Lansoprazole, Leminoprazole, Perprazole, Rabeprazole, and pharmaceutically acceptable salts thereof.

19. The composition of claim **1**, wherein said substrate further comprises a filler.

20. The composition of claim **19**, wherein said filler is selected from the group consisting of microcrystalline cellulose, sodium carboxymethycellulose, ethylcellulose, cellulose acetate, starch, lactose, glucose, fructose, sucrose, dicalcium phosphate, sorbitol, manitol, mantitol, lactitol, xylitol, isomalt, erythritol, and hydrogenated starch hydrolysates, or a mixture thereof.

21. The composition of claim **1**, wherein said substrate further comprises a disintegrant.

22. The composition of claim **21**, wherein said disintegrant is selected from the group consisting of low-substituted carboxymethyl cellulose sodium, cross-linked polyvinyl pyrrolidone, sodium starch glycolate, cross-linked sodium carboxymethyl cellulose, pregelatinized starch, microcrystalline starch, water insoluble starch, calcium carboxymethyl cellulose, and low substituted hydroxypropyl cellulose magnesium aluminum silicate, or a mixture thereof.

23. The composition of claim **1**, wherein said substrate further comprises a lubricant.

24. The composition of claim **23**, wherein said lubricant is selected from the group consisting of sodium stearyl fumarate, polyethylene glycol, silica colloidal anhydrous and magnesium stearate, or a mixture thereof.

25. The composition of claim **1**, wherein said substrate further comprises an alkalinizing agent.

26. The composition of claim **25**, wherein said alkalinizing agent is selected from the group consisting of sodium stearate, meglumine, disodium phosphate, and ammonia, or a mixture thereof.

27. The composition of claim **1**, wherein said coating layer further comprises a plasticizer.

28. The composition of claim **24**, wherein said plasticizer is selected from the group consisting of a citric acid ester and a phthalic acid ester.

29. The composition of claim **1**, wherein said coating layer further comprises a surfactant.

30. The composition of claim **29**, wherein said surfactant is selected from the group consisting of polysorbate 80 and sodium lauryl sulfate.

31. The composition of claim **1**, wherein said coating layer further comprises a glidant.

32. The composition of claim **31**, wherein said glidant is selected from the group consisting of talc and titanium dioxide.

33. The composition of claim **1**, wherein said coating layer further comprises at least one of a coloring agent and a polishing agent.

34. A method for preparing a stable composition for a benzimidazole derivative, comprising:

neutralizing one or more enteric polymers to a pH of at least 6.5 with at least one volatile alkalizing agent; and

layering said one or more enteric polymers over a substrate comprising the benzimidazole derivative to form a coating layer, the composition comprising said substrate and said coating layer, such that the composition comprises less than 1000 parts per million of residual volatile alkalizing agents relative to composition weight.

35. The method of claim **34**, wherein said at least one alkalizing agent comprises one or more of amino alcohols, alkylene diamines, arginine, lysine, and ammonia solution.

36. A method for preparing a stable composition for a benzimidazole derivative, comprising:

Dissolving one or more enteric polymers in an organic solvent;

neutralizing said one or more enteric polymers to a pH of at least 6.5 with at least one volatile alkalizing agent; and

layering said one or more enteric polymers over a substrate comprising the benzimidazole derivative to form a coating layer, the composition comprising said substrate and said coating layer, such that the composition comprises less than 1000 parts per million of residual solvent relative to composition weight.

37. The method of claim **36**, wherein said neutralizing said one or more enteric coating layers comprises forming an enteric polymer suspension having a pH value of at least about 6.5.

38. The method of claim **37**, wherein said pH value of said enteric polymer suspension is from about 7 to about 10.

39. The method of claim **1**, wherein said pH is in the range of from about 7 to about 10.

40. A stable composition for a benzimidazole derivative, the composition comprising:

a substrate, said substrate comprising the benzimidazole derivative; and

a single coating layer consisting essentially of at least one neutralized enteric polymer, wherein said enteric polymer is neutralized to a pH of at least 6.5 by at least two alkalizing agents prior to applying to said substrate, wherein at least one of said at least two alkalinizing agents is a volatile alkalinizing agent and at least one of said at least two alkalinizing agents is a non-volatile alkalinizing agent,

said single coating layer layered directly over said substrate, without an intermediate layer between said substrate and said enteric coating,

wherein said composition comprises less than about 500 parts per million of residual alkalizing agent relative to the total weight of the composition.

41. The composition of claim **40**, wherein at least one of said alkilizing agents is selected from the group consisting of amino alcohols, alkylene diamines, arginine and lysine.

42. The composition of claim **40**, wherein at least one of said alkilizing agents is ammonia.

* * * * *