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(54) Titre : COMPOSITION DE COMPRIMES A MULTIPLES UNITES DE COMPOSES DE BENZIMIDAZOLE
(54) Title: MULTIPLE UNIT TABLET COMPOSITIONS OF BENZIMIDAZOLE COMPOUNDS

(57) Abrégé/Abstract:
The present invention relates to multiple unit tablet compositions of benzimidazole compounds and process of preparation thereof. The compositions are useful against various gastrointestinal disorders. The multiple unit tablet composition comprises: a) tablet excipients, and b) multiple enteric coated core units containing a benzimidazole compound, wherein each core unit is covered with an enteric coating layer comprising a plasticizer in an amount of less than 15% by weight of the enteric coating layer polymer.

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(54) Title: MULTIPLE UNIT TABLET COMPOSITIONS OF BENZIMIDAZOLE COMPOUNDS

(57) Abstract: The present invention relates to multiple unit tablet compositions of benzimidazole compounds and process of preparation thereof. The compositions are useful against various gastrointestinal disorders. The multiple unit tablet composition comprises: a) tablet excipients, and b) multiple enteric coated core units containing a benzimidazole compound, wherein each core unit is covered with an enteric coating layer comprising a plasticizer in an amount of less than 15% by weight of the enteric coating layer polymer.

MULTIPLE UNIT TABLET COMPOSITIONS OF BENZIMIDAZOLE COMPOUNDS

Field of the Invention

The present invention relates to multiple unit tablet compositions of benzimidazole compounds and process of preparation thereof. The compositions are useful against various gastrointestinal disorders.

Background of the Invention

Benzimidazole compounds such as omeprazole, lansoprazole, pantoprazole, rabeprazole or single enantiomers thereof are strong inhibitors of proton pump and thus are widely used as therapeutic agents for stomach ulcer, duodenal ulcer, gastro esophageal reflux disorders etc. by inhibiting gastric acid secretion.

The single isomers of corresponding benzimidazole compounds are reported to be more useful in therapy compared to the racemic benzimidazole compounds. U.S. Patent No. 5,877,192 describes the use of the (-)-enantiomer of omeprazole (esomeprazole), or a pharmaceutically acceptable salt thereof, in the treatment of gastric acid related diseases.

Because of the instability of benzimidazole compounds under neutral and acidic environment, moisture, heat, organic solvents and to some degree by light, numerous approaches have been tried to form a stable pharmaceutical formulation comprising a benzimidazole compound. Most oral benzimidazole preparations are enteric-coated, due to the rapid degradation of the drug in the acidic conditions of the stomach. This is most commonly achieved by formulating multiple unit formulations i.e. enteric-coated granules within capsules, enteric-coated granules compressed into tablets etc., and single unit enteric-coated tablets.

The pharmacokinetics of the two formulations differ considerably. The multiple unit formulation (capsules or tablets) is usually emptied gradually from the stomach into the intestine. In contrast to this, the single unit tablet will enter the intestine and dissolve as one unit. Further, the enteric- coated pellets of the multiple unit formulations disperse readily in contact with fluid, and are therefore suitable for patients with swallowing difficulties (can be dispersed in water or juice and the contents taken orally by the patient) or for patients with feeding tubes. Among the multiple unit formulations, tablets offer the

advantage of good mechanical stability and being more tamper-resistant than capsules, which is an important consideration in OTC settings.

U.S. Patent Nos. 4,786,505 and 4,853,230 teach compositions of benzimidazole compounds having an alkaline core, separating layer and enteric coating.

When preparing multiple unit tablets, the application of compression forces to the tablet mixture comprising enteric-coated particles present a problem with respect to the strength of the coating and specifically the requirement to maintain the gastro-resistance and the integrity of the tablet and of the enteric- coated units after tableting.

It is known that the film-forming agents generally used to coat particles cannot under normal conditions absorb the mechanical stresses applied during tableting. Films composed of only enteric polymers or copolymers have very mediocre mechanical properties, such that they do not withstand tableting. The application of these compression forces can result in the appearance of cracks in the enteric coating film or by the splitting thereof, resulting in the partial or complete loss of the properties of the film coating.

The prior art provides solutions such as for example modifying the composition of the enteric coating films, so as to substantially improve its mechanical characteristics with regard to tableting properties, i.e. to withstand the application of compression forces. Improvements in gastro-resistance and less film damage can also be achieved by using excipients that deform plastically during tableting. Alternative solutions consist of diluting/mixing the enteric-coated particles with auxiliary substances, which substances can absorb the physical stresses during tableting.

The document "Drugs made in Germany", 37(2) p. 53 (1994) teaches combination of Eudragit®. L30D and Eudragit®. NE30D to produce multiparticulate tablets comprising the enteric coated particles.

European Patent No. 0 723 436 B1 teaches an oral pharmaceutical multiple unit tableted dosage form comprising tablet excipients and individually enteric coating layered units of a core material containing active substance in the form of omeprazole or one of its single enantiomers, the core material being covered with one or more layer(s), of which at least one is an enteric coating layer, characterized in that the enteric coating layer comprises a plasticizer in the amount of 20 - 50% by weight of the enteric coating layer

polymer. This patent teaches that the enteric coating layer contains pharmaceutically acceptable plasticizers to obtain the desired mechanical properties, such as flexibility and hardness of the enteric coating layers. The amount of the plasticizer is optimized for each enteric coating layer formula, in relation to selected enteric coating layer polymer, selected plasticizer and the applied amount of said polymer, in such a way that the mechanical properties, i.e. flexibility and hardness of the enteric coating layer are adjusted so that the acid resistance of the pellets covered with enteric coating layer does not decrease significantly during the compression of pellets into tablets.

European Patent No. 0 723 437 B1 teaches an oral pharmaceutical multiple unit tableted dosage form of an acid labile H^+K^+-ATPase inhibitor or one of its single enantiomers, the core material being covered with one or more layer(s) of which at least one is an enteric coating layer, characterized in that the enteric coating layer has a thickness of at least 10 µm and said layer comprises a plasticizer in an amount of 15 - 50 % by weight of the enteric coating layer polymer.

European Patent Application No. 0 723 777 A1 teaches a tablet containing enteric granules prepared by tabletting a mixture of enteric granules with at least one member selected from the group consisting of synthetic hydrotalcite, dried aluminium hydroxide gel, a coprecipitate of aluminium hydroxide with sodium hydrogencarbonate, aluminium magnesium hydroxide, synthetic aluminium silicate and dihydroxyaluminium aminoacetate. The enteric-coated granules include a plasticizer, preferably added during formulation of the coating to be coated on the granules, at 15-40% w/w, and preferably 30-40 % w/w with respect to the total amount of the enteric coating.

PCT Application No. WO 02/19991 teaches a multiparticulate dosage form, produced from particles compressed with conventional binding agents. Said particles contain a pharmaceutical active ingredient and are covered with a gastric juice resistant coating consisting of a methacrylate copolymer and more than 15 and up to 50 wt % of the plasticizer propylene glycol in relation to the methacrylate copolymer.

U.S. Patent Application No. 2006/0018964 discloses a multiparticulate tablet comprising a pharmaceutically active substance in the form of enteric-coated particles, and a mixture of tableting excipients, wherein the mixture of excipients comprises: a first diluent selected from the group consisting of xylitol, maltitol, and mixtures thereof,

wherein the first diluent is in a directly compressible form; a disintegrating agent; a lubricant; and at least one other diluent, and wherein the ratio of a) the first diluent to b) the other diluent(s) is less than 5/95 (weight/weight). The enteric coating composition can also comprise a plasticizer. The plasticizer is usually used in a total proportion of at most 40%, preferably between 10% and 30%, expressed by weight with respect to the dry weight of polymer. However, the examples disclosed in this patent application state that the enteric coated microgranules are manufactured according to the teaching of the prior art WO 96/01623 (PCT application corresponding to EP 0 723 436 B1).

However, there is still a need for development of new enteric coating layered multiple unit preparations with good mechanical and chemical stability. We have surprisingly found that multiple unit tablets of benzimidazole compounds having desired mechanical properties and good acid resistance can be prepared by using a plasticizer in the enteric coating layer in an amount lower than that disclosed in the prior art.

Summary of the Invention

Multiple unit tablet compositions of benzimidazole compounds are disclosed.

According to one embodiment the multiple unit tablet composition comprises: a) one or more tablet excipients, and b) a multiple of enteric coating layered core units containing a benzimidazole compound, wherein each core unit is covered with an enteric coating layer comprising a plasticizer in an amount of less than 15% by weight of the enteric coating layer polymer.

According to another embodiment the multiple unit tablet composition comprises: a) one or more tablet excipients, and b) a multiple of enteric coating layered core units containing a benzimidazole compound, wherein each core unit is covered with an enteric coating layer comprising a plasticizer in an amount ranging from 8% to 14% by weight of the enteric coating layer polymer.

According to still another embodiment the multiple unit tablet composition comprises: a) one or more tablet excipients, and b) a multiple of enteric coating layered core units containing a benzimidazole compound, wherein each core unit is covered with an enteric coating layer comprising a plasticizer in an amount of less than 15% by weight

of the enteric coating layer polymer and the enteric coating layer is further covered by an over-coating layer.

According to further embodiment the multiple unit tablet composition comprises: a) one or more tablet excipients, and b) a multiple of enteric coating layered core units containing a benzimidazole compound, wherein each core unit is covered with an enteric coating layer comprising a plasticizer in an amount ranging from 8% to 14% by weight of the enteric coating layer polymer and the enteric coating layer is further covered by an over-coating layer comprising a plasticizer in an amount ranging from 0-30% by weight of the enteric coating layer polymer.

According to further embodiment the process of preparation of multiple unit tablet composition of the present invention is disclosed.

Detailed Description of the Invention

The term benzimidazole compound used herein refers to any of the compounds belonging to the category of benzimidazole used for gastrointestinal disorders and may be selected from omeprazole, lansoprazole, rabeprazole, pantoprazole, leminoprazole and pariprazole, including their single enantiomers, pharmaceutically accepted salts, solvates and mixtures. For example, the benzimidazole compound may be esomeprazole in the form of a pharmaceutically acceptable alkaline salt such as esomeprazole calcium or esomeprazole magnesium. The benzimidazole compound may be either in the crystalline or amorphous form.

The core may be in the form of pellets, granules or beads. The core may be acidic, alkaline or neutral depending on the type of formulation. The core may contain one or more pharmaceutically acceptable excipients selected from the group consisting of inert carriers, binders, diluents, disintegrants, lubricants/glidants, solubilizers/wetting agents and mixtures thereof. The inert carrier may be coated with the benzimidazole compound and one or more of the binders, diluents, disintegrants, lubricants/glidants, solubilizers/wetting agents and mixtures thereof.

The inert carrier may comprise starch, microcrystalline cellulose or sugar sphere such as nonpareil sugar seeds.

Generally the diluents may be selected from one or more of sugars like dextrose, glucose, lactose; sugar alcohols like sorbitol, xylitol, mannitol; cellulose derivatives like powdered cellulose, microcrystalline cellulose; starches like corn starch, pregelatinized starch, maize starch and mixtures thereof.

Generally the binders are selected from one or more of cellulose derivatives like hydroxypropylmethyl cellulose, hydroxypropyl cellulose, methylcellulose; gums like xanthan gum, gum acacia, tragacanth; water-soluble vinylpyrrolidone polymers like polyvinylpyrrolidone, copolymer of vinylpyrrolidone and vinyl acetate; sugars like sorbitol, mannitol and mixtures thereof.

Generally the disintegrants are selected from one or more of sodium starch glycolate, croscarmellose sodium, crospovidone, cornstarch and mixtures thereof.

The solubilizers/wetting agents may be selected from one or more of sodium lauryl sulphate, polysorbate 80 and mixtures thereof. The lubricant/glidants may be selected from one or more of magnesium stearate, talc, sodium stearyl fumarate, colloidal silicon dioxide and mixtures thereof.

The core may be coated with a separating layer prior to the enteric coating layer. The separating layer is made up of substantially water-soluble material, which is capable of dissolving or forming a gel in contact with water. Such material may include substantially water-soluble polymer and/or substantially water-soluble excipients. The substantially water-soluble excipients may be selected from glucose, lactose, mannitol, sorbitol, sucrose, dextrose and mixtures thereof. The substantially water-soluble polymers may be selected from hydroxypropylmethylcellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, sodium alginate, sodium carboxymethyl cellulose, copolymer of vinylpyrrolidone and vinyl acetate.

An enteric coating layer is applied onto the core coated with the separating layer by using suitable coating techniques. The enteric coating layer may include polymers such as cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, polyvinyl acetate phthalate, carboxymethylethylcellulose, methacrylic acid copolymers, for example, compounds known under the trademarks of Eudragit NE30D, Eudragit L, Eudragit S, Eudragit L 100 55 or mixtures thereof. The enteric coating layer contains plasticizers and may also include inert excipients such as talc, titanium dioxide, colloidal silicon dioxide,

hydroxypropyl methylcellulose and crospovidone. The plasticizer is used in an amount of less than 15% by weight of the enteric coating layer polymer. For example, the amount of the plasticizer may range from 8% to 14% by weight of the enteric coating layer polymer. For example, the amount of plasticizer is 13% by weight of the enteric coating layer polymer. These amounts of the plasticizer in the enteric coating layer provide the desired mechanical properties, such as flexibility and hardness of the enteric coating layers. The acid resistance of the core covered with enteric coating layer does not decrease significantly during the compression of core into tablets. The plasticizers may be selected from one or more of triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene glycols, polysorbates and mixtures thereof.

The core covered with enteric coating layer may further be covered with one or more over-coating layers. The materials for over-coating layers are pharmaceutically acceptable compounds such as sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methylcellulose and carboxymethylcellulose sodium, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers, anti-tacking and anti-static agents, such as magnesium stearate, titanium dioxide and talc may also be included into the over-coating layer. The over coating layer may contain plasticizers in an amount ranging from 0-30 % by weight of the enteric coating layer polymer. For example, the amount of the plasticizer may range from 5-20 % by weight of the enteric coating layer polymer. Said over-coating layer may further prevent potential agglomeration of enteric coating layered core, protect the enteric coating layer towards cracking during the compaction process and enhance the tableting process.

The separating layer, enteric coating layer and the over-coating layer can be applied to the core by coating or layering procedures in suitable equipments such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the layering process.

The multiple enteric-coating layered core units are mixed with one or more tablet excipients and compressed into a multiple unit tablet dosage form. The enteric coating layered core units, with or without an over-coating layer, are mixed with tablet excipients

such as fillers, binders, disintegrants, lubricants and other pharmaceutically acceptable additives and compressed into tablets.

Generally the fillers may be selected from one or more of sugars like dextrose, glucose, lactose; sugar alcohols like sorbitol, xylitol, mannitol; cellulose derivatives like powdered cellulose, microcrystalline cellulose; starches like corn starch, pregelatinized starch, maize starch and mixtures thereof.

Generally the binders are selected from one or more of cellulose derivatives like hydroxypropylmethyl cellulose, hydroxypropyl cellulose, methylcellulose; gums like xanthan gum, gum acacia, tragacanth; water-soluble vinylpyrrolidone polymers like polyvinylpyrrolidone, copolymer of vinylpyrrolidone and vinyl acetate; sugars like sorbitol, mannitol and mixtures thereof.

Generally the disintegrants are selected from one or more of sodium starch glycolate, croscarmellose sodium, crospovidone, cornstarch and mixtures thereof.

The lubricant/glidants may be selected from one or more of magnesium stearate, talc, sodium stearyl fumarate, colloidal silicon dioxide and mixtures thereof.

According to one embodiment the process for the preparation of the multiple unit tablet composition comprises the steps of:

a) preparing a multiple of core units comprising the benzimidazole compound and one or more pharmaceutically acceptable excipients.

b) coating the core of step (a) with a separating layer,

c) covering the core of step (b) with an enteric coating layer comprising a plasticizer in an amount of less than 15% by weight of the enteric coating layer polymer,

d) mixing the multiple of enteric coating layered core units of step (c) with one or more tablet excipients, and

e) compressing the mixture of step (d) into tablets.

According to another embodiment the process for the preparation of the multiple unit tablet composition comprises the steps of:

a) preparing a multiple of core units comprising the benzimidazole compound and one or more pharmaceutically acceptable excipients.

b) coating the core of step (a) with a separating layer,

c) covering the core of step (b) with an enteric coating layer comprising a plasticizer in an amount of less than 15% by weight of the enteric coating layer polymer,

d) covering the enteric coating layered core units of step (c) with an over-coating layer,

e) mixing the multiple of over coating layered core units of step (d) with one or more tablet excipients, and

f) compressing the mixture of step (e) into tablets.

The compressed tablet is optionally coated with a non-functional film coating to obtain a smooth surface of the tablet and further enhance the stability of the tablet during packaging and transport.

The following non-limiting examples describe the various embodiments:

Example 1

Ingredients	**Qty (mg/unit)**	
	Strength (40mg) 40 mg	**Strength (20mg) 20 mg**
Sugar spheres	60	30
Drug Layer		
Esomeprazole Magnesium eqv. to Esomeprazole	44.5	22.25
Hydroxypropylcellulose	16.0	8.0
Crospovidone	5.0	2.5
Purified water	q. s.	q.s.
Total	125.5	62.75
Separating layer		
Polyvinyl pyrrolidone	14.5	7.25
Polyethylene Glycol 400	1.0	0.5
Talc	4.0	2.0
Purified water/Isopropyl alcohol	q. s.	q.s.

Total	145.0	72.5
Enteric Coating layer		
Hydroxypropylmethyl cellulose phthalate HPMCP (HP-55S)	98.77	49.39
Hydroxypropylmethyl cellulose phthalate HPMCP (HP-50)	42.33	21.17
Diethyl phthalate	18.4	9.2
Acetone	q.s.	q.s.
Purified water	q.s.	q.s.
Total	304.5	152.25
Overcoating layer		
Hydroxypropylcellulose	6.0	3.0
Polyethylene glycol (PEG 6000)	9.0	4.5
Isopropyl alcohol/Dichloromethane	q.s.	q.s.
Total	319.5	159.75
Compression		
Crospovidone	58	29
Cellulose microcrystalline PH 101	502.5	251.25
Cellulose microcrystalline PH 112	211	105.5
Polyvinylpyrrolidone/Hydroxypropylcellulose	105	52.5
Sodium stearyl Fumarate	4.0	2.0
Total	1200	600
Film Coating		
Opadry pink	30	15
Isopropyl alcohol	q.s.	q.s.
Dichloromethane	q.s.	q.s.

Process of preparation:

Drug Layering

1. Sugar spheres were sifted through # 36 BSS and # 60 BSS and the fraction retained between # 36-60 BSS was collected.
2. Hydroxypropylcellulose and Crospovidone was sifted through # 30 BSS followed by dispersing in purified water under mechanical stirring to obtain a dispersion.
3. Esomeprazole Magnesium was sifted through # 30 BSS followed by dispersing in step 2 dispersion.
4. The sugar spheres of step 1 were loaded into Wurster coater and coated with the dispersion of step 3 to obtain drug layered beads.
5. The beads obtained in step 4 were dried at product temperature of 35 ± 5 ^{0}C for 15-30 minutes.

Separating layer

6. Polyvinylpyrrolidone was sifted through # 30 BSS and dissolved in purified water/Isopropyl alcohol followed by addition of polyethylene glycol (PEG 400) in the solution.

7. Talc was sifted through # 30 BSS and dispersed in solution of step 6.

8. The drug-layered beads of step 5 were coated with the dispersion of step 7 to obtain separating layer coated beads.

9. The beads were dried at product temperature of 35 ± 5 ^{0}C for 15-30 minutes.

Enteric Coating

10. Diethylpthalate was dissolved in acetone followed by hydroxypropylmethylcellulose phthalate under continuous stirring.

11. Purified water was added in the dispersion of step 10 under stirring.

12. The separating layer coated beads of step 9 was coated with dispersion of step 11 to obtain enteric-coated beads.

13. The beads obtained in step 12 were dried at product temperature of 35 ± 5 ^{0}C for 12 hrs in vacuum tray drier.

Overcoating

14. Hydroxypropylcellulose was sifted through # 30 BSS and dissolved in Isopropyl alcohol/Dichloromethane followed by addition of Polyethylene glycol (PEG 400) in the solution to obtain a dispersion.

15. The enteric-coated beads of step 13 were coated with the dispersion of step 14 to obtain overcoated coated beads.

16. The beads were dried at product temperature of 35 ± 5 ^{0}C for 15-30 minutes.

Compression

17. The overcoated beads of step 16 were sifted through # 22 BSS.

18. Microcrystalline cellulose, polyvinylpyrrolidone/Hydroxypropylcellulose-L and crospovidone was sifted through # 30 BSS.

19. The material of step 17 & 18 were blended in a blender.

20. Sodium stearyl fumarate was sifted through # 30 BSS and added to the material of step 19 and blended further.

21. The material of step 20 was compressed using approved tooling.

Film Coating

22. Opadry pink was dispersed in isopropyl alcohol/dichloromethane.

23. The tablets of step 21 were coated with the dispersion of step 22.

Example 2

Ingredients	**Qty (mg/unit)** **Strength (40mg)** 40 mg
Sugar spheres (#40-60)	60
Drug Layer	
Esomeprazole Magnesium eqv. to Esomeprazole	45.44
Hydroxypropylcellulose	16.0
Crospovidone	8.0
Purified water	q. s.
Total	131.44
Separating layer	
Polyvinyl pyrrolidone	8.5
Polyethylene Glycol 400	0.8
Talc	14.5
Purified water/Isopropyl alcohol	q. s.
Total	155.24
Enteric Coating layer	
Methacrylic acid copolymer (Eudragit L100D 55)	121
Hydroxypropylmethyl cellulose phthalate HPMCP	30
Triethyl citrate	19.63
Talc	15.8
Acetone	q.s.
Purified water	q.s.
Total	341.67
Overcoating layer	
Hydroxypropylcellulose	5.6
Polyethylene glycol (PEG 6000)	8.4

Isopropyl alcohol/Dichloromethane	q.s.
Total	355.67
Compression	
Crospovidone	60
Cellulose microcrystalline PH 101	478
Cellulose microcrystalline PH 112	189
Hydroxypropylcellulose	110
Sodium stearyl Fumarate	18
Total	1200
Film Coating	
Opadry pink	27
Isopropyl alcohol	q.s.
Dichloromethane	q.s.

Drug Layering

1. Sugar spheres were sifted through # 36 BSS and # 60 BSS and the fraction retained between # 36-60 BSS was collected.
2. Hydroxypropylcellulose and Crospovidone was sifted through # 30 BSS followed by dispersing in purified water under mechanical stirring to obtain a dispersion.
3. Esomeprazole Magnesium was sifted through # 30 BSS followed by dispersing in step 2 dispersion.
4. The sugar spheres of step 1 were loaded into Wurster coater and coated with the dispersion of step 3 to obtain drug-layered beads.
5. The beads obtained in step 4 were dried at product temperature of 35 ± 5 ^{0}C for 15-30 minutes.

Separating layer

6. Polyvinylpyrrolidone was sifted through # 30 BSS and dissolved in purified water/Isopropyl alcohol followed by addition of Polyethylene glycol (PEG 400) in the solution.
7. Talc was sifted through # 30 BSS and dispersed in solution of step 6.
8. The drug-layered beads of step 5 were coated with the dispersion of step 7 to obtain separating layer coated beads.

9. The beads obtained in step 8 were dried at product temperature of 35 ± 5 ^{0}C for 15-30 minutes.

Enteric Coating

10. Triethylcitrate was dissolved in acetone followed by hydroxypropylmethylcellulose phthalate and Eudragit L 100D 55 under continuous stirring.

11. Purified water was added in the dispersion of step 10 under stirring to obtain a dispersion.

12. The separating layer coated beads of step 9 were coated with dispersion of step 11 to obtain enteric-coated beads.

13. The beads obtained in step 12 were dried at product temperature of 35 ± 5 ^{0}C for 12 hrs in vacuum tray drier.

Overcoating

14. Hydroxypropylcellulose was sifted through # 30 BSS and dissolved in Isopropyl alcohol/Dichloromethane followed by addition of Polyethylene glycol (PEG 400) in the solution.

15. The enteric-coated beads of step 13 were coated with the dispersion of step 14 to obtain overcoated coated beads.

16. The beads obtained in step 15 were dried at product temperature of 35 ± 5 ^{0}C for 15-30 minutes.

Compression

17. The overcoated beads of step 16 were sifted through # 18 BSS.

18. Microcrystalline cellulose, L- Hydroxypropylcellulose and crospovidone was sifted through # 30 BSS.

19. The material of step 17 & 18 were blended in a blender.

20. Sodium stearyl fumarate was sifted through # 30 BSS and added to the material of step 19 and blended further.

21. The material of step 20 was compressed using approved tooling.

Film Coating

22. Opadry pink was dispersed in isopropyl alcohol/dichloromethane.

23. The tablets of step 21 were coated with the dispersion of step 22.

Acid resistance test of the multiple unit tablet was performed in 0.1N HCl at 75 rpm paddle for 120min (at initial time point and after 3 months storage at accelerated conditions). The result is given in the following table 1 below:

Table 1: Acid resistance test of Example 2

	Initial	**After 3M storage at 40°C/75% RH**
Acid resistance (%)	101	96

Dissolution of the multiple unit tablet was carried out in 0.1N HCl (300ml) at 75rpm paddle for 2hrs followed by pH 6.8 (700ml) at 75rpm paddle for 45 minutes (at initial time point and after 3 months storage at accelerated conditions). The result for Example 2 is given in Table 2 given below:

Table 2: Dissolution test of Example 2

	Initial	**After 3M storage at 40°C/75% RH**
% Drug release	100	98

Further, it was observed that the multiple unit tablet dosage form according to the present invention has good stability. The assay values and the amount of impurities (at initial time point and after 3 months storage at accelerated conditions) for Example 2 is provided in Table 3 below:

Table 3: Stability data for Example 2

	Initial	**3M (40^0 / 75% RH)**
Assay (%)	98	94.5
Impurity 1	0.077	0.130
Impurity 2	0.018	0.015
Impurity 3	0.145	0.157
Impurity 4	0.047	0.100
Impurity 5	0.062	0.197
Total Impurity	0.753	1.481

The above results show that composition of the present invention is stable even after storage for 3 months at 40^0 C and 75% RH.

Example 3

S. No	**Ingredients**	**Qty (mg/unit)**
		Strength (40mg)
		40 mg
	Sugar spheres	60
A	**Drug Layer**	
	Esomeprazole calcium eqv. to Esomeprazole	45.44
	Hydroxypropylcellulose	16.0
	Crospovidone	8.0
	Purified water	q. s.
	Total	131.44
B	**Separating layer**	
	Polyvinyl pyrrolidone	8.5
	Polyethylene Glycol 400	0.8
	Talc	14.5
	Purified water/Isopropyl alcohol	q. s.
	Total	155.24
C	**Enteric Coating layer**	
	Hydroxypropylmethyl cellulose phthalate HPMCP (HP-55)	119
	Hydroxypropylmethyl cellulose phthalate HPMCP (HP-50)	29.66
	Diethyl phthalate	19.1
	Talc	3
	Acetone	q.s.
	Purified water	q.s.
	Total	326

D	**Overcoating layer**	
	Hydroxypropylcellulose	5.6
	Polyethylene glycol (PEG 6000)	8.4
	Isopropyl alcohol/Dichloromethane	q.s.
	Total	341.23
E	**Compression**	
	Crospovidone	60
	Cellulose microcrystalline PH 101	478
	Cellulose microcrystalline PH 112	189
	Hydroxypropylcellulose (L-HPC)	110
	Sodium stearyl Fumarate	18
	Total	1200
F	**Film Coating**	
	Opadry pink	27
	Isopropyl alcohol	q.s.
	Dichloromethane	q.s.

Process of preparation:

Drug Layering

1. Sugar spheres were sifted through # 36 BSS and # 60 BSS and the fraction retained between # 36-60 BSS was collected.
2. Hydroxypropylcellulose (HPC-L) and Crospovidone was sifted through # 30 BSS followed by dispersing in purified water under mechanical stirring.
3. Esomeprazole calcium was sifted through # 30 BSS followed by dispersing in step 2 dispersion.
4. The sugar spheres of step 1 were loaded into Wurster coater and coated with the dispersion of step 3 to obtain drug-layered beads.
5. The beads obtained in step 4 were dried at product temperature of $35 \pm 5\ ^{0}C$ for 15-30 minutes.

Separating layer

6. Polyvinylpyrrolidone was sifted through # 30 BSS and dissolved in purified water/Isopropyl alcohol followed by addition of Polyethylene glycol (PEG 400) in the solution.
7. Talc was sifted through # 30 BSS and dispersed in solution of step 6 to obtain a dispersion.

8. The drug-layered beads of step 5 were coated with the dispersion of step 7 to obtain separating layer coated beads.

9. The beads were dried at product temperature of 35 ± 5 ^{0}C for 15-30 minutes.

Enteric Coating

10. Diethyl phthalate was dissolved in acetone followed by hydroxypropylmethylcellulose phthalate under continuous stirring.

11. Purified water was added in the dispersion of step 10 under stirring to obtain a dispersion.

12. The separating layer coated beads of step 9 was coated with dispersion of step 11 to obtain enteric-coated beads.

13. The beads were dried at product temperature of 35 ± 5 ^{0}C for 12 hrs in vacuum tray drier.

Over coating

14. Hydroxypropylcellulose was sifted through # 30 BSS and dissolved in Isopropyl alcohol/Dichloromethane followed by addition of Polyethylene glycol (PEG 400) in the solution to obtain a dispersion.

15. The enteric-coated beads of step 13 were coated with the dispersion of step 14 to obtain overcoated coated beads.

16. The beads were dried at product temperature of 35 ± 5 ^{0}C for 15-30 minutes.

Compression

17. The overcoated beads of step 16 were sifted through # 18 BSS.

18. Microcrystalline cellulose, L- hydroxypropylcellulose and crospovidone was sifted through # 30 BSS.

19. The material of step 17 & 18 were blended in a blender.

20. Sodium stearyl fumarate was sifted through # 30 BSS and added to the material of step 19 and blended further.

21. The material of step 20 was compressed using approved tooling.

Film Coating

22. Opadry pink was dispersed in isopropyl alcohol/dichloromethane.

23. The tablets of step 21 were coated with the dispersion of step 22.

Example 4

S. No	Ingredients	Qty (mg/unit)
		Strength (40mg) 40 mg
	Sugar spheres	60
A	**Drug Layer**	
	Esomeprazole magnesium eqv. to Esomeprazole	44.5
	Hydroxypropylcellulose	18.0
	Crospovidone	8.0
	Purified water	q. s.
	Total	130.5
B	**Separating layer**	
	Polyvinyl pyrrolidone	15.0
	Polyethylene Glycol 400	1.0
	Talc	3.2
	Purified water/Isopropyl alcohol	q. s.
	Total	150.0
C	**Enteric Coating layer**	
	Eudragit L30D55	96.51
	Triethyl citrate	12.53
	Talc	23.67
	Acetone	q.s.
	Purified water	q.s.
	Total	282.72
D	**Overcoating layer**	
	Hydroxypropylmethylcellulose (HPMC-E5)	12.0
	Polyethylene glycol (PEG 6000)	16.0
	Isopropyl alcohol/Dichloromethane	q.s.
	Total	310.72
E	**Compression**	
	Crospovidone	58
	Cellulose microcrystalline PH 101	511.28
	Cellulose microcrystalline PH 112	211
	Polyvinylpyrrolidone /Hydroxypropylcellulose / low substituted hydroxypropylcellulose (L-HPC)	105

	Sodium stearyl Fumarate	4.0
	Total	1200
F	**Film Coating**	
	Opadry pink	30
	Isopropyl alcohol	q.s.
	Dichloromethane	q.s.

Process of preparation:

Drug Layering

1. Sugar spheres were sifted through # 36 BSS and # 60 BSS and the fraction retained between # 36-60 BSS was collected.
2. Hydroxypropylcellulose and Crospovidone was sifted through # 30 BSS followed by dispersing in purified water under mechanical stirring.
3. Esomeprazole magnesium was sifted through # 30 BSS followed by dispersing in step 2 dispersion.
4. The sugar spheres of step 1 were loaded into Wurster coater and coated with the dispersion of step 3 to obtain drug-layered beads.
5. The beads obtained in step 4 were dried at product temperature of 35 ± 5 ^{0}C for 15-30 minutes.

Separating layer

6. Polyvinylpyrrolidone was sifted through # 30 BSS and dissolved in purified water/Isopropyl alcohol followed by addition of Polyethylene glycol (PEG 400) in the solution.
7. Talc was sifted through # 30 BSS and dispersed in solution of step 6 to obtain a dispersion.
8. The drug-layered beads of step 5 were coated with the dispersion of step 7 to obtain separating layer coated beads.
9. The beads were dried at product temperature of 35 ± 5 ^{0}C for 15-30 minutes.

Enteric Coating

10. Triethylcitrate was dissolved in purified water followed by addition of talc under continuous stirring.

11. Eudragit dispersion was added to step 10 under continuous stirring.

12. The separating layer coated beads of step 9 were coated with dispersion of step 11 to obtain enteric-coated beads.

13. The beads obtained in step 12 were dried at product temperature of 35 ± 5 ^{0}C for 12 hrs in vacuum tray drier.

Overcoating

14. Hydroxypropylmethylcellulose (HPMC-E5) was sifted through # 30 BSS and dissolved in Isopropyl alcohol/Dichloromethane followed by addition of Polyethylene glycol (PEG 400) in the solution.

15. The enteric-coated beads of step 13 were coated with the dispersion of step 14 to obtain overcoated coated beads.

16. The beads obtained in step 15 were dried at product temperature of 35 ± 5 ^{0}C for 15-30 minutes.

Compression

17. The overcoated beads of step 16 were sifted through # 18 BSS.

18. Microcrystalline cellulose, Polyvinylpyrrolidone /Hydroxypropylcellulose / low substituted hydroxypropylcellulose (L-HPC) and crospovidone were sifted through # 30 BSS.

19. The material of step 17 & 18 were blended in a blender.

20. Sodium stearyl fumarate was sifted through # 30 BSS and added to the material of step 19 and blended further.

21. The material of step 20 was compressed using approved tooling.

Film Coating

22. Opadry pink was dispersed in isopropyl alcohol/dichloromethane.

23. The tablets of step 21 were coated with the dispersion of step 22.

We claim:

1. A multiple unit tablet composition comprising: a) one or more tablet excipients, and b) a multiple of enteric coating layered core units containing a benzimidazole compound, wherein each core unit is covered with an enteric coating layer comprising a plasticizer in an amount of less than 15% by weight of the enteric coating layer polymer.

2. The composition according to claim 1, wherein the enteric coating layered core units comprise: a) a core comprising the benzimidazole compound and one or more pharmaceutically acceptable excipients, and b) a separating layer surrounding the core, and c) an enteric coating layer surrounding the separating layer.

3. The composition according to claim 1, wherein the benzimidazole compound is selected from one or more of omeprazole, lansoprazole, rabeprazole, pantoprazole, leminoprazole, pariprazole and their single enantiomers, pharmaceutically accepted salts, solvates and their mixtures.

4. The composition according to claim 3, wherein the benzimidazole compound is in the form of a pharmaceutically acceptable alkaline salt.

5. The composition according to claim 1, wherein the enteric coating layer polymer is selected from one or more of cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, polyvinyl acetate phthalate, carboxymethylethylcellulose and methacrylic acid copolymers.

6. The composition according to claim 1, wherein the plasticizer is selected from one or more of triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene glycols and polysorbates.

7. The composition according to claim 1, wherein the amount of the plasticizer ranges from 8% to 14% by weight of the enteric coating layer polymer.

8. The composition according to claim 1, wherein the tablet excipients are selected from one or more of binders, fillers, disintegrants and lubricants.

9. The composition according to claim 8, wherein the binders are selected from one or more of cellulose derivatives selected from hydroxypropylmethyl cellulose, hydroxypropyl cellulose and methylcellulose; gums selected from xanthan gum, gum acacia and tragacanth; water-soluble vinylpyrrolidone polymers selected from

polyvinylpyrrolidone and copolymer of vinylpyrrolidone vinyl acetate; and sugars selected from sorbitol and mannitol.

10. The composition according to claim 8, wherein the fillers are selected from one or more of sugars selected from dextrose, glucose and lactose; sugar alcohols selected from sorbitol, xylitol and mannitol; cellulose derivatives selected from powdered cellulose and microcrystalline cellulose and starches selected from corn starch, pregelatinized starch and maize starch.

11. The composition according to claim 8, wherein the disintegrants are selected from one or more of sodium starch glycolate, croscarmellose sodium, crospovidone and corn starch.

12. The composition according to claim 8, wherein the lubricants are selected from one or more of magnesium stearate, talc, sodium stearyl fumarate and colloidal silicon dioxide.

13. The composition according to claim 2, wherein the enteric coating layer is further covered by an over-coating layer.

14. The composition according to claim 13, wherein the over-coating layer comprises a plasticizer in an amount ranging from 0-30% by weight of the enteric coating layer polymer.

15. The process for the preparation of composition of any of claims 2-12, wherein the process comprises the steps of:

a) preparing a multiple of core units comprising the benzimidazole compound and one or more pharmaceutically acceptable excipients.

b) coating the core of step (a) with a separating layer,

c) covering the core of step (b) with an enteric coating layer comprising a plasticizer in an amount of less than 15% by weight of the enteric coating layer polymer,

d) mixing the multiple of enteric coating layered core units of step (c) with one or more tablet excipients, and

e) compressing the mixture of step (d) into tablets.

16. The process for the preparation of composition of any of claims 13 or 14, wherein the process comprises the steps of:

a) preparing a multiple of core units comprising the benzimidazole compound and one or more pharmaceutically acceptable excipients.

b) coating the core of step (a) with a separating layer,

c) covering the core of step (b) with an enteric coating layer comprising a plasticizer in an amount of less than 15% by weight of the enteric coating layer polymer,

d) covering the enteric coating layered core units of step (c) with an over-coating layer,

e) mixing the multiple of over coating layered core units of step (d) with one or more tablet excipients, and

f) compressing the mixture of step (e) into tablets.

17. A method of inhibiting gastric acid secretion, the method comprising administering to a patient in need thereof a multiple unit tablet composition according to claim 1.