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(54) Title: GASTRIC ACID RESISTANT BENZIMIDAZOLE MULTIPLE UNIT TABLET COMPOSITION

(57) Abstract: The present invention relates to a stable, gastric acid resistant multiple unit tableted dosage form of benzimidazole compound comprising of a cushioning agent such as polyethylene glycol and at least one pharmaceutically acceptable excipient. The invention also relates to the process involved therein.

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GASTRIC ACID RESISTANT BENZIMIDAZOLE MULTIPLE UNIT TABLET COMPOSITION

FIELD OF THE INVENTION

The present invention relates to a stable, gastric acid resistant multiple unit tableted dosage form of benzimidazole compound comprising of a cushioning agent such as polyethylene glycol. The invention also relates to the process involved therein.

BACKGROUND OF THE INVENTION

Benzimidazole compounds are effectively used as proton-pump inhibitor for the treatment of acid peptic disorders such as stomach ulcer, duodenal ulcer and gastro-esophageal reflux disorders. They act by inhibiting gastric acid secretion. This class of compound can be exemplified by esomeprazole, pantoprazole, omeprazole, lansoprazole, rabeprazole etc.

Benzimidazole compounds get degraded in presence of gastric acid. So they pose a difficult task to formulate them as an oral dosage form. In order to stabilize these substances, most conventional and reliable approach is to coat them with multiple coatings or single coating. The essential features in such coating material is that, these are practically insoluble in the gastric media whereas dissolve completely in presence of alkaline environment. Stability of these acid labile compounds may further be improved by adding inactive alkaline reacting compound to the drug core or else to the barrier coat.

The active benzimidazole compound may be available in multiple unit dosage forms like enteric coated granules or enteric coated pellets inside the capsule, enteric coated granules or enteric coated pellets compressed into tablets and single unit dosage form like single unit enteric-coated tablets.

Multiple unit dosage form generally scatters freely in the gastrointestinal tract and act like liquids, leaving the stomach within a short period of time, which results in:

- Improved biopharmaceutical characteristics, such as improved bioavailability, reduced food effect on plasma profiles and ultimately reduced variability of plasma profiles,
- Lower possibility of local irritation in gastrointestinal tract,

The pharmacokinetics of the drug release from multiple unit dosage form is more uniform than from the single unit dosage form, because the pharmacokinetics of the drug release from multiple unit dosage form is the average value of the kinetics of the drug release from individual subunits. Multiple unit dosage forms are commonly filled into hard capsules. The other method of formulating multiple units is compressing multiple units into tablets.

The multiple unit compressed tablet dosage form is less susceptible to tampering than the capsule dosage form. It also provides good mechanical strength than the capsule dosage form.

However, manufacturing of multiple unit tablet dosage form requires application of high compression pressure which results in the loss of integrity of the enteric coating and reduces the gastric resistant capacity of the dosage form.

This problem has been resolved in various prior art by following different approaches like altering the composition of enteric coating layer, which may improve the mechanical strength of the coating layer, mostly by using high percentage of plasticizer to modify the mechanical strength of the enteric layer or by using diluents having different particle sizes, which will help in reducing the compression force on enteric coated pellets.

Another issue in developing benzimidazole composition is availability and / or conversion of benzimidazole compounds in various polymorphic forms. Different polymorphic forms of the same compound may have completely different properties, especially when compared with an amorphous form of the same active benzimidazole compound. Amorphous

compounds have properties that can be of advantage in the preparation of solid dosage forms, such as solubility, dissolution rate, bioavailability, etc. However, the increased reactivity of an amorphous compound to transform to the crystalline state at a certain conditions such as for example humidity, pressure and temperature may negatively affect the physical and chemical stability of the dosage form. The use of drugs in crystalline form or amorphous form have potential advantage and disadvantages. In such a case it is very important that the dosage form should retain the same polymorphic form in formulation throughout the shelf life in order to ensure the same therapeutical activity of the drug on the patients.

The various prior art related to multiple unit tablet dosage form of benzimidazole compound is discussed hereunder:

EP 0723436 and EP 0723437 claims an oral pharmaceutical multiple unit tableted dosage form. The tablet comprises enteric coated core having plasticizer between 15 to 50% in the enteric layer. It also discloses that the reduction in gastric acid resistance capability is not more than 10% after the individual enteric coated units are compressed into a tablet dosage form. According to these patents, the amount of plasticizer in the range of 15 to 50% with respect to the enteric layer polymer is mandatory for providing the mechanical strength to the pellets to overcome the compression pressure.

WO 2008047320 discloses a multiple unit tablet dosage form of benzimidazole compound comprising of coated core materials. It uses plasticizing agent in an amount of less than 15% by weight of the enteric coating. It achieves to protect the enteric layer from breaking under compaction pressure by using less amount of plasticizer than the previously disclosed inventions. The examples disclosed in the patent application comprises overcoating layer over enteric layer. The overcoating layer comprises plasticizer, which provides mechanical strength to the pellets to overcome the compression pressure. The tablet weight disclosed in the example is also very high as compared to marketed formulation.

WO 2008006534 discloses multiple unit tablets comprising multiple units compacted together with at least two tablet filler-binders and optionally other pharmaceutically acceptable excipients, wherein at least one of said tablet filler-binder is a tablet filler-binder having mean particle size-to-mean multiple unit size ratio from 10% to 40%, and at least one of said tablet filler-binder is a tablet filler-binder having mean particle size-to-mean multiple unit size ratio from 1 % to 10%. The patent application discloses very specific particle size of diluent are required preparing multiple unit tablets.

Inventors of instant invention surprisingly found stable, gastric acid resistant multiple unit tableted dosage form of benzimidazole compounds with good mechanical, chemical and polymorphic stability by using cushioning agent. The multiple unit tablets of benzimidazole compounds having desired mechanical properties and satisfactory acid resistance can be prepared by using cushioning agent such as polyethylene glycol and using plasticizer in the enteric coating layer in an amount lower than that disclosed in the prior art.

SUMMARY OF THE INVENTION

The present invention relates to a novel, stable, gastric acid resistant multiple unit tableted dosage form of benzimidazole compound comprising of a cushioning agent such as polyethylene glycol.

The present invention relates to a novel, stable, gastric acid resistant multiple unit tableted dosage form of benzimidazole compound comprising of a cushioning agent such as polyethylene glycol wherein cushioning agent is not a part of enteric coated benzimidazole pellets or units.

One embodiment of the present invention is to provide stable, gastric acid resistant multiple unit tableted dosage form of benzimidazole compound in which the active substance is in the form of individually enteric coating layered units compressed into a tablet.

Another embodiment of the present invention is to provide stable, gastric acid resistant multiple unit tableted dosage form of benzimidazole compound comprising of multiple layered units, cushioning agent such as polyethylene glycol and pharmaceutically acceptable excipients, wherein each unit comprises of :

a) an inert core;

b) a seal coating over inert core;

c) seal coated inert core is coated with drug layer, wherein drug layer comprises of benzimidazole compound and one or more pharmaceutically acceptable additives in one or more solvents,

d) a barrier layer is coated over drug layer;

e) an enteric coating layer is coated over barrier layer.

Another embodiment of the present invention is to provide stable, gastric acid resistant multiple unit tableted dosage form of benzimidazole compound comprising of multiple layered units, cushioning agent such as polyethylene glycol and pharmaceutically acceptable excipients, wherein each unit comprises of :

a) an inert core;

b) inert core is coated with drug layer, wherein drug layer comprises of benzimidazole compound and one or more pharmaceutically acceptable additives in one or more solvents,

c) a barrier layer is coated over drug layer;

d) an enteric coating layer is coated over barrier layer.

Another embodiment of the present invention is to provide stable, gastric acid resistant multiple unit tableted dosage form of benzimidazole compound comprising of multiple layered units, cushioning agent such as polyethylene glycol and pharmaceutically acceptable excipients, wherein each unit comprises of :

a) an inert core;

b) inert core is coated with drug layer, wherein drug layer comprises of benzimidazole compound and one or more pharmaceutically acceptable additives in one or more solvents,

c) an enteric coating layer is coated over drug layer

Another embodiment of the present invention is to provide stable, gastric acid resistant pharmaceutical composition of benzimidazole compounds comprising of multiple layered units and pharmaceutically acceptable excipients, wherein the inert core is being coated by seal coating layer, drug layer comprising amorphous benzimidazole compound and one or more pharmaceutically acceptable additives in one or more of non-aqueous solvents, barrier coating layer, enteric coating layer and compressing the enteric coated pellets with polyethylene glycol and other pharmaceutically acceptable excipients.

Another embodiment of the present invention is to provide stable, gastric acid resistant multiple unit tableted dosage form of benzimidazole compound comprising of multiple layered units, cushioning agent such as polyethylene glycol and pharmaceutically acceptable excipients, wherein each unit comprises of :

a) core comprising benzimidazole compound and atleast one pharmaceutically acceptable excipient;

b) optionally a barrier layer is coated over drug core;

c) an enteric coating layer is coated over barrier layer or drug core.

Another embodiment of the present invention is to provide stable, gastric acid resistant multiple unit tableted dosage form of benzimidazole compound comprising of multiple layered units, cushioning agent such as polyethylene glycol and pharmaceutically acceptable excipients, wherein each unit comprises of :

a) core comprising benzimidazole compound and atleast one pharmaceutically acceptable excipient;

b) optionally a barrier layer is coated over drug core;

c) an enteric coating layer is coated over barrier layer or drug core;

With the proviso that cushioning agent is not added in manufacturing of said drug units.

Another embodiment of the present invention is to provide stable, gastric acid resistant multiple unit tableted dosage form comprising benzimidazole compound, in which the active substance is in the form of individually enteric coating layered units compressed into a tablet. The enteric coating layer(s) covering the individual units of active substance has properties such that the compression of the units into a tablet does not significantly affect the acid resistance of the individually enteric coating layered units. The active substance is prevented from degradation and dissolution in acidic media and has a good stability during long-term storage. The enteric coating layer covering the individual units disintegrates/dissolves rapidly in near neutral or alkaline media.

Another embodiment of the present invention is to provide stable, gastric acid resistant multiple unit tableted dosage form of benzimidazole compound containing of multiple layered units, cushioning agent such as polyethylene glycol, and disintegrant.

Another embodiment of the present invention is to provide stable, gastric acid resistant multiple unit tableted dosage form comprising benzimidazole compound, which is suitable for press-through blister packages and which also has an improved patient acceptance.

Another embodiment of the present invention is to provide stable, gastric acid resistant multiple unit tableted dosage form comprising benzimidazole compound which is divisible and easy to handle. The multiple unit tableted dosage form may be dispersed in an aqueous liquid and can be given to patients with swallowing disorders and in pediatric patients. Such

a suspension of dispersed benzimidazole units of appropriate size can be used for oral administration and also for feeding through a nasogastric tube.

DETAILED DESCRIPTION OF THE INVENTION

The term "benzimidazole" or "benzimidazole compound" or "active substance" or "active compound" or "drug" used herein refers to any of the compounds belonging to the category of benzimidazole used for gastrointestinal disorders and it includes but not limited to omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole, pariprazole, leminoprazole, nepaprazole, tenatoprazole and their single enantiomers. It also includes pharmaceutically accepted salts, solvates, polymorphs, prodrugs of active compound and their single enantiomers and mixtures thereof. For example, the benzimidazole compound may be esomeprazole in the form of a pharmaceutically acceptable alkaline salt such as esomeprazole magnesium. The benzimidazole compound may be either in the crystalline or amorphous form. In general the daily dose will be in the range of 1-400 mg of benzimidazole compound.

The term "gastric acid resistant composition or dosage form or formulation" as described herein is to encompass solid oral dosage form having gastric acid resistance capacity such that not more than 10% of active compound is degraded or dissolved, when the tableted dosage form is exposed to atleast 300 mL, 0.1 N HCl for atleast two hours in paddle dissolution apparatus at 100 RPM.

The term "core" as described herein may be in the form of pellets, granules, or beads. Core may contain benzimidazole compound, pharmaceutically acceptable excipients like diluents, diluents, disintegrant, lubricants, glidants, wetting agent, solubilizers, pH modulating agents etc. The core may be manufactured by wurster coating, granulation, extrusion-spheronization and other procedure known to person having ordinary skill in the art. The core may be acidic, neutral or basic in nature. The inert core used may be selected from sugar spheres, non peril seeds, cellulose or cellulose derivatives, starch derivatives, sugar derivatives or mixtures

thereof. The inert core is devoid of benzimidazole compound. The enteric coated core will be known as unit, multiple layered unit or enteric coating layered unit.

The term "cushioning agent" as used herein encompasses inert substances which protect the enteric layer from breaking when the enteric coated pellets or granules are compressed. Different substances that can be used as cushioning agent in the present invention can be exemplified by waxy materials like poly ethylene glycol, paraffin wax, bees wax, and the like. The preferred cushioning agent in the present invention is polyethylene glycol 8000. The cushioning agent is preferably added in lubrication stage before compression stage of tablets.

The term "stable" as used herein refers to dosage form which is physically, or polymorphically stable. The dosage form according to present invention may remain physically stable that is there are no substantial change with respect to physical attributes like colour etc. The dosage form according to present invention may remain polymorphically stable that is the polymorph (crystalline or amorphous) in the dosage form does not rearranges into another form during formulation development or upon storage.

The Core

The term "core" as described herein is in the form of pellets, granules, or beads. The core for the enteric coating layered pellets can be manufactured according to different principles.

Inert core layered with benzimidazole compounds, optionally mixed with alkaline pH modulating agents, can be used as the core material for the further processing. The inert cores, which are to be layered with the benzimidazole compound, can be water insoluble inert cores comprising different oxides, celluloses, cellulose derivatives, starch derivatives, organic polymers and other materials, alone or mixtures thereof or water soluble inert cores comprising different sugars, sugar spheres, non peril seeds, or mixtures thereof. The inert core may be coated with seal coating layer to add in the stability of the dosage form. The seal

coat comprises of filmcoating agent, solvent, lubricants / glidants and optionally other pharmaceutically acceptable excipients. The filmcoating agent that can be most commonly used in the seal coating can be one or more of the following like ethyl cellulose, hypromellose, gums like xanthan gum, copolyvidone, povidone, shellac, hydoxypropyl methyl cellulose, poly vinyl acetate phthalate, zein, and the like. The solvents used in the seal coating are preferably organic in nature.

Before the inert cores are layered, the active compound may be mixed with further excipients. Such components can be binders, surfactants, fillers, disintegrating agents, pH modulating agent or other pharmaceutically acceptable ingredients, alone or in mixtures thereof. The binders are for example celluloses such as hydroxypropyl methylcellulose, hydroxypropyl cellulose and carboxymethyl-cellulose sodium, povidone, copolyvidone, sugars, starches and other pharmaceutically acceptable excipients with cohesive properties. The drug layer may be manufactured using both aqueous and non-aqueous solvent. The active compound may be amorphous or crystalline in nature.

Alternatively, benzimidazole compound may be mixed with pharmaceutically acceptable excipients and formulated into core. Said core may be produced by extrusion/spheronization, wet granulation, or compression utilizing different process equipments. The size of the formulated core materials is approximately between 0.1 and 4mm and preferably between 0.1 and 2 mm.

The active compound may also be mixed with pH modulating agent. Such substances can be chosen among, but are not restricted to, substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminium hydroxide/sodium bicarbonate coprecipitate; aluminium, calcium and magnesium hydroxides; magnesium oxide; organic alkaline pH modulating agent such as trihydroxymethylaminomethane, basic amino acids and

their salts or other similar pharmaceutically acceptable pH modulating agent. The preffered alkaline pH modulating agent is magnesium oxide (light).

Alternatively, the aforementioned core can be prepared by using spray drying or spray congealing technique.

The Barrier Coating

The barrier coating according to present invention comprises of water soluble filmcoating agent or water insoluble filmcoating agent. The preffered filmcoating agent may be selected from one or more of the following like; povidone, copolyvidone, hydroxyl propyl methyl cellulose, hydroxyl propyl cellulose, sodium alginate, sodium carboxy methyl cellulose, copolymer of vinyl pyrrolidone and vinyl acetate, gums, ethyl cellulose, zein, shellac, saccharides or mixture thereof. The barrier coating may contain pH modulating agent, like sodium, calcium, potassium, magnesium or aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids, hydroxides or oxides of aluminium, magnesium, calcium. Most preferably magnesium oxide (light) is used in the present disclosure. The barrier layer may also contain other pharmaceutically acceptable excipients like binding agent, lubricants/glidants, solvents, diluents etc. The barrier layer is applied on the drug coated pellets, granules or beads by suitable coating technique. In one of the embodiment the barrier coating may be absent.

The Enteric Coating

The barrier layer coated pellets, beads, granules or benzimidazole cores are than coated with enteric coating. The enteric coating of the present invention comprises of polymers such as cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, polyvinyl acetate phthalate, carboxy methyl cellulose, and methacrylic acid copolymers such as available in the brand name of Eudragit® NE30D, Eudragit® L, Eudragit S®, Eudragit® L30D 55 or mixtures thereof. The enteric coating layers may contain other pharmaceutically acceptable excipients like diluents, glidants/ lubricating agents, binding agents, plasticizers, anti-tacking agent,

opacifying agent, colouring agent, solvents etc. The enteric coating layer can be prepared by using both aqueous and non-aqueous solvent. Then the layer is coated by using suitable coating techniques.

The enteric coating layers contain pharmaceutically acceptable plasticizers to obtain the desired mechanical properties, such as flexibility and hardness of the enteric coating layers. Such plasticizers are for instance, but not restricted to, triacetin, citric acid esters, triethyl citrate, phthalic acid esters, diethyl phthalate, dibutyl sebacate, cetyl alcohol, polyethylene glycols, propylene glycol, polysorbates or other plasticizers.

The amount of plasticizer is in the range of 0% to 15% by weight of the enteric coating layer polymer(s). Additives such as dispersants, colorants, pigments, anti-tacking and antifoaming agents may also be included into the enteric coating layer(s).

The Tablets

The enteric coated pellets / granules /beads of the active compounds as obtained above, are mixed with cushioning agent such as polyethylene glycol and other pharmaceutically acceptable excipients such as fillers, binders, disintegrants, lubricants. Then this mixture is compressed into a multiple unit tableted dosage form, according to the present invention. The compressed tablet is optionally covered with film forming agent(s) to obtain a smooth surface of the tablet and further enhance the stability of the tablet during packaging and transport. Such a tablet coating layer may further comprise additives like anti-tacking agents, colorants and pigments or other additives to obtain a tablet of good appearance. The tablet polishing can also be done to provide good appearance to the tablet.

Suitable diluents / fillers may include but not limited to sugars, such as dextrose, glucose; sugar alcohols, such as sorbitol, xylitol, mannitol; cellulose derivatives, such as powdered cellulose, microcrystalline cellulose; starch, starch derivatives, lactose, lactose monohydrate, dicalcium phosphate dihydrate, modified (spray processed) lactose, spray dried mixture of

lactose and microcrystalline cellulose (Microcelac® 100, Manufacturer: Meggle Pharma), mannitol, Spray dried Mannitol (Pearlitol SD® 200), sorbitol and the like. The other coprocessed excipients which may be used in the instant invention are Ran Explo-C® (Microcrystalline cellulose, Colloidal silicon dioxide, Crospovidone), Ran Explo-S® (Microcrystalline cellulose, Colloidal silicon dioxide and Sodium starch glycollate), StarLac® (spray-dried compound consisting of 85% alpha-lactose monohydrate and 15% maize starch), silicified microcrystalline cellulose (e.g. Prosolv® HD 90),or mixtures thereof and other diluents / fillers known to person having ordinary skill in the art.

Suitable binders or binding agents include but not limited to cellulose derivatives such as hydroxypropylmethyl cellulose, hydroxypropyl cellulose, methylcellulose; gums such as xanthan gum, gum acacia, copolyvidone, tragacanth; water-soluble vinylpyrrolidone polymers such as polyvinylpyrrolidone, copolymer of vinylpyrrolidone and vinyl acetate; sugars such as sorbitol, mannitol and mixtures thereof.

Suitable disintegrants include but not limited to sodium starch glycolate, croscarmellose sodium, crospovidone, low substituted hydroxypropyl cellulose, starch or starch derivatives, polacrilin potassium.

Suitable solubilizers/wetting agents may include but not limited to sodium lauryl sulphate, polysorbate 80 or mixtures thereof.

Tablets may be prepared using direct compression by mixing directly compressible excipients with enteric coated pellets or granules or beads of benzimidazole compound. The blend so obtained can be compressed using suitable tablet tooling with the help of rotary tablet presses. Tablets can be prepared using wet granulation, wherein excipients are granulated, dried, milled and sifted to get a desired particle size and blended with enteric coated pellets or granules of benzimidazole compound, with or without desired pharmaceutical excipients such as disintegrants, glidants, lubricants, and colorants. The blend

so obtained can be compressed using suitable tooling with equipment such as rotary tablet presses, or other equipment as will be apparent to those skilled in the art. Pharmaceutical dosage forms of the present invention may contain one or more diluents to increase the final composition mass so that it becomes easier for the patient and the caregiver to handle.

Glidants that can be used in the present invention can be one or more of the following: colloidal silicon dioxide, magnesium silicate, magnesium trisilicate, starch talc and mixtures thereof.

Suitable lubricants may include but not limited to calcium stearate, glycerin monostearate, glyceryl behenate, hydrogenated castor oil, hydrogenated vegetable oil, magnesium lauryl sulphate, magnesium stearate, sodium stearyl fumarate, medium-chain triglycerides, polyethylene glycol, stearic acid, talc, sucrose stearate or zinc stearate.

Suitable solvent includes but not limited to aqueous, alcoholic, hydro-alcoholic or organic solvent. In yet another embodiment, a suitable solvent system for the coating comprises solvents such as, but not limited to, water, ethanol, methanol, isopropanol, acetone, methylene chloride, and the like.

The general procedure for manufacturing is given as below:

The process of manufacturing stable, gastric acid resistant multiple unit tableted dosage form of benzimidazole compounds comprising following steps:

a) Preparing core comprising benzimidazole compound and atleast one pharmaceutically acceptable excipient;

b) Optionally coating barrier layer over drug core;

c) Coating of enteric coating layer over barrier layer or drug core.

d) Compressing enteric coated benzimidazole pellets, cushioning agent such as polyethylene glycol and pharmaceutically acceptable excipients into tablets.

EXAMPLES

The invention can be illustrated in a better way by the following example. These examples are for illustration purposes only. In no way they limit the scope of the present invention.

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Example-1

Table 1

Seal coating	Mg /Tablet
Sugar pellets	32.000
Ethyl Cellulose	2.560
Magnesium Stearate	0.640
Methanol*	q.s
Methylene Chloride*	q.s
Total	**35.200**
Drug Coating	
Seal coated pellets	35.200
Esomeprazole Magnesium	44.500
Povidone K-90 D	10.689
Magnesium Oxide Light	11.120
Methanol*	q.s
Total	**101.509**
Barrier Coating	
Drug coated pellets	101.509
Povidone K-90 D	12.610
Magnesium Oxide Light	2.000
Magnesium Stearate	2.610
Methanol*	q.s
Total	**118.729**
Enteric Coating	
Barrier coated pellets	**118.729**
Eudragit® L30D 55 (Solid)	62.253
Diethyl Pthalate	6.091
Talc	62.253
Purified Water*	q.s
Total	**249.326**
Tablets Compression	
Enteric coated pellets	250.00
Lactose monohydrate + Maize Starch (StarLac®)	75.000

Silicified Microcrystalline Cellulose	245.400
Copolyvidone (Kollidone® VA 64)	48.750
Crospovidone	36.000
Polyethylene Glycol 8000	130.000
Colloidal Silicondioxide	1.600
Magnesium Stearate	3.250
Uncoated Tablet Weight	**790.000**

Table 1 (Contd.)

Tablet Coating	
Uncoated tablet	790.000
Hypromellose	18.010
Talc	19.650
Colloidal Silicondioxide	2.750
Titanium Dioxide	4.280
Iron oxide red	2.710
Purified Water*	q.s
Coated Tablet Weight	**837.400**
Tablets polishing	
Filmcoated tablet	837.400
Polyethylene Glycol 8000	3.000
Purified Water*	q.s
Polished Tablet Weight	**840.400**

* doesn't remain in final product.

Manufacturing process:

1. **Seal coating:** The sugar pellets were sifted through the sieves of mesh size 40/60 and seal coated with ethyl cellulose, magnesium stearate solution dispersed in methanol and methylene chloride using FBC bottom spray.
2. **Drug coating:** Esomeprazole magnesium was dissolved in methanol. Then Povidone K-90 D and Magnesium oxide light was added to the solution and stirred to get homogeneous suspension. This suspension was coated onto Step No-1 seal coated pellets using FBC bottom spray.

3. **Barrier coating:** Magnesium stearate and Povidone K-90D was dispersed in methanol and stirred well. This suspension was coated onto the drug pellets of Step No-2 using FBC bottom spray.
4. **Enteric coating:** Diethyl Phthalate and Talc was dispersed in purified water with stirring to get uniform dispersion. The dispersion was milled in colloidal mill for 10-15 minutes. Eudragit L-30D-55 dispersion was passed through 80# sieve. Then the milled dispersion of talc and DEP was added into Eudragit L-30D-55 manually and homogenized for 10-15 minutes. The barrier coated pellets of step no 3 was coated using this suspension.
5. **Tablet Compression:** Prosolve SMCC HD 90D, Starlac, Copovidone, Crospovidone, PEG 8000, Colloidal silicon dioxide and Magnesium stearate were sifted through appropriate sieve. These ingredients were mixed with enteric pellets of Step No-4 and compressed into tablets.
6. **Film coating:** Materials of film coating were dispersed in water and coated onto tablets using film coating equipments.
7. **Polishing:** PEG 8000 was dissolved in water and sprayed onto film coated tablets.

Analytical Results:

S.No	Test	Results					
1.	Assay	100.8 %					
2.	% Dissolution						
2A.	Gastric Resistance	2 hrs : 6.9%					
2B.	Buffer Stage	**5 min**	**10 min**	**15 min**	**20 min**	**30 min**	**45 min**
		6.6	29.9	63.8	84.5	92.5	91.6

* Dissolution Condition:

Apparatus : USP apparatus II (Paddle)

Speed : 100 RPM

Medium : A: Gastric Resistance: 0.1N HCl, 300 ml, Time:2 hours;
B: Buffer Stage: pH 6.8, Phosphate Buffer, 1000 ml.

Example-2

Further, in the above example the amount of cushioning agent is modified and studied for their effect on the % of dissolution in gastric pH (0.1NHCl for 4 hrs). Another dosage form without using cushioning agent was prepared and tested for % degradation. The result are summarized below:

Formulation	Gastric resistance at 4hrs
Test Formulation With PEG130 mg/Tab	~10%
Test Formulation Without PEG	~22.6%

CLAIMS

1. A stable, gastric acid resistant multiple unit tableted dosage form comprises benzimidazole compound and cushioning agent.

2. The dosage form of claim 1, wherein cushioning agent is selected from the group comprising of poly ethylene glycol, paraffin wax, bees wax and a mixture thereof.

3. The dosage form of claim 1, wherein cushioning agent is poly ethylene glycol.

4. The dosage form of claim 1, wherein cushioning agent is not a part of enteric coated benzimidazole unit.

5. A stable, gastric acid resistant multiple unit tableted dosage form comprises multiple layered units, cushioning agent and pharmaceutically acceptable excipients, wherein each unit comprises of:

a) core comprising benzimidazole compound and at least one pharmaceutically acceptable excipients;
b) optionally a barrier layer over the core; and
c) an enteric coating layer.

6. The dosage form of claim 5, wherein enteric coating layer contains less than 15% plasticizer by wt of enteric coating polymer.

7. The dosage form of claim 1, wherein benzimidazole compound is selected from the group comprising of omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole,

pariprazole, leminoprazole, nepaprazole, tenatoprazole, their single enantiomers and pharmaceutically accepted salts thereof.

8. The dosage form of claim 7, wherein benzimidazole compound is in an amorphous form.

9. The dosage form of claim 8, wherein benzimidazole compound is esomeprazole magnesium.

10. A process for preparing stable, gastric acid resistant multiple unit tableted dosage form of benzimidazole compounds comprising following steps:

a) Preparing core comprising benzimidazole compound and atleast one pharmaceutically acceptable excipient;

b) Optionally coating barrier layer over drug core;

c) Coating of enteric coating layer over barrier layer or drug core;

d) Compressing enteric coated benzimidazole pellets, cushioning agent and pharmaceutically acceptable excipients into tablets.

11. The dosage form comprising benzimidazole compound as substantially described and exemplified herein.