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(54) Title: A PROCESS FOR MANUFACTURE OF STABLE ORAL MULTIPLE UNITS PHARAMCEUTICAL COMPOSITION CONTAINING BENZIMIDAZOLES

(57) Abstract: This invention relates to process for manufacture of a stable, oral, multiple unit pharmaceutical composition containing high concentration of benzimidazole upto about 40%w/w without the use of micronized benzimidazole, disintegrating agent and fillers. Surfactants in these compositions are in enteric polymer layer and not in contact with benzimidazole. Multiple unit pharmaceutical composition of the invention shows minimum acid degradation in 0.1 N HCI after two h ours a nd pH 6.8 buffer release of more than 85% w/w after 45 minutes. Multiple unit pharmaceutical composition is in the form unagglomerated, uniformly shaped and sized enteric-coated pellets, which are processed continuously or in batches in single equipment such as fluid bed bottom spray processor. The invention involves sequential deposition of a) alkaline material layer on non-pariel seeds to obtain treated non-pariel seeds b) drug layer to obtain drug pellets c) sealant polymer layer to obtain sealed pellets d) enteric polymer layer to obtain enteric coated pellets. The enteric-coated pellets obtained are capable of being filled in smallest size capsule (size 5) for ease of administration and patient acceptance.

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A PROCESS FOR MANUFACTURE OF STABLE ORAL MULTIPLE UNITS PHARMACEUTICAL COMPOSITION CONTAINING BENZIMIDAZOLES

Background:

Benzimidazolic compounds such as Omeprazole, Lansoprazole, Pantoprazole, Pariprazole, Leminoprazole, and Rabeprazole are potent proton pump inhibitor known for inhibition of gastric acid secretion. They are used in the therapeutics of diseases related to gastric acidity in mammals, especially in humans, including gastric and duodenal ulcers, reflux oesophagitis, gastritis, duodenitis and Zollinger-Ellison syndrome.

Benzimidazole such as omeprazole, lansoprazole are sensitive to light, heat and moisture. They exhibit fast decomposition below pH 7.8 and has maximum stability at pH 11. Hence the oral dosage form containing benzimidazole needs to be protected from the acidic ingredient used to manufacture the dosage form and from the acidic gastric fluid so that they reach intactly in the small intestine from where they are absorbed systemically. They also have very low aqueous solubility and the solubility is pH dependent. Various related art have addressed and have tried to overcome the issue of

- Stabilizing benzimidazole and protecting benzimidazole from acidic ingredients acidic and physiological environment.
- Releasing benzimidazole from enteric-coated pellet preferably more than 85% w/w in pH 6.8 after 45 minutes with minimum acid degradation in 0.1N HCl after 2 hours.
- Manufacturing pharmaceutical composition containing benzimidazole in single equipment without involving use of organic solvents for making the process operator and environment friendly.

U.S. Patent No. 4,786,505 describes extrusion spheronization process for omeprazole preparation wherein omeprazole core is prepared by granulating the mixture of mannitol powder with lactose anhydrous, hydroxypropylcellulose and microcrystalline cellulose with water containing alkaline compound and surfactant. Omeprazole is either suspended in granulating liquid or added in above powder mixture. Separating layer that separates the omeprazole core and enteric layer contains alkaline pH buffering compounds and film coating polymer, which is deposited on the pellets, followed by deposition of enteric layer in coating pan or fluidized bed coater. Efficient drying is essential to reduce the water content of the final dosage form of not more than 1.5 % w/w, which is an absolute requirement for the stable formulation. The process involves

use of surfactant, disintegrating agent and filler in the composition, which are in contact with omeprazole thereby helping in the dissolution of omeprazole. The process is a batch process using multiple equipments, which makes it laborious and time consuming.

U.S. Patent No. 5385739 describes microgranules dosage form containing omeprazole. Powder mixture of omeprazole, mannitol, disintegrating agent carboxymethylstarch and surfactant sodium lauryl sulfate is layered on neutral core of sugar and starch in circular turbine with inclined flat bottom. Further the core contains protective layer consisting of mannitol, sucrose and binding agent, which isolate the active agent from external enteric coating layer. Omeprazole and excipients used require additional micronisation steps to achieve particle size below 100 microns. Efficient drying is essential to reduce the moisture level of active layer to preferably less than 0.5 % to ensure good stability. The process also requires stringent temperature control for the granules to be maintained between 32°C and 38°C.

U.S. Patent No. 6077541 describes process for manufacture of omeprazole enteric-coated pellets wherein the drug layer comprises of 20-70% w/w omeprazole. Enteric coating layer is directly applied to the drug layer. The process requires additional step of micronization of omeprazole. The process also requires alkaline agents, surface-active agents and binder, which along with micronised omeprazole is suspended in aqueous or non-aqueous solvents. This suspension containing omeprazole is coated on non-pariel sugar sphere in fluid bed coater.

EP 1108425 describes multiunit pharmaceutical preparation manufactured by coating aqueous suspension of substituted benzimidazole or its acceptable salts in the micronized form onto inert core to obtain drug core. The invention requires use of surfactants and disaggregants in the layer-containing drug, which are mixed in a suitable proportion in order to allow disaggregation of the formulations and dissolution of the active ingredients. Drug core in turn is coated with an insulating layer free from alkaline agent of minimum thickness of 15-mu m, and finally with gastro resistant layer of minimum thickness of 30-mu m. The formulation has stringent requirement to have humidity less than 1.5% for good stability.

PCT Publication W0 9819668 describes delayed drug delivery system where micronised omeprazole in aqueous suspension containing water soluble binder is deposited on core containing alkaline material. The alkaline core structure is obtained by depositing powder blend of alkaline material and spheronizing / disintegrating agent on non-pariel seeds with the help of polymeric binding agent in fluid bed granulator with rotor insert. The drug core is further coated with non-enteric moisture barrier followed

by delayed release enteric barrier. The formulation releases only 60 – 80% of omeprazole after 45 minutes in buffer of pH 6.8.

U.S. Patent No. 6207198 describes omeprazole composition where alkaline reacting substance is not present in the composition. It describes a process, which involves granulating omeprazole with inert nuclei or aqueous layering containing suspended omeprazole onto inert nuclei. The granules or the layered nuclei are compressed to form micro tablets, which are coated with intermediate layer followed by enteric layer. The composition makes use of disintegrants and surfactants in the intermediate layer, which is in immediate contact with a core containing omeprazole to improve the dissolution of omeprazole. The process described is operator dependant and makes use of multiple equipments making it time laborious and consuming.

US Application 20010053387 describes Omeprazole composition where omeprazole along with alkaline material is layered on non-pariel seeds in centrifugal coater. These drug cores are then coated with moisture barrier, which contains hydrophobic material (Polydimethylsiloxane) followed by enteric coating. The pellets are compressed into tablets or filled into hard gelatin capsules.

Thus the related art

- Manufactures pharmaceutical composition containing less than 15% w/w benzimidazole enabling low aqueous soluble benzimidazole to be distributed over a wide surface area to obtain desired optimum dissolution.
- Manufactures pharmaceutical composition containing high concentration of benzimidazole specifically utilizing micronized benzimidazole or surfactant or disintegrating agent or filler or their combination which are in contact with benzimidazole for achieving optimum dissolution (pH 6.8 buffer release of more than 85%w/w after 45 minutes).
- Makes use of micronized benzimidazole, which becomes an additional step before actual production takes place.
- Has stringent requirement to have moisture content less than 1.5% w/w, which is essential for stable formulation thereby increasing the drying time and processing time.
- Makes use of multiple equipments thereby exposing the operator to potent drug, which may be hazardous, and increases the chances of cross contamination.
- Has low batch yields thereby making the product expensive as it utilizes suspension of micronized benzimidazole for deposition.

None of the related art teaches process for manufacture of a stable, oral, multiple unit pharmaceutical composition containing high concentration of benzimidazole upto about 40%w/w without the use of micronized benzimidazole, disintegrating agent, fillers and

surfactant in contact with benzimidazole, having minimum acid degradation in 0.1N HCl after two hours and buffer release of more than 85% w/w in pH 6.8 after 45 minutes in a single equipment fluid bed bottom spray processor and capable of being filled in smallest size (size 5) capsule for ease of administration and patient acceptance.

Summary of the invention:

The object of the invention is to provide a process for manufacture of a stable, oral, multiple unit pharmaceutical composition containing high concentration of benzimidazole upto about 40%w/w without the use of micronized benzimidazole, disintegrating agent, fillers and surfactants in contact with benzimidazole, having minimum acid degradation in 0.1N HCl after two hours and pH 6.8 buffer release of more than 85% w/w after 45 minutes in a single equipment fluid bed bottom spray processor and capable of being filled in capsule size 5 to size 0 for ease of administration and patient acceptance.

Further the object of the invention is to provide a process for manufacture of stable, oral, multiple unit pharmaceutical composition containing high concentration of benzimidazole upto about 40%w/w which may be carried out continuously or in batches and is unaffected by high moisture content, which may be present in the composition.

Further the object of the invention is to provide a process for manufacture of a stable, oral, multiple unit pharmaceutical composition containing high concentration of benzimidazole upto about 40%w/w capable of being filled in capsule size 5 for the dose of upto 40mg for omeprazole or upto 30mg for lansoprazole.

Further objects of the invention is to provide a process for manufacture of alkaline material treated non-pariel seeds suitable for deposition of alkaline benzimidazole dispersion containing dissolved benzimidazole and to withstand rigors and attrition of fluid bed processor.

Further the object of the invention is to provide a process, which consists of spraying aqueous or hydroalcoholic solution of benzimidazole in alkali metal hydroxide solution on treated non-pariel seeds to obtain drug pellets, which are further coated with sealant polymer followed by enteric polymer in a single equipment to obtain unagglomerated, uniformly shaped and sized pellets.

Description:

This invention relates to process for manufacture of a stable, oral, multiple unit pharmaceutical composition containing high concentration of benzimidazole upto about 40%w/w without the use of micronized benzimidazole, disintegrating agent and fillers. Surfactants in these compositions are part of enteric polymer system and are not in

contact with benzimidazole. Multiple unit pharmaceutical composition is in the form unagglomerated, uniformly shape and sized enteric-coated pellets that are processed continuously or in batches in single equipment fluid bed bottom spray processor. The enteric-coated pellets obtained by the process of the invention are capable of being filled in smallest size capsule (size 5) for ease of administration and patient acceptance. The process is environmental friendly as it involves aqueous or hydroalcoholic media.

Benzimidazole derivative is selected form omeprazole, lansoprazole, rabeprazole, pantoprazole, or their optically active isomer. For the purpose of this invention omeprazole is selected as the benzimidazole derivative. The process may be carried out in batches or continuously in single equipment to give enteric-coated pellets. The invention involves sequential deposition of:

a) alkaline material layer on non-pariel seeds to obtain treated non-pariel seeds
b) drug layer to obtain drug pellets
c) sealant polymer layer to obtain sealed pellets
d) enteric polymer layer to obtain enteric coated pellets

Enteric coated pellets containing benzimidazole has minimum acid degradation after 2 hours in 0.1N HCl and buffer release of not less than 85% after 45 minutes when tested in-vitro and is capable of being filled into size 5 to size 0 capsule.

This is distinct from the prior art as

- It provides a process for manufacturing pharmaceutical composition containing high concentration of benzimidazole upto about 40%w/w without the use of micronized benzimidazole, disintegrating agent, fillers and surfactant in contact with benzimidazole, having minimum acid degradation in 0.1N HCl after two hours and pH 6.8 buffer release of more than 85% w/w after 45 minute.
- The moisture content in the formulation is less than 5% w/w and preferably less than 3% w/w without having adverse effect on the stability of the formulation.
- It does not make use of micronized benzimidazole thereby decreasing drug micronization step in production and making the process more economical.
- It makes use of single equipment thereby decreasing the chances of cross contamination and limiting the exposure of potent drug to the operator making the process operator friendly.
- It has high batch yields with minimum drug losses as it utilizes solution of benzimidazole for deposition.

Following are the different stages of manufacturing, which involves sequential deposition of following layers.

Stage I: Treated Non-pariel Seeds

The first stage in the manufacture of pharmaceutical composition as enteric-coated pellets containing omeprazole is the deposition of alkaline material layer on the non-pariel seeds. When aqueous alkaline dispersion containing dissolved omeprazole was sprayed on non-pariel seeds there was problem of breakages of non-pariel seeds in fluid bed bottom spray processor. It was surprisingly found that when non – pariel seeds were treated with alkaline material the problem of breakage was solved. This treatment to non-pariel seeds involves spraying alkaline material along with binder on non-pariel seeds to produce treated non-pariel seeds. Alternatively, treated non-pariel seeds may also be obtained by blending alkaline material with starch during the production of non-pariel seeds. This alkaline material treated non-pariel seeds produced are possessing high integrity and strength and can withstand the further process of manufacturing enteric-coated pellets containing benzimidazole leading to uniform loading of benzimidazole thus resulting into high processing and batch yields.

Treatment of non-pariel seeds is carried out in fluid bed bottom processor wherein the non-pariel seeds are coated with mixture of water-soluble polymer, which is selected from the group of hydroxypropylmethylcellulose and alkaline material for e.g. light magnesium carbonate. The ratio of the polymer to alkaline material is about 1: 0.1 to 0.1: 1 and is preferably about 1: 0.5 to 0.5: 1. The total coating of this mixture is 1 - 4 % w/w of non-pariel seeds and the solid content of the spraying suspension is about 5 - 15 % w/w. The process is carried out in fluid bed processor with inlet air temperature between 60 - 90°C, outlet air temperature 40 - 55°C, atomization air pressure 1.0 - 3.5 bars, fluidization flap open between 15 - 90% and continuous spray rate between 1 - 300 ml / min. These treated non-pariel seeds are used for the production of drug pellet and subsequent stage.

Stage II: Drug Pellets

The next stage is the deposition of drug layer on treated non-pariel seeds to obtain drug pellets or drug core. It involves deposition of suspension of dissolved omeprazole on treated non-pariel seeds. The solution of omeprazole is prepared by dissolving omeprazole in aqueous solution of alkali metal hydroxide. The next step is the preparation of binder solution wherein the binder is dispersed and dissolved in water. The drug solution is mixed with aqueous binder solution. Antitack agent is added to above solution. The suspension is filtered through appropriate mesh and is sprayed on treated non pariel seeds in fluid bed processor with inlet air temperature between 60 - 90°C, outlet air temperature 40 - 55°C, atomization air pressure 1.0 - 3.5 bars, fluidization flap open between 15 - 90% and continuous spray rate between 1 - 300 ml /

min. Drug pellets are obtained after complete spraying of aqueous suspension containing omeprazole in dissolved form. The drug pellets are dried in Fluid bed bottom spray processor to arrive moisture content of less than 5%w/w and preferably less than 3%w/w. The yield of the process is about 98% w/w.

The content of omeprazole in the drug pellets is 5-60% w/w. The moisture content of the drug pellets is less than 5% w/w preferably less than 3% w/w. The particle size of the drug pellets ranges from about 600 – 2057 microns and preferably about 710 – 1680 microns. The particle size of treated non-pariel seeds size may be from 420-1405 microns and preferably from about 710-1204 microns.

The alkali metal hydroxide is selected from the group consisting of sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, ammonium hydroxide and their mixtures thereof and preferably is sodium hydroxide. The concentration of sodium hydroxide in the drug pellets is about between 12 – 30 % w/w of omeprazole and is preferably about 12 – 25% w/w.

The binder is selected from the group of water soluble binder which can withstand high pH, consisting of hydroxypropylmethylcellulose, hydroxypropylcellulose, polyvinylpyrollidone, sodiumcarboxymethylcellulose, methylcellulose and their mixtures and is preferably hydroxypropylmethylcellulose alone or in combination with polyvinylpyrollidone.

Hydroxypropylmethylcellulose used as a binder has a nominal viscosity of 5 – 100cps and preferably about 5 - 15 cps measured on 2% w/w solution at 20°C. The concentration of the binder in drug pellets is about 10 - 40 % w/w of omeprazole and is preferably about 15 - 35 % w/w of omeprazole.

Antitack agents is selected form the group consisting of talc, colloidal silicon dioxide, glyceryl monostearate, glyceryl behenate and their mixtures, the preferable choice being talc with or without colloidal silicon dioxide and are used in the concentration level of about 7.5 - 25 % w/w of omeprazole.

The total solid content of the spraying suspension containing dissolved omeprazole is not more than 30 % w/w and is preferably about 15 - 20 % w/w.

The final pH of the spraying suspension is in the range of about 11-14.

The drug pellets after drying shows about 100% of drug release within about 10 minutes in pH 6.8 buffer when tested in-vitro using USP 24 type II dissolution apparatus.

Stage III: Sealed pellets

The next stage is deposition of sealant polymer layer on drug pellets to obtain sealed layer. Seal coating suspension is prepared by dispersing and / or dissolving sealant

polymer in water. Antitack agent is added to the above solution. Suspension is filtered through appropriate mesh and is sprayed on drug pellets in fluid bed processor to form a seal coat, which prevents the contact of acidic enteric coating material with drug layer.

The coating parameters are same as per the drug pellets stage. The sealed pellets are dried for about 20 - 40 minutes to achieve the moisture level less than 5% and preferably less than 3%w/w. The sealant polymer is selected from group consisting of hydroxypropylmethylcellulose, hydroxypropylcellulose, polyvinylpyrollidone, sodium carboxymethylcellulose, methylcellulose and their mixtures and is preferable hydroxypropylmethylcellulose. The concentration of hydroxypropylmethylcellulose is about 10 to 150 % w/w of omeprazole.

Hydroxypropylmethylcellulose used as a sealant polymer has a nominal viscosity of about 3 – 100 cps and preferably about 5 - 15 cps measured on 2% w/w solution at 20°C.

The solid content of the above seal coating suspension is between about 8 - 12% w/w. The antitack agent is selected from the group consisting of talc, colloidal silicon dioxide, glyceryl monostearate, glyceryl behenate and their mixtures used in the concentration level of about 10 - 30 % w/w of the sealant polymer and preferably talc.

Optionally alkaline agent such as light magnesium carbonate may also be added to these seal coating suspension to improve the barrier property of the membrane.

The sealed pellets after drying shows about 100% of drug release within about 10 minutes in pH 6.8 buffer when tested in-vitro using USP 24 type II dissolution apparatus.

Stage IV Enteric-Coated Pellets

The final stage in the process for manufacture of the pharmaceutical composition as enteric-coated pellets containing omeprazole is deposition of enteric layer on sealed pellets. Enteric coating suspension is prepared by dissolving neutralizing agent in water, which is slowly added under stirring to aqueous dispersion of methacrylic acid copolymer. This aqueous dispersion of methacrylic acid is ready to use dispersion and may contain upto about 3% w/w of surfactants of the total solid content present in the dispersion. Hence the surfactants are present in enteric polymer layer only and in no way comes in contact with omeprazole. This is in contrast to the formulations and processes in the related art as in U.S. Patent No. 4786505, U.S. Patent No. 5385739, U.S. Patent No. 6077541, EP 1108425, U.S. Patent No. 6207198 where the surfactant in fairly large quantities (upto about 5%w/w of drug layer) is in contact with drug. Plasticizer, antitack and colorant are added to water to form a fine suspension and this

suspension is added to the above dispersion. The final enteric coat suspension is then filtered through appropriate mesh. The pH of enteric coat suspension is about 5.2 – 5.8. The sealed pellets after drying are coated with above enteric coat suspension. The coating parameters are same as drug pellets stage. The enteric coat polymer is methacrylic acid copolymer and is used in the concentration of about 12.5 - 30 % w/w of sealed pellets.

The plasticizers are selected from the group consisting of polyethylene glycol, triethyl citrate, triacetin, tributyl citrate, castor oil, dibutyl sebacate, tween 80 and is used in the concentration of about 10 - 25 % w/w of the enteric coat polymer and preferably is polyethylene glycol. The neutralizing agent is selected from the group consisting of sodium, potassium, calcium, magnesium, ammonium hydroxide and their mixtures and preferably is sodium hydroxide and is used in the concentration of about 1 - 2 % w/w of enteric coat polymer. Any other agent that is capable of neutralizing the acidic group of methacrylic acid copolymer may also be used.

The antitack agent is selected from the group consisting of talc, colloidal silicon dioxide, glyceryl monostearate, glyceryl behenate and their mixtures used in the concentration level of about 10 - 30 % w/w of the polymer for enteric coating. The preferable choice is talc with or without colloidal silicon dioxide. The solid content of the final enteric coating suspension is in the range of about 15 - 25% w/w.

The amount of enteric polymer guarantees gastric resistance and allows the dissolution of omeprazole in proximal part of the small intestine. The final enteric-coated product is sieved through appropriate mesh and is capable of being encapsulated in hard gelatin capsules from size 5 to size 0. The entire manufacturing process is aqueous and it results in spherical, glossy pellets containing negligible amount of twins or triplet. The benzimidazole content in the final enteric-coated pellets is about upto 40% w/w. The yield of the final product is about in the range of 95 – 100% and usually above 98% w/w.

In one of the embodiments of the invention the process involving all the stages that is treated non-pariel seed stage, drug pellet stage, sealed pellets stage and enteric-coated pellets stage are carried out continuously in a single equipment fluid bed processor.

In another embodiment of the invention the process is a batch process, but all the stages that is treated non-pariel seed stage, drug pellet stage, sealed pellets stage and enteric-coated pellets stage are carried out in a single equipment fluid bed processor, where the representative sample are sampled at the end of each stages that is drug pellet stage, sealed pellets stage and enteric-coated pellets stage for analysis.

Other equipments such as coating pan, tangential spray coater may also be used for manufacturing enteric-coated pellets containing benzimidazole using the above process.

Examples:

The invention is further described by following sets of non – limiting examples.

Enteric-coated pellets containing omeprazole involves following manufacturing stages, which are as follows.

Stage I: Preparation of treated non-pariel seeds

Sr. No.	Ingredients	Quantity (kg)
1.	Non pariel seeds 18 – 20#	100
2.	Hydroxypropylmethylcellulose	1.5
3.	Magnesium Carbonate	1.5
4.	Water	30

Hydroxypropylmethylcellulose (HPMC) is dispersed and dissolved in water. Magnesium carbonate is added to this solution to obtain a fine suspension, which is filtered through appropriate mesh. This suspension is sprayed on non-pariel seeds in fluid bed bottom spray processor to obtain treated non – pariel seeds, which are used for further process.

Hydroxypropylmethylcellulose and magnesium carbonate are used in the ratio of 1:0.5 to 0.5:1 and are used in the concentration level of 1 – 4% w/w of the non-pariel seeds.

Examples 1: Omeprazole Enteric Coated Pellets

Sr. No.	Ingredients	Quantity (% w/w)	Quantity (% w/w)	Quantity (% w/w)	Quantity (% w/w)
Stage II: Drug Pellets					
1	Omeprazole	24.5	13.8	8.5	40.00
2	Treated Non-Pariel Seeds	32.3	56.5	61.9	15.00
3	Sodium Hydroxide	3.2	1.8	1.1	5.26
4	Talc	3.7	2.1	1.3	3.00
5	HPMC E15	7.3	3.4	2.6	6.00
6	Water	Qs	Qs	Qs	Qs
Stage III: Sealed Pellets					
7.	HPMC E5	4.3	4.7	4.9	4.35
8.	Talc	0.4	0.5	0.5	0.47
9.	Water	Qs	Qs	Qs	Qs

Stage IV: Enteric Coated Pellets

10	Methacrylic acid copolymer type C (solid content)	17.3	12.4	13.7	18.5
11.	Polyethylene Glycol 6000	1.7	1.2	1.4	1.9
12.	Talc	3.8	2.6	2.9	3.9
13.	Titanium dioxide	1.2	0.8	1.0	1.3
14.	Sodium hydroxide	0.3	0.2	0.2	0.32
15.	Water	Qs	Qs	Qs	Qs
	Particle size of treated non – pariel seeds	18 – 20 mesh ASTM	16 – 18 mesh ASTM	16 – 18 mesh ASTM	20 – 22 mesh ASTM
	Dose	20 mg	20 mg	20 mg	40 mg
	Size of capsule for encapsulation	5	4	2	5

Stage II: Drug Pellets

Sodium hydroxide is dissolved in water followed by cooling to room temperature. Omeprazole is added to this solution. Separately disperse and / or dissolve hydroxypropylmethylcellulose E15 in water. Omeprazole solution is mixed with hydroxypropylmethylcellulose solution. Talc is added to above solution and the resulting suspension is filtered through appropriate mesh. The above suspension is sprayed on treated non-pariel seeds in fluid bed bottom spray processor to obtain drug pellets, which are dried in the same equipment to moisture content of less than 5% w/w and preferably less than 3% w/w. The drug pellets after drying shows about 100% of drug release within about 10 minutes in pH 6.8 buffer when tested in-vitro using USP 24 type II dissolution apparatus.

Stage III: Sealed Pellets

Seal coating suspension is prepared by dispersing and / or dissolving hydroxypropylmethylcellulose E5 in water. Talc is added to above solution. The resulting suspension is filtered through appropriate mesh and is sprayed on drug pellets in fluid bed processor to form sealed pellets. These sealed pellets are dried to moisture content of less than 5% w/w and preferably less than 3% w/w. The sealed pellets after drying shows about 100% of drug release within about 10 minutes in pH 6.8 buffer when tested in-vitro using USP 24 type II dissolution apparatus.

Stage IV: Enteric Coated Pellets

Enteric coating suspension is prepared by dissolving sodium hydroxide in water, which is slowly added under stirring to aqueous dispersion of methacrylic acid copolymer type C. Polyethylene glycol 6000 is dissolved separately in water. To this solution talc and titanium dioxide is added to form a fine suspension and this suspension is added to the above dispersion. The final enteric coat suspension is then filtered through appropriate mesh. This suspension is sprayed on sealed pellets in fluid bed processor to obtain enteric-coated pellets containing omeprazole. These enteric-coated pellets are then dried to have moisture content of less than 5% w/w and preferably less than 3% w/w.

The process of the invention results in the production of enteric-coated pellets containing omeprazole that does not require micronisation of omeprazole or any additional excipients like disintegrating agents, fillers or surfactant in contact with omeprazole for improving the dissolution of omeprazole.

The enteric-coated pellets containing omeprazole thus obtained is tested in-vitro for acid resistance in 0.1N HCl after 2 hours and buffer dissolution in pH 6.8 after 45 which is described below. The acceptance criteria for these pellets are laid down in the specification below.

The pellets may receive an additional coat of an enteric layer if it does not comply with the specification for acid degradation as specified below.

The enteric-coated pellets containing omeprazole are filled in capsule of varying sizes that is from size 5 to size 0 depending on the final concentration of omeprazole in enteric-coated pellets.

Example 2: Lansoprazole enteric-coated pellets

Formulation for encapsulation in size 5 hard gelatin capsules.

Sr. No.	Ingredients	Quantity (%w/w)
Stage I : Drug Pellets		
1.	Lansoprazole	30.0
2.	Treated Non- Pariel Seeds 18 – 20 mesh ASTM	22.7
3.	Sodium Hydroxide	7.5
4.	Talc	3.0
5.	Hydroxypropylmethylcellulose E15	6.0
6.	Colloidal Silicon dioxide	0.5
7.	Water	QS
8.	Isopropyl Alcohol	QS

Stage II : Sealed Pellets

9.	Hydroxypropylmethylcellulose E5	4.2
10.	Talc	0.4
11.	Water	Qs

Stage III : Enteric Coated Pellets

12.	Methacyrlic acid copolymer type C (solid content)	18.6
13.	Polyethylene Glycol 6000	1.86
14.	Talc	3.9
15.	Colloidal Silicon dioxide	0.24
16.	Titanium dioxide	0.85
17.	Sodium hydroxide	0.25
18.	Water	Qs
	Size of capsule for encapsulation	'5'
	Dose	30 mg

The process for the manufacture of enteric-coated pellets containing Lansoprazole is same as described above except that Lansoprazole is dissolved in sodium hydroxide solution in water containing small quantity of isopropyl alcohol.

In-vitro dissolution studies of these pellets are carried out as described below. The acceptance criteria for these pellets are laid down in the specification below.

The pellets may receive an additional coat of an enteric layer if it does not comply with the specification for acid degradation as specified below.

Dissolution Studies:

The pellets containing omeprazole or lansoprazole, which are manufactured, as described in above examples are tested for acid resistance in 0.1N HCl after 2 hours and buffer dissolution in pH 6.8 after 45 minutes using USP 24 Type II dissolution test apparatus. The results obtained are as follows.

Time	pH	% Drug release	Specification
2 hours	0.1 N HCl	0 – 7	NMT 15% degrades in 2 hours
45 minutes	pH 6.8 buffer	90 – 100	NLT 85%

These pellets which meets the requirements of the above mentioned specification are filled in capsule of different sizes containing unit dose of benzimidazole.

The pellets containing upto about 40% w/w of omeprazole are capable of being filled in size 5 capsule for the dose of upto about 40mg of omeprazole. The enteric-coated pellets containing about 30% w/w of lansoprazole are capable of being filled in size 5 capsule for the dose of upto about 30 mg of lansoprazole.

Stability:

The enteric-coated pellets containing about 20 mg omeprazole prepared as described in example above were encapsulated in size 5 hard gelatin capsules and subjected to accelerated stability condition at 40° C/75% RH and 25°C/60 % RH. The stability results are as follows.

Period	Condition	Assay %w/w	Dissolution Profile	
			Acid Stage (%w/w)	Buffer Stage (%w/w)
Initial	-	98.5	1.0	99.85
1 Month	25°C/ 60%RH	99.9	0.24	98.68
1 Month	40°C/ 75%RH	100.05	0.0	99.04
3 Month	25°C/ 60%RH	97.25	1.5	98.45
3 Month	40°C/ 75%RH	99.7	0.31	97.56
6 Month	25°C/ 60%RH	98.45	0.1	101.1
6 Month	40°C/ 75%RH	96.15	0.0	92.59

The results presented above shows that enteric-coated pellets containing omeprazole of the present invention are stable atleast for a period 2 years.

Bioequivalence Study:

A bioequivalence study was carried out in 12 healthy human volunteers using Losec RTM as reference. The results are as follows.

Pharmacokinetic parameters	Test	Reference
Cmax (μg/ml) (Avg. ± std. dev.)	0.92 (±0.22)	0.88 (±0.17)
Tmax (hrs.) (Avg. ± std. dev.)	3.67 (±0.47)	3.25 (±0.43)
AUC (0-24) μg.hr/ml (Avg. ± std. dev.)	6.70 (±1.39)	7.70 (±1.62)

Various modification and alteration may be made in the process and the product without varying the spirit and scope of the invention. The process and the product described in the invention are merely illustrative of the preferred embodiments of the invention and do not limit the scope of the invention.

We Claim:

1. A novel operator friendly batch or continuous process in a single equipment for manufacture of stable oral multiple unit pharmaceutical composition containing upto about 40 %w/w of benzimidazole wherein the process comprises of sequential deposition of:
   a) alkaline material layer to obtain treated non-pariel seeds
   b) drug layer to obtain drug pellets
   c) sealant polymer layer to obtain sealed pellets
   d) enteric polymer layer containing surfactants to obtain enteric coated pellets
   on non-pariel seeds wherein the enteric coated pellets has minimum acid degradation and buffer release of not less than 85% after 45 minutes and is capable of being filled into size 5 to size 0 capsule, the pharmaceutical composition being exempt of surfactants in contact with benzimidazole, disintegrating agents and fillers.
2. A process as claimed in claim 1 wherein the alkaline material layered non-pariel seeds are prepared by depositing about 1 to 4% by weight of non-pariel seeds, the mixture of hydroxypropylmethylcellulose and light magnesium carbonate in the ratio of about 1: 0.1 to 0.1: 1 and is preferably about 1: 0.5 to 0.5: 1 on non pariel seeds.
3. A process as claimed in claim 1, wherein the deposition of drug layer to obtain drug pellets comprises:
   a) dissolving alkali hydroxide in aqueous or hydroalcoholic media;
   b) dissolving benzimidazole in alkaline solution;
   c) dispersing and / or dissolving binder in aqueous media;
   d) mixing of alkaline benzimidazole solution with binder solution;
   e) adding antitack agent to benzimidazole - binder dispersion;
   f) spraying the suspension containing benzimidazole in dissolved form on alkaline material treated non-pariel seeds followed by drying to obtain drug pellets.
4. A process as claimed in claim 1 wherein the deposition of sealant polymer layer to obtain sealed pellets comprises:
   a) dispersing and / or dissolving the sealant polymer/s in aqueous media followed by addition of antitack agent;
   b) seal coating the drug pellets by spraying the suspension containing one or more sealant polymers in aqueous media with anti-tack agent followed by drying to obtain sealed pellets;
5. A process as claimed in claim 1 wherein the deposition of enteric polymer layer to obtain enteric coated pellets comprises:

a) dissolving neutralizing agent in aqueous media;
b) adding neutralizing agent solution to aqueous dispersion of enteric polymer;
c) dissolving plasticizer in aqueous media followed by addition of antitack agent and colorant;
d) mixing suspension containing plasticizer with dispersion containing enteric polymer;
e) spraying the enteric coating suspension on sealed pellets followed by drying to obtain enteric coated pellets.

6. A process as claimed in claims 1 and 3 wherein drug layer comprises of benzimidazole upto about 40 %w/w of the final enteric-coated pellets, the alkali metal hydroxide used is about 12 – 30 %w/w of benzimidazole and preferably about 12 – 25% w/w and is selected form sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, ammonium hydroxide and their mixtures the preferable one being sodium hydroxide, binder is about 10 - 40 % w/w of benzimidazole and is preferably about 15 - 35 % w/w selected from hydroxypropylmethylcellulose, hydroxypropylcellulose, methylcellulose, sodiumcarboxymethylcellulose, polyvinylpyrollidone and their mixtures, the preferable choice being hydroxypropylmethylcellulose with or without polyvinylpyrollidone, antitack agent is about 7.5 – 25 %w/w of benzimidazole selected form the group consisting of talc, colloidal silicon dioxide, glyceryl monostearate, glyceryl behenate and their mixtures, the preferable choice being talc with or without colloidal silicon dioxide.

7. A process as claimed in claims 1 and 4 wherein the sealant polymer is about 10 to 150 % w/w of benzimidazole selected from the group consisting of hydroxypropylmethylcellulose, hydroxypropylcellulose, methylcellulose, sodium carboxymethylcellulose, polyvinylpyrollidone, preferably hydroxypropylmethylcellulose, antitack agent is about 10 – 30 %w/w of sealant polymer selected from talc, colloidal silicon dioxide, glyceryl monostearate, glyceryl behenate and their mixtures preferably talc.

8. A process as claimed in claims 1 and 5 wherein the enteric polymer is about 12.5 - 30 % w/w of sealed pellets is methacrylic acid copolymer, neutralizing agent is about 1 – 2 % w/w of enteric polymer selected form sodium, potassium, calcium, magnesium and ammonium hydroxide and their mixtures preferably sodium hydroxide, plasticizer is about 10 – 25 %w/w of enteric polymer selected from polyethylene glycol, triethyl citrate, triacetin, tributyl citrate, castor oil, dibutyl sebacate and tween 80 preferably polyethylene glycol, antitack agent is about 10 - 30 % w/w of enteric polymer selected from talc, colloidal silicone dioxide, glyceryl

monostearate, glyceryl behenate and their mixtures, the preferable choice being talc with or without colloidal silicon dioxide.

9. A process as claimed in claim 1 wherein the benzimidazole is selected from omeprazole, lansoprazole and their combination thereof.
10. A process as claimed in claims 1 and 3 – 5 wherein the process carried out in fluid bed processor at inlet air temperature about 60 - 90°C, outlet air temperature about 40 - 55°C, atomization air pressure about 1.0 - 3.5 bars fluidization flap open to about 15 - 90% and spray rate about between 1 – 300 ml per minute.
11. A process as claimed in claim 1 wherein the pellets containing unit dose of benzimidazole is capable of being filled in size 5 capsule.
12. A process as claimed in claims 1, 9 and 11 wherein the pellets containing upto about 40mg omeprazole or upto about 30mg lansoprazole is capable of being filled in size 0 to size 5 capsule.
13. A process as claimed in claims 1, 9, 11 and 12 wherein the pellets containing upto about 40mg omeprazole or upto about 30mg lansoprazole is capable of being filled in size 5 capsule.
14. A process as claimed in claim 1 – 5 wherein the process is batch or continuous process carried in a single equipment fluid bed bottom spray processor.
15. A process as claimed in claim 1 wherein the moisture content of pellets containing benzimidazole is not more than 5% w/w and is preferably not more than 3%w/w.
16. A process as claimed in claims 1, 3 and 5 wherein the pH of benzimidazole suspension is in the range of about 11 – 14 and of enteric coating suspension is about 5.2 – 5.8.
17. A stable oral multiple unit pharmaceutical composition as enteric coated pellet containing upto about 40 %w/w of benzimidazole wherein the enteric coated pellet comprises of four layers:

a) alkaline material layer
b) drug layer
c) sealant polymer layer
d) enteric polymer layer containing surfactants

sequentially deposited on non-pariel seeds wherein the enteric coated pellets has minimum acid degradation and buffer release of not less than 85% after 45 minutes and is capable of being filled into size 5 to size 0 capsule, the pharmaceutical composition being exempt of surfactants in contact with benzimidazole, disintegrating agents and fillers.

18. A pharmaceutical composition as claimed in claim 17 wherein the alkaline material layer comprises of about 1 to 4% by weight of non-pariel seeds the mixture of

hydroxypropylmethylcellulose and light magnesium carbonate in the ratio of about 1: 0.1 to 0.1: 1 and is preferably about 1: 0.5 to 0.5: 1.

19. A pharmaceutical composition as claimed in claim 17 wherein the drug layer comprises of benzimidazole upto about 40 %w/w of the final enteric-coated pellets, alkali metal hydroxide in the range of about 12 – 30 %w/w and preferably between about 12 – 25 %w/w of benzimidazole, binder in the range of about 10 – 40 %w/w and preferably between about 15 – 35 %w/w of benzimidazole, antitack agent in the range of about 7.5 – 25 %w/w of benzimidazole.

20. A pharmaceutical composition as claimed in claim 17 wherein the sealant polymer layer comprises of sealant polymer in the range of about 10 – 150 %w/w of benzimidazole, antitack agent in the range of about 10 – 30 %w/w of sealant polymer.

21. A pharmaceutical composition as claimed in claim 17 wherein the enteric layer comprises of enteric polymer in the range of about 12.5 - 30 % w/w of sealed pellets, neutralizing agent in the range of about 1 – 2 %w/w of enteric polymer, plasticizer in the range of about 10 – 25% w/w of enteric polymer, antitack agent in the range of about 10 – 30% w/w of enteric polymer.

22. A pharmaceutical composition as claimed in claims 17 and 19 wherein the drug layer comprising of alkali metal hydroxide is selected form sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, ammonium hydroxide and their mixtures the preferable one being sodium hydroxide in the range of about 12 – 25 %w/w of benzimidazole, binder is selected from hydroxypropylmethylcellulose, hydroxypropylcellulose, methylcellulose, sodiumcarboxymethylcellulose, polyvinylpyrollidone and their mixtures, the preferable choice being hydroxypropylmethylcellulose with or without polyvinylpyrollidone in the range of 15 – 35 %w/w of benzimidazole, antitack agent is selected form the group consisting of talc, colloidal silicon dioxide, glyceryl monostearate, glyceryl behenate and their mixtures, the preferable choice being talc with or without colloidal silicon dioxide in the range of about 7.5 – 25 %w/w of benzimidazole.

23. A pharmaceutical composition as claimed in claims 17 and 20 wherein the sealant polymer layer comprising of sealant polymer is selected from the group consisting of hydroxypropylmethylcellulose, hydroxypropylcellulose, methylcellulose, sodium carboxymethylcellulose, polyvinylpyrollidone and their mixtures and is preferably hydroxypropylmethylcellulose in the range of 10 – 150 %w/w of benzimidazole, antitack agent is selected from talc, colloidal silicon dioxide, glyceryl monostearate,

glyceryl behenate and their mixtures preferably talc in the range of 10 – 30 %w/w of sealant polymer.

24. A pharmaceutical composition as claimed in claims 17and 21 wherein the enteric layer comprising of enteric polymer is methacrylic acid copolymer in the range of 12.5 - 30 % w/w of sealed pellets, neutralizing agent is selected form sodium, potassium, calcium, magnesium and ammonium hydroxide and their mixtures preferably sodium hydroxide in the range of about 1 – 2 %w/w of enteric polymer, plasticizer is selected from polyethylene glycol, triethyl citrate, triacetin, tributyl citrate, castor oil, dibutyl sebacate and tween 80 preferably polyethylene glycol in the range of about 10 – 25% w/w of enteric polymer, antitack agent is selected from talc, colloidal silicone dioxide, glyceryl monostearate, glyceryl behenate and their mixtures, the preferable choice being talc with or without colloidal silicon dioxide in the range of about 10 – 30 %w/w of enteric polymer.

25. A pharmaceutical composition as claimed in claim 17 wherein the benzimidazole is selected from omeprazole, lansoprazole and their combination thereof.

26. A pharmaceutical composition as claimed in claim 17 wherein the enteric coated pellets containing unit dose of benzimidazole is capable of being filled in size 5 capsule.

27. A pharmaceutical composition as claimed in claims 17, 25 - 26 wherein the enteric coated pellets containing upto about 40mg omeprazole or upto about 30mg lansoprazole is capable of being filled in size 0 to size 5 capsule

28. A pharmaceutical composition as claimed in claims 17, 25 - 26 wherein the enteric coated pellets containing upto about 40mg omeprazole or upto about 30mg lansoprazole is capable of being filled in size 5 capsule.

29. A pharmaceutical composition as claimed in claim 17 – 21 wherein the process is batch or continuous process carried in a single equipment fluid bed bottom spray processor.

30. A pharmaceutical composition as claimed in claim 17 wherein the moisture content of pellets containing benzimidazole is not more than 5% w/w and is preferably not more than 3%w/w.

31. A process and pharmaceutical composition as claimed in claims 1, 3, 6, 9, 17, 19 and 25 wherein the benzimidazole used may not be micronized.