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(54) Title: SOLID ORAL DOSAGE FORMS OF RABEPRAZOLE

(57) Abstract: The present invention relates to oral solid pharmaceutical dosage forms comprising proton pump inhibitor, as single active drug. The present specification specifically relates to orally disintegrating tablets that readily disintegrates in the mouth, releasing enteric coated drug pellets or units, comprising a proton pump inhibitor, Rabeprazole or a pharmaceutically acceptable salt thereof. The specification also relates to modified release oral dosage forms, which comprise of a core and a combination of a release modifying layers that together achieve beneficial release properties, suitable for once daily administration. The application also relates to processes for preparing the dosage forms as well as their use in the treatment of gastrointestinal diseases.

SOLID ORAL DOSAGE FORMS OF RABEPRAZOLE

CROSS REFERENCE

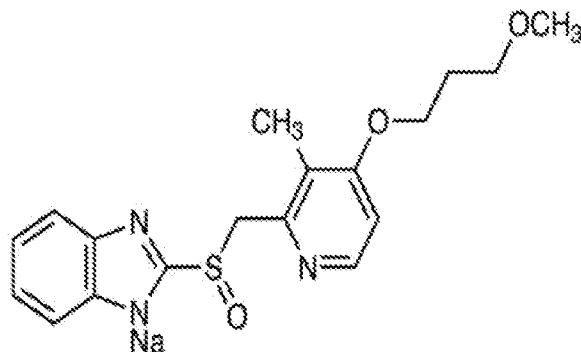
This application claims priority from Indian Patent Application No. 202141060162 filed on December 23, 2021.

TECHNICAL FIELD OF THE INVENTION

The present invention relates to oral solid pharmaceutical dosage forms comprising proton pump inhibitor, as single active drug. The present specification specifically relates to orally disintegrating tablets that readily disintegrates in the mouth, releasing enteric coated drug pellets or units, comprising a proton pump inhibitor, Rabeprazole or a pharmaceutically acceptable salt thereof. The specification also relates to modified release oral dosage forms, which comprise of a core and a combination of a release modifying layers that together achieve beneficial release properties, suitable for once daily administration. The application also relates to processes for preparing the dosage forms as well as their use in the treatment of gastrointestinal diseases.

BACKGROUND OF THE INVENTION

Rabeprazole is a substituted benzimidazole derivative, chemically known as 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl]sulfinyl]-1H-benzimidazole. Rabeprazole belongs to a class of proton-pump inhibitors that inhibits gastric acid secretion by inhibiting the enzyme H^+ , K^+ ATPase at the secretory surface of the gastric parietal cell and is useful for the prevention and treatment of ulcers, gastro esophageal reflux disease (GERD or heartburn) and other conditions involving excessive acid secretion. It is represented by the following structural formula:



Gastro esophageal reflux disease (GERD) is among the most common disorders seen by gastroenterologists and general practitioners. H2 receptor antagonists are widely prescribed for GERD. They are advantageous and offer more potent and a longer duration of action on gastric acidity. Proton pump inhibitors, such as Rabeprazole, are known to offer significant advantages over H2 receptor antagonists in terms of symptom resolution, healing and prevention of relapse for GERD, and are rapidly replacing H2 receptor antagonists, for the treatment of GERD.

Proton pump inhibitors are, however, susceptible to degradation/transformation in acidic reacting and neutral media. The degradation is catalyzed by acidic reacting compounds. The active compounds are stabilized with alkaline reacting compounds.

WO 2004014345 describes the pharmaceutical preparations of pellets containing benzimidazole compounds with an inert core to which a layer containing an active ingredient is applied. Further one or more optional inert layers and an outer layer comprising an enteric coat, that is, an enteric layer are applied.

WO 9601623 and WO 9601624 describe tableted dosage forms of omeprazole and other proton pump inhibitors, wherein enteric coating layered pellets together with other excipients are compressed into a multiple unit tableted dosage form. It is essential in these tableted formulations that the enteric coating layer can withstand the compression forces during tableting.

WO 9932093 A1 discloses an enteric coated pharmaceutical dosage form comprising an H⁺, K⁺-ATPase inhibitor. The formulation comprises at least two portions of the H⁺, K⁺-ATPase inhibitor to be released in at least two consecutive pulses. At least one of the portion has a delayed release. Those pellets or tablets giving the delayed release pulse include a surrounding lag time controlling layer, which is a semipermeable membrane comprising a water resistant polymer, and which disrupts after a desired time.

EP 1194131 B1 discloses a controlled release dosage form producing at least a timed pulse. The delayed release is achieved with a coating comprising one or more ammonio methacrylate copolymers (water insoluble polymers).

Despite different approaches disclosed in the art and a wide range of oral dosage forms available for administration of proton pump inhibitors, there is an unmet need for geriatric and pediatric patients, or patients with dysphagia, who have difficulty in swallowing conventional oral dosage forms.

Orally disintegrating tablets (ODTs) have become a preferred dosage form for delivering active agents to patients having difficulty swallowing or who experience dysphagia. These compositions rapidly disintegrate in the oral cavity providing minimum patient discomfort.

Even though the oral disintegrating formulations are advantageous, there is no approved oral disintegrating formulation of Rabeprazole in the world and thus there remains need for oral disintegrating formulations of Rabeprazole which is easier to consume, melts in mouth and can be taken with and without water, have quick absorption and quick onset of action.

Also, there is a need for oral dosage form comprising Rabeprazole that has been developed with the aim of securing an effective acid control over the whole 24- hour period, thus removing the necessity for twice daily dosing. This will provide an aid of use and enhance patient compliance. Such a modified release formulation would also result in a greater efficacy in acid secretion inhibition, especially at night, compared with the conventional formulations of proton pump inhibitors.

OBJECT OF THE INVENTION

An object of the present invention is to provide oral solid pharmaceutical dosage forms comprising Rabeprazole, as single active drug.

Another object of the present invention is to provide oral disintegrating solid pharmaceutical formulations of Rabeprazole with quick absorption, good taste, easy swallowing, good disintegrated effect, and convenient to use for patients and the method for preparing the same.

Another object of the present specification is to provide oral disintegrating pharmaceutical formulations of Rabeprazole or a pharmaceutical acceptable salt thereof comprising a plurality of units or cores or pellets comprising:

- i. inert core comprising sugar spheres, coated by an optional seal coating layer
- ii. a drug layer comprising a plurality of cores or units or pellets comprising a therapeutically effective amount of a proton pump inhibitor stabilized with an alkalizing agent;
- iii. a barrier coating or sub coating around the drug layer comprising polymer, an alkalizing agent;
- iv. an enteric coating comprising an enteric polymer having solubility at pH higher than 5.5;
- v. a reverse enteric coating or top coating comprising reverse enteric polymer to protect the integrity of enteric layer in salivary pH, and
- vi. extragranular materials comprising pharmaceutically acceptable excipients.

Yet another object of the present specification is to provide oral disintegrating pharmaceutical formulations of Rabeprazole or a pharmaceutical acceptable salt thereof comprising a plurality of units or cores or pellets comprising:

- i. an inert core comprising sugar spheres, coated by an optional seal coating layer, and sugar spheres is present in an amount of about 2% to about 15% by weight of a total tablet weight
- ii. a drug layer comprising a plurality of cores or units or pellets comprising a therapeutically effective amount of a proton pump inhibitor stabilized with an alkalizing agent; wherein the alkalizing agent is selected from sodium hydroxide, magnesium hydroxide, magnesium oxide, sodium oxide or combination thereof and the drug layer is present in an amount of about 5% to about 15% by weight of a total tablet weight,
- iii. a barrier coating or sub coating around the drug layer comprising ethyl cellulose and hypermellose polymer and its derivatives in all grades like phthalate, acetate, HPC SSL, HPC LF and or combinations thereof, an alkalizing agent which is selected from sodium hydroxide, magnesium hydroxide, magnesium oxide, sodium oxide or combination thereof; and the Barrier coating or sub coating layer is present in an amount of about 5% to about 20% by weight of a total tablet weight
- iv. an enteric coating comprising enteric polymer having solubility at pH higher than 5.5 and selected from acrylic polymers and copolymers for example eudragit in all grades, hypermellose, hypermellose phthalate or combinations thereof and the enteric coating layer is present in an amount of about 15% to about 30% by weight of a total tablet weight.
- v. a coating comprising reverse enteric polymer or top coating to protect the enteric coating, and is selected from one or more of acrylic polymers or copolymers like tertbutyl amino ethyl (meth)acrylate, butyl methacrylate, dimethylaminoethyl methacrylate, methyl

methacrylate copolymer or combinations thereof and is present in an amount of about 2.5% to about 30% by weight of a total tablet weight, and

- vi. extragranular material comprising pharmaceutically acceptable excipients selected from at least one disintegrant, filler, glidant, lubricant, binder, diluent, surfactant, plasticizer, anti-tacking agent, alkaline substance, tonicity enhancing agent, wetting agent, buffering substance, preservative, flavoring agent, an opacifier, colorant, anti-oxidant or a mixture thereof.

Yet another object of the present invention is to provide modified release oral dosage forms, which comprise of a core and a combination of a release modifying layers that together achieve beneficial release properties, suitable for once daily administration.

Another object of the present specification is to provide a modified release solid oral dosage form of Rabeprazole, wherein the drug is released at a rate allowing controlled absorption thereof over a twenty-four-hour period following oral administration, comprising:

- i) a core comprising a therapeutically effective amount of Rabeprazole stabilized with an alkalizing agent;
- ii) a barrier coating or sub coating around the drug core comprising ethyl cellulose, hypermellose polymer and its derivatives in all grades like phthalate, acetate, HPC SSL, HPC LF and or combinations thereof, and an alkalizing agent;
- iii) an enteric coating comprising enteric polymer having solubility at pH higher than 5.5, and
- iv) optionally, a pulse coating layer comprising water-insoluble polymers, water soluble polymers, enteric polymers, waxes and mixtures thereof.

Another object of the present invention is to provide processes for preparing the dosage forms as disclosed herein.

In yet another aspect, the present specification relates to solid oral dosage compositions of Rabeprazole or its pharmaceutically acceptable salts thereof, as described herein, useful in treating a gastric disorder. In one aspect, the gastric disorder comprises gastric reflux, gastroesophageal reflux disease, laryngopharyngeal reflux, laryngitis, dyspepsia, Barrett's esophagus, eosinophilic esophagitis, gastritis, gastrinomas, Zollinger-Ellison syndrome, peptic ulcers, or excessive helicobacter pylori or combinations thereof.

DESCRIPTION OF INVENTION

In one aspect the present invention relates to oral solid pharmaceutical dosage forms comprising Rabeprazole, as single active drug.

An embodiment of the present invention is solid oral pharmaceutical compositions of Rabeprazole comprising:

- i) a core comprising a therapeutically effective amount of Rabeprazole stabilized with an alkalizing agent;
- ii) a barrier coating or sub coating around the drug core comprising one or more polymer, and an alkalizing agent; and
- iii) an enteric coating comprising enteric polymer having solubility at pH higher than 5.5.

An embodiment of the present invention is solid oral pharmaceutical compositions of Rabeprazole comprising:

- i) a core comprising a therapeutically effective amount of Rabeprazole stabilized with an alkalizing agent;
- ii) a barrier coating or sub-coating around the drug core comprising ethyl cellulose, hypermellose polymer and its derivatives in all grades like phthalate, acetate, HPC SSL, HPC LF and or combinations thereof, and an alkalizing agent; and
- iii) an enteric coating comprising enteric polymer having solubility at pH higher than 5.5;
- iv) optionally, reverse enteric coating or top coating comprising reverse enteric polymer to protect the integrity of enteric layer in salivary pH;
- v) optionally, a pulse coat layer over the barrier coat or the sub-coat comprising water-insoluble polymers, water soluble polymers, enteric polymers, waxes and mixtures thereof

5 An embodiment of the present invention is solid oral pharmaceutical compositions of Rabeprazole or its pharmaceutically acceptable salts, wherein the composition comprises additional one or more pharmaceutically acceptable excipients selected from the group consisting of a binder, a filler, a diluent, a surfactant, a glidant, a lubricant, a plasticizer, an anti-tacking agent, an alkaline substance, a tonicity enhancing agent, a wetting agent, a buffering substance, a preservative, a flavoring agent, an opacifier, a colorant, an anti-oxidant or a mixture or combination thereof.

The finished dosage form may be an orally disintegrating tablet, a modified-release capsule, pellet or a conventional tablet that provide target plasma concentrations suitable to achieve the desired efficacy.

The term "Rabeprazole" as used herein includes Rabeprazole, a pharmaceutically acceptable salt of Rabeprazole, a single enantiomer of Rabeprazole or a pharmaceutically acceptable salt of the single enantiomer. And also all optical isomers, such as enantiomers, diastereomers, ineso compounds, and the like, as well as pharmaceutically acceptable salts, solvates, and prodrugs (such as esters) thereof.

The pharmaceutical composition of the present invention typically comprises from 5mg to 100mg of Rabeprazole. The formulation of this invention preferably comprises 10mg to 40mg Rabeprazole.

The term "about" includes all values having substantially the same effect, or providing substantially the same result, as the reference value. Thus, the range encompassed by the term "about" will vary depending on context in which the term is used, for instance the parameter that the reference value is associated with. Thus, depending on context, "about" can mean, for example, $\pm 15\%$, $\pm 10\%$, $\pm 5\%$, $\pm 4\%$, $\pm 3\%$, $\pm 2\%$, $\pm 1\%$, or $\pm$ less than 1%. Importantly, all recitations of a reference value preceded by the term "about" are intended to also be a recitation of the reference value alone.

The term "satisfactory in vitro dissolution" refers to a percent dissolution of not more than 10 % release in 0.1N HCl and not less than 70% of the labelled amount of Rabeprazole Sodium dissolved in 20 minute in buffer stage as measured using the general procedure of the United States Pharmacopeia (Apparatus 2).

"Pharmaceutical composition" refers to a formulation of a compound of the disclosure, such as Rabeprazole or its pharmaceutically acceptable salts thereof, and a medium generally accepted in the art for the delivery of the biologically active compound to mammals, e.g., humans. Such a medium includes all pharmaceutically acceptable carriers, diluents or excipients therefor. The pharmaceutical composition may be in various dosage forms or contain one or more-unit dose formulations. The terms pharmaceutical composition or pharmaceutical formulation or composition or formulation are herein used interchangeably.

"Pharmaceutically acceptable" means suitable for use in contact with the tissues of humans and animals without undue toxicity, irritation, allergic response, and the like, commensurate with a

reasonable benefit/risk ratio, and effective for their intended use within the scope of sound medical judgment.

"Salts" include derivatives of an active agent, wherein the active agent is modified by making acid or base addition salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid addition salts of basic residues such as amines; alkali or organic addition salts of acidic residues; and the like, or a combination comprising one or more of the foregoing salts. The pharmaceutically acceptable salts include salts and the quaternary ammonium salts of the active agent. For example, acid salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; other acceptable inorganic salts include metal salts such as sodium salt, potassium salt, cesium salt, and the like; and alkaline earth metal salts, such as calcium salt, magnesium salt, and the like, or a combination comprising one or more of the foregoing salts.

"Substantially similar to" means having a great extent or degree of likeness to the reference item, term, quantity, etc.

"Prodrug" refers to a precursor of the active agent wherein the precursor itself may or may not be pharmaceutically active but, upon administration, will be converted, either metabolically or otherwise, into the active agent or drug of interest. For example, prodrug includes an ester or an ether form of an active agent.

"Therapeutically effective amount" or "effective amount" refers the amount of a pharmaceutically active agent, such as Rabeprazole, that, when administered to a patient for treating a disease according to the dosing regimen as described herein, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" will vary depending on the disease and its severity, and the age, weight, and other conditions of the patient to be treated.

A composition or dosage form is "therapeutically equivalent" to a reference composition or dosage form if it has a therapeutic effect that is substantially similar to the therapeutic effect of the reference composition or dosage form, for example, therapeutically equivalent dosage forms can have substantially similar efficacy towards a particular disease or condition when administered over a substantially similar time period.

"Treating" includes ameliorating, mitigating, and reducing the instances of a disease or condition, or the symptoms of a disease or condition, in addition to providing directions or prescribing a drug for such purpose.

"Patient" or "subject" refers to a mammal, e.g., a human, in need of medical treatment.

The term "commercially available Rabeprazole formulation" refers to the Pariet® DR tablets available from Eisai.

5 In another aspect the present specification relates to oral disintegrating solid pharmaceutical formulations of Rabeprazole with quick absorption, good taste, easy swallowing, good disintegrated effect, and convenient to use for patients and the method for preparing the same.

An embodiment of the present specification is oral disintegrating pharmaceutical formulations of Rabeprazole or a pharmaceutical acceptable salt thereof comprising a plurality of units or cores or pellets comprising:

- 10 i. inert core comprising sugar spheres, coated by an optional seal coating layer
- ii. a drug layer comprising a plurality of cores or units or pellets comprising a therapeutically effective amount of a proton pump inhibitor stabilized with an alkalizing agent;
- iii. a barrier coating or sub coating around the drug layer comprising polymer, an alkalizing agent;
- 15 iv. an enteric coating comprising an enteric polymer having solubility at pH higher than 5.5;
- v. a reverse enteric coating or top coating comprising reverse enteric polymer to protect the integrity of enteric layer in salivary pH, and
- vi. extragranular materials comprising pharmaceutically acceptable excipients.

20 An embodiment of the present specification is oral disintegrating pharmaceutical formulations of Rabeprazole or a pharmaceutical acceptable salt thereof comprising a plurality of units or cores or pellets comprising:

- i. an inert core comprising sugar spheres, coated by an optional seal coating layer, and sugar spheres is present in an amount of about 2% to about 15% by weight of a total tablet weight
- 25 ii. a drug layer comprising a plurality of cores or units or pellets comprising a therapeutically effective amount of a proton pump inhibitor stabilized with an alkalizing agent; wherein the alkalizing agent is selected from sodium hydroxide, magnesium hydroxide, magnesium oxide, sodium oxide or combination thereof and the drug layer is present in an amount of about 5% to about 15% by weight of a total tablet weight
- 30 iii. a barrier coating or sub coating around the drug layer comprising ethyl cellulose and hypermellose polymer and its derivatives in all grades like phthalate, acetate, HPC SSL, HPC LF and or combinations thereof, an alkalizing agent which is selected from sodium

hydroxide, magnesium hydroxide, magnesium oxide, sodium oxide or combination thereof; and the Barrier coating or sub coating layer is present in an amount of about 5% to about 20% by weight of a total tablet weight

iv. an enteric coating comprising enteric polymer having solubility at pH higher than 5.5 and selected from acrylic polymers and copolymers for example eudragit in all grades, hypermellose, hypermellose pthalate or combinations thereof and the enteric coating layer is present in an amount of about 15% to about 30% by weight of a total tablet weight.

v. a coating comprising reverse enteric polymer or top coating to protect the enteric coating, and is selected from one or more of acrylic polymers or copolymers like tertbutyl amino ethyl (meth)acrylate, butyl methacrylate, dimethylaminoethyl methacrylate, methyl methacrylate copolymer or combinations thereof and is present in an amount of about 2.5% to about 30% by weight of a total tablet weight, and

vi. extragranular material comprising pharmaceutically acceptable excipients selected from at least one disintegrant, filler, glidant, lubricant, binder, diluent, surfactant, plasticizer, anti-tacking agent, alkaline substance, tonicity enhancing agent, wetting agent, buffering substance, preservative, flavoring agent, an opacifier, colorant, anti-oxidant or a mixture thereof.

The term "orally disintegrating tablet" as used herein refers to a tablet which substantially disintegrates in an oral cavity of a subject in need thereof within less than about 60 seconds after administration. In one embodiment, disintegration is measured in vitro using e.g. the USP <701> Disintegration Test. In another embodiment, "orally disintegrating tablet" refers to a loss of structural integrity of the tablet following administration to the buccal cavity of a subject when in contact with the mucosal tissue of the tongue, cheek, and/or mouth. The orally disintegrating tablet is typically placed on the tongue (lingual administration) which stimulates saliva generation and enhances disintegration of the composition. Following disintegration, a suspension of undissolved particles in saliva is typically formed. The particles can then be swallowed, usually without water or other fluids, allowing for absorption of the active pharmaceutical ingredient in the GI tract, generally in the upper intestine. In some embodiments, the active pharmaceutical ingredient comprises a proton pump inhibitor, such as a Rabeprazole or its pharmaceutically acceptable salt, which is a benzimidazole derivative.

The orally disintegrating tablets described herein comprise a plurality of coated units or pellets comprising a plurality of cores comprising a therapeutically effective amount of an active

pharmaceutical ingredient. Therefore, “each unit/ pellet” within the total plurality of units comprises a core comprising an active pharmaceutical ingredient. These cores are further coated with coating layers comprising a subcoating/barrier coating, followed by an enteric coating layer and a coating comprising a reverse enteric polymer. The barrier coating/ subcoating separates the drug layer from the enteric layer and the polymers used in the barrier coating is important to achieve better dissolution, better stability and the ratio of the different polymers used needs to be optimized to achieve a bioequivalence and also stable formulation. The enteric coating layer modulates the release characteristics of the active ingredient to afford its delayed release. Finally, a coating over the enteric coating is reverse enteric coating layer comprising a reverse enteric polymer that affords the increase in tablet strength and reduced friability, protects the integrity of enteric layer in mouth (saliva pH= 6.2-7.6) and in some embodiments provides a taste masking effect for bitter active ingredients.

The orally disintegrating tablet as described herein comprises a plurality of units or pellets comprising multiple cores comprising a therapeutically effective amount of one or more proton pump inhibitors such as, but not limited to, Rabeprazole or its pharmaceutically acceptable salts thereof. In one embodiment, each core is in a form such as, but not limited to, a granule, a pellet, a bead or a powder. Each possibility represents a separate embodiment. The cores typically comprise one or more pharmaceutically acceptable excipients (e.g. a filler, a binder, an alkalizing agent etc.) and a proton pump inhibitor and may be generated through methods well-known in the pharmaceutical arts, for example, dry or wet granulation, extrusion or spheronization.

The oral disintegration time of the "orally disintegrable tablet" of the present invention (the time for complete disintegration by buccal saliva) is one minute or less, usually about 50 seconds or less, preferably about 40 seconds or less, more preferably about 30 seconds or less.

The term “plurality of pellets” described herein comprises a plurality of cores comprising the one or more active pharmaceutical ingredients. In some embodiments, each core of the plurality of pellets is coated with a barrier coating/ subcoating, then an enteric coating which is over-coated with a coating comprising a reverse enteric polymer. In various embodiments, each unit further comprises a subcoating between the core and the enteric coating. The orally disintegrating tablet further comprises a disintegrant. Optionally, the orally disintegrating tablet further comprises other pharmaceutically acceptable tableting excipients in addition to the disintegrant. In one embodiment the terms multiple units or pellets or cores can be used interchangeably.

In one aspect, the present specification relates to oral disintegrating pharmaceutical formulations of Rabeprazole or a pharmaceutical acceptable salt thereof comprising a plurality of units or cores or pellets comprising:

- i. an inert core comprising sugar spheres, coated by an optional seal coating layer
- 5 ii. a drug layer comprising a plurality of cores or units or pellets comprising a therapeutically effective amount of a proton pump inhibitor stabilized with an alkalizing agent;
- iii. a barrier coating or sub coating around the drug layer comprising polymer; polymer, an alkalizing agent;
- iv. an enteric coating comprising enteric polymer having solubility at pH higher than 5.5;
- 10 v. a reverse enteric coating or top coating comprising reverse enteric polymer to protect the integrity of enteric layer in salivary pH and
- vi. an extragranular material with pharmaceutically acceptable excipients selected from at least one disintegrant, filler, glidant, lubricant, binder, diluent, surfactant, plasticizer, anti-tacking agent, alkaline substance, tonicity enhancing agent, wetting agent, buffering
- 15 substance, preservative, flavoring agent, an opacifier, colorant, anti-oxidant or a mixture thereof.

In one aspect, the present specification relates to oral disintegrating pharmaceutical formulations of Rabeprazole or a pharmaceutical acceptable salt thereof comprising a plurality of units or cores or pellets comprising:

- 20 i. an inert core comprising sugar spheres, coated by an optional seal coating layer, and sugar spheres is present in an amount of about 2% to about 15% by weight of a total tablet weight
- ii. a drug layer comprising a plurality of cores or units or pellets comprising a therapeutically effective amount of a proton pump inhibitor stabilized with an alkalizing agent; wherein the alkalizing agent is selected from sodium hydroxide, magnesium hydroxide, magnesium
- 25 oxide, sodium oxide or combination thereof and the drug layer is present in an amount of about 5% to about 15% by weight of a total tablet weight
- iii. a barrier coating or sub coating around the drug layer comprising Ethyl cellulose and hypermellose polymer and its derivatives in all grades like phthalate, acetate, HPC SSL, HPC LF and or combinations thereof; an alkalizing agent which is selected from sodium
- 30 hydroxide, magnesium hydroxide, magnesium oxide, sodium oxide or combination thereof and the Barrier coating or sub coating layer is present in an amount of about 5% to about 20% by weight of a total tablet weight
- iv. an enteric coating comprising enteric polymer having solubility at pH higher than 5.5 and is selected from acrylic polymers and copolymers for example eudragit in all grades,

Hypermellose, Hypermellose Pthalate or combinations thereof and the enteric coating layer is present in an amount of about 15% to about 30% by weight of a total tablet weight.

- v. a coating comprising reverse enteric polymer or top coating to protect the enteric coating, and is selected from one or more of acrylic polymers or copolymers like tertbutyl amino ethyl (meth)acrylate, butyl methacrylate, dimethylaminoethyl methacrylate, methyl methacrylate copolymer or combinations thereof and is present in an amount of about 2.5% to about 30% by weight of a total tablet weight and
- vi. an extragranular material comprising one or more pharmaceutically acceptable excipients and combinations thereof.

The term “drug layer” refers to the layer comprising drug i.e., Rabeprazole or its pharmaceutically acceptable salts thereof, stabilized with an alkalizing agent and is present around the inert core.

One embodiment of the present specification is an oral disintegrating solid pharmaceutical formulations comprising Rabeprazole or a pharmaceutically acceptable salt thereof, wherein the alkalizing agent in the drug layer of the said composition is selected from sodium hydroxide, magnesium hydroxide, magnesium oxide, sodium oxide or combination thereof.

One embodiment of the present specification is an oral disintegrating solid pharmaceutical formulations comprising Rabeprazole or a pharmaceutically acceptable salt thereof, where the ratio of drug: alkalizing agent in the drug layer is in the ratio of about 10:1, about 8:1, about 6:1, about 4:1, about 2:1, about 1:1. More preferably the ratio of drug: alkalizing agent in the drug layer is in the ratio of about 4:1 to about 6:1.

One embodiment of the present specification is an oral disintegrating solid pharmaceutical formulations comprising Rabeprazole or a pharmaceutically acceptable salt thereof, where the ratio of ethyl cellulose: HPC polymer in the in the barrier coating/subcoating layer is about 0:100, about 20: 80, about 25:75, about 30:70, about 50:50, about 40:60. In particular and more preferably the ratio of ethyl cellulose: HPC polymer in the barrier coating/subcoating layer is about 20:80, about 25:75, about 30:70 to provide a satisfactory *in vitro* dissolution.

In one aspect the present specification relates to oral disintegrating tablet comprising Rabeprazole or a pharmaceutical acceptable salt thereof, wherein the composition is bioequivalent to commercially available Rabeprazole DR tablets (Pariet® 20mg DR tablets)

In one aspect the present specification relates to oral disintegrating tablet comprising Rabeprazole or a pharmaceutical acceptable salt thereof, wherein said composition exhibits bioequivalence to a commercially available Rabeprazole 20mg DR tablets in a human subject under fasting condition is established by:

- 5 a) a 90% Confidence Interval for mean AUC(0-t), which is between 80% and 125%, and
 b) a 90% Confidence Interval for mean AUC(0-∞), which is between 80% and 125%.

In another aspect, the present specification relates to oral disintegrating solid pharmaceutical formulations comprising Rabeprazole or its pharmaceutically acceptable salts, wherein the said composition exhibits a Cmax of about 600 ng.hr/mL to about 1200 ng.hr/mL.

- 10 In another aspect, the present specification relates to oral disintegrating solid pharmaceutical formulations comprising Rabeprazole or its pharmaceutically acceptable salts, wherein the said composition exhibits a Tmax which is in the range of 2Hrs to 2.5Hrs, a reduced Tmax compared to commercially available Pariet® 20mg DR tablets formulation which is 4.17Hrs.

- 15 In one another aspect, the orally disintegrating tablet has a hardness of about 20N to about 100N and substantially disintegrates in an oral cavity of a subject in need thereof within less than about 60 seconds after administration.

- 20 In certain embodiments, water soluble core materials such as sugar spheres may be coated with a seal coating layer. The purpose of sealing is to offer an initial protection and to prevent core ingredients from migrating into a coating, such as a drug-containing layer and also to offer smooth finishing. Sealing may be accomplished by the application of polymer based coating materials onto the surface of the core particles. Examples of the polymers that can be used include, without limitation thereto, shellac, zein, hydroxypropyl methylcellulose (HPMC), polyvinyl acetate phthalate (PVAP), and cellulose acetate phthalate (CAP). This sealing agent may be dissolved in an appropriate aqueous or non-aqueous solvent.

- 25 In an embodiment the seal coating is in an amount of about 2% to about 15% (w/w) of the total weight of the tablet. In certain embodiments the seal coating is in amount of about 2%, about 3%, about 5%, about 12%, about 15% of the total weight of the tablet including each integer within the specified range.

In another aspect the present invention discloses modified release oral dosage forms, which comprise of a core and a combination of a release modifying layers that together achieve beneficial release properties, suitable for once daily administration.

Thus, one embodiment of the present invention is modified release solid oral dosage forms of Rabeprazole, wherein the drug is released at a rate allowing controlled absorption thereof over a twenty-four-hour period following oral administration, comprising:

- i) a core comprising a therapeutically effective amount of Rabeprazole stabilized with an alkalizing agent;
- ii) a barrier coating or sub coating around the drug core comprising one or more polymers or combinations thereof, and an alkalizing agent;
- iii) an enteric coating comprising enteric polymer having solubility at pH higher than 5.5, and
- iv) optionally, a pulse coating layer comprising water-insoluble polymers, water soluble polymers, enteric polymers, waxes and mixtures thereof.

Another embodiment of the present invention is modified release solid oral dosage forms of Rabeprazole, wherein the drug is released at a rate allowing controlled absorption thereof over a twenty-four-hour period following oral administration, comprising:

- i. a core comprising a therapeutically effective amount of Rabeprazole stabilized with an alkalizing agent; wherein the alkalizing agent is selected from sodium hydroxide, magnesium hydroxide, magnesium oxide, sodium oxide or combination thereof,
- ii. a barrier coating or sub coating around the drug core comprising ethyl cellulose and hypermellose polymer and its derivatives in all grades like phthalate, acetate, HPC SSL, HPC LF and or combinations thereof, an alkalizing agent which is selected from sodium hydroxide, magnesium hydroxide, magnesium oxide, sodium oxide or combination thereof; and the Barrier coating or sub coating layer is present in an amount of about 5% to about 20% by weight of a total tablet weight,
- iii. an enteric coating comprising enteric polymer having solubility at pH higher than 5.5 and is selected from acrylic polymers and copolymers for example eudragit in all grades, hypermellose, hypermellose pthalate or combinations thereof and the enteric coating layer is present in an amount of about 15% to about 30% by weight of a total tablet weight, and
- iv. optionally, a pulse coating layer comprising water-insoluble polymers, water soluble polymers, enteric polymers, waxes and mixtures thereof.

As used herein, the term “modified release” encompasses “controlled release”, “sustained release,” “extended release,” “delayed release,” and “timed, pulsatile release”.

- 5 One aspect of the invention provides modified release pharmaceutical formulation of Rabeprazole, comprising an amount of Rabeprazole between 5 and 60 mg.

In one aspect the present specification provides modified release pharmaceutical formulation of Rabeprazole or a pharmaceutical acceptable salt thereof, wherein the composition is bioequivalent to Pariet® 20mg DR tablets

- 10 In one aspect the present specification provides modified release pharmaceutical formulation of Rabeprazole or a pharmaceutical acceptable salt thereof, wherein said composition exhibits bioequivalence to a commercially available Rabeprazole 20mg DR tablets in a human subject under fasting condition is established by:

- a) a 90% Confidence Interval for mean AUC(0-t), which is between 80% and 125%, and
15 b) a 90% Confidence Interval for mean AUC(0-∞), which is between 80% and 125%.

In another aspect, the present specification provides modified release pharmaceutical formulation of Rabeprazole or its pharmaceutically acceptable salts, wherein the said composition exhibits a C_{max} of about 600 ng.hr/mL to about 1200 ng.hr/mL.

- 20 In another aspect, the present specification provides modified release pharmaceutical formulation of Rabeprazole or its pharmaceutically acceptable salts, wherein the therapeutic agent is released into the stomach and upper gastrointestinal tract subsequent to administration of the dosage form.

Embodiments of the modified release oral dosage form, as described herein include oral dosage forms known in the art, for example, capsule dosage forms or tablet dosage forms or other formulations.

- 25 In an embodiment the alkalizing agent in the drug layer or the drug containing core is selected from one or more of sodium hydroxide, potassium hydroxide, magnesium oxide, sodium oxide, potassium oxide or mixtures thereof. In a more preferable embodiment the alkalizing agent is sodium hydroxide in the drug layer.

Exemplary and non-limiting alkaline substances include organic and inorganic alkaline substances. Suitable organic alkaline substances include, but are not limited to, basic amino acids such as arginine and lysine, amine derivatives and salts, amino sugars such as meglumine, salts of stearic acid such as sodium stearate and the like, with each possibility representing a separate
5 embodiment. Suitable inorganic alkaline agents include, but are not limited to, hydroxides such as sodium or potassium hydroxide, carbonates such as calcium, magnesium or zinc carbonate, oxides such as magnesium oxide, Sodium oxide, Lithium oxide, potassium oxide and the like.

In one aspect, the present specification relates to oral disintegrating solid pharmaceutical formulations comprising Rabeprazole or a pharmaceutically acceptable salt thereof, where the
10 ratio of drug: alkalizing agent in the drug layer is in the ratio of about 10:1, about 8:1, about 6:1, about 4:1, about 2:1, about 1:1. More preferably the ratio of drug: alkalizing agent in the drug layer is in the ratio of about 4:1 to about 6:1. The alkalizing agent i.e., sodium hydroxide is used to stabilize the drug in the drug layer.

In one embodiment, the drug-containing core can take the form of a bead, a pellet, a granulate, a
15 microgranule, a drug crystal, a mini-tablet, etc.

This “subcoating layer or barrier coating” as described herein may prevent an interaction between the enteric coating layer having free carboxyl groups and the core that comprises one or more active pharmaceutical ingredients which are typically benzimidazole derivatives known to be acid-labile. The subcoating layer is designed to afford physical separation between the alkaline core
20 containing one or more proton pump inhibitors and the acidic enteric coating. In certain embodiments, the subcoating layer comprises one or more polymers, one or more of a binder, a filler, and an anti-tacking agent, with each possibility representing a separate embodiment. In an embodiment the subcoating layer is present in an amount of about 5% to about 20%, about 15%, about 17%, about 18%, about 20%, about 25%, including each integer within the specified range
25 represent a separate embodiment.

The “barrier coating layer or sub-coating layer” as described herein refers to a layer between the drug layer and the enteric coating layer comprising a release controlling polymers. The layer further comprises alkalizers, buffering agents, anti-tacking agents in the layer. The alkalizers in the barrier coating is selected from sodium hydroxide, magnesium hydroxide, magnesium oxide,
30 sodium oxide or combination thereof and the alkalizer in the barrier coating neutralizes the acidic material if any, in case it migrates from enteric coating through barrier coating

In one aspect, the present specification relates to oral solid pharmaceutical formulations comprising Rabeprazole or a pharmaceutically acceptable salt thereof, where the ratio of ethyl cellulose: hypromellose polymer in the barrier coating/Subcoating layer is about 0:100, about 20: 80, about 25:75, about 30:70, about 50:50, about 40:60. In particular and more preferably the ratio of Ethyl cellulose: HPC polymer in the barrier coating/subcoating layer is about 20:80, about 25:75, about 30:70. In particular and more preferably the ratio of Ethyl cellulose: HPC polymer in the Barrier coating/Subcoating layer is 25:75 to provide a satisfactory *in vitro* dissolution. In an embodiment the ethyl cellulose in the barrier coating or subcoating is used to provide increased stability and to provide dissolution. The ratio of ethylcellulose to hypromellose is optimized to achieve a formulation bioequivalence with the commercially available Rabeprazole DR tablets (i.e., Pariet® 20mg DR tablets).

In an embodiment the subcoating/ barrier coating layer as used herein comprises one or more polymers selected from one or more of cellulosic polymers/copolymers or its derivatives including, but not limited to methyl cellulose, ethyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, HPC SSL, HPC LF and various grades of hydroxypropyl celluloses, hydroxyethyl methylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose; polyacrylates, methyl acrylates, polyethylene oxides, polyethylene glycols, chitosan, gums, starch derivatives, polyurethanes, galactomannans, polysaccharides, polyalcohols, acrylic acid or acrylamide derivatives, and the combination of polymers thereof.

The “Enteric Coating” as used herein refers to the coating around the plurality of units / pellets, which protects the active ingredients (e.g., a proton pump inhibitor like Rabeprazole/ Rabeprazole sodium) from the acidic environment of the stomach. The enteric coating includes one or more enteric polymers and optionally other pharmaceutically acceptable excipients, such as a plasticizer, a glidant, and an opacifier described herein. Plasticizers are known to increase the flexibility of the coating and help prevent or reduce cracking of the enteric coat upon compression. Further, plasticizers may also increase the adhesion of the enteric coating polymer chains.

In some embodiments, the enteric coating is applied directly over the cores/ or pellets comprising an active ingredient. In other embodiments, the enteric coating is applied over the subcoating layer, which is over the subcoated cores or pellets. Generally, enteric coatings include pH dependent polymers. These polymers are typically characterized by increase in permeability at pH values of above pH 5.0 (e.g., intestinal fluid) while remaining insoluble at low pH values, such as those found in the environment of the stomach. "Enteric polymer" as used herein refers to a polymer that

is poorly soluble in aqueous medium at a pH of about 4.5 or less, but becomes soluble in aqueous medium at a pH of greater than about 5. For example, an enteric polymer is poorly soluble in gastric juice, but is soluble in the lower GI tract environment.

The term “acid resistance” as used herein refers to defined as the amount of proton pump inhibitor or the Rabeprazole or its pharmaceutically acceptable salts in the unit composition after being exposed to simulated gastric fluid USP, or to 0.1 M HCl (aq) relative to that of unexposed unit compositions, respectively. The test is accomplished in the following way. Individual unit compositions of the present invention are exposed to simulated gastric fluid of a temperature of 37° C. The unit compositions disintegrate rapidly and release the enteric coating layered pellets to the medium. After two hours the enteric coating layered pellets are removed and analyzed for content of the proton pump inhibitor using High Performance Liquid Chromatography (HPLC).

In an embodiment the enteric coating applied to the core/ pellets obtained after subcoating comprises one or more of (meth) acrylate polymer or copolymer, methyl methacrylate-butyl methacrylate-dimethylaminoethyl methacrylate copolymer, dimethyl amino ethyl (meth)acrylate, diethyl amino ethyl (meth)acrylate, piperidine ethyl (meth)acrylate, tertbutyl amino ethyl (meth)acrylate, cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), hydroxypropyl methylcellulose acetate succinate (HPMCAS), polyvinyl acetate phthalate, cellulose acetate trimellitate, shellac, polymethacrylic acid, polymethyl methacrylate, polyethyl methacrylate, polyethyl acrylate or a mixture or combination thereof, with each possibility representing a separate embodiment. The coating further coated by reverse enteric polymer coating.

Exemplary and non-limiting enteric polymers include acrylic and methacrylate acid copolymers, cellulose acetate phthalate (CAP), cellulose acetate butyrate, hydroxypropyl methylcellulose phthalate (HPMCP), hydroxypropyl methylcellulose acetate succinate (HPMCAS), polyvinyl acetate phthalate, cellulose acetate trimellitate, alginic acid salts, such as sodium or potassium alginate, and shellac. Each possibility represents a separate embodiment. Acrylic and methacrylate acid copolymers are anionic copolymers based on (meth)acrylic acid and alkyl (meth)acrylate, such as, but not limited to, polymethacrylic acid, polymethyl methacrylate, polyethyl methacrylate, and polyethyl acrylate among others. Commercial acrylic acid and methacrylate copolymers are available under the trade name EUDRAGIT® (Evonik Industries AG, Essen, Germany) and are typically provided as powder or aqueous dispersions, including, but not limited to, EUDRAGIT® L 30 D-55; EUDRAGIT® L 100-55; EUDRAGIT® L 100; EUDRAGIT® L 12.5; EUDRAGIT®

NE 40 D, EUDRAGIT® RL 100, EUDRAGIT® S 100; EUDRAGIT® S 12.5; EUDRAGIT® FS 30 D; EUDRAGIT® RL PO; EUDRAGIT® RL 12.5, EUDRAGIT® RL 30 D; EUDRAGIT® RS 100; EUDRAGIT® RS PO; EUDRAGIT® RS 30 D; EUDRAGIT® RS 12.5; EUDRAGIT® NE 30 D; EUDRAGIT® NM 30 D; or combinations and mixtures thereof. In certain embodiments, the enteric coating comprises hydroxypropyl methylcellulose phthalate (HPMCP).

In some embodiments, the enteric coating of the present invention comprises an enteric polymer which is in an amount of from about 10% (w/w) to about 30% (w/w) of a total weight of the tablet, including each integer within the specified range. In yet other embodiments, the enteric polymer is in an amount of about 12% to about 15% of the total weight of the tablet, including each integer within the specified range. In certain embodiments, the enteric polymer is in an amount of about 10%, about 12%, about 14%, about 15%, about 18%, about 20%, about 22%, about 25%, about 27%, about 30% of the total weight of the tablet, with each possibility representing a separate embodiment.

In some embodiments, the enteric coated cores or pellets or units are over-coated with a coating layer comprising a reverse enteric polymer. This coating was surprisingly found to increase the compressibility of the orally disintegrating tablets described herein, and also protects the integrity of enteric layer in mouth (saliva pH= 6.2-7.6). In particular, coatings having a reverse enteric polymer were found to reduce the friability and increase the overall stability of the orally disintegrating tablets described herein while affording adequate release profile of the active pharmaceutical ingredient. In certain embodiments, the coating layer comprising a reverse enteric polymer is an over-coating that is an outermost coating layer which is layered on the penultimate coating of the coated core (e.g., over the enteric coating layer).

As used herein and in the appended claims, the term "reverse enteric polymer" refers to pH sensitive polymers, which are insoluble at pH values greater than those found in the stomach i.e. at pH values greater than 5.0 while being soluble at acidic pH values. Suitable reverse enteric polymers are thus insoluble in the oral cavity and soluble in the stomach.

In some embodiments, the reverse enteric polymer is a copolymer of hydrophobic monomers and/or basic monomers; non-limiting examples of such reverse enteric polymers are described in U.S. Patent Application No. 2006/0134054. In an embodiment, the present specification relates to oral disintegrating solid pharmaceutical formulations comprising Rabeprazole or its pharmaceutically acceptable salts, wherein the reverse enteric polymer coating comprises a reverse enteric polymer coated on to the cores/pellets obtained after the enteric coating is selected

from one or more of acrylic polymers, copolymers, a (a (meth) acrylate polymer or copolymer, methyl methacrylate-butyl methacrylate-dimethylaminoethyl methacrylate copolymer, dimethyl amino ethyl (meth)acrylate, diethyl amino ethyl (meth)acrylate, piperidine ethyl (meth)acrylate, tertbutyl amino ethyl (meth)acrylate, butyl methacrylate, dimethylaminoethyl methacrylate, methyl methacrylate copolymer or combinations thereof.

In one embodiment, the reverse enteric polymer includes a (meth)acrylate polymer or copolymer, such as acrylate and methacrylate copolymers having primary, secondary or tertiary amino groups or quaternary ammonium groups. These reverse enteric polymers are commercially available as EUDRAGIT® E 100; EUDRAGIT® E 12.5; EUDRAGIT® EPO; or EUDRAGIT® RL 100 (Evonik Industries). Each possibility represents a separate embodiment. Currently preferred reverse enteric polymer is a methyl methacrylate-butyl methacrylate-dimethylaminoethyl methacrylate copolymer (e.g., poly(butyl methacrylate-co-(2-dimethylaminoethyl) methacrylate-co-methyl methacrylate) 1 :2: 1).

In some embodiments, the reverse enteric polymer coating layer further comprises additional polymers. The additional polymers that may be present in this coating layer include, but are not limited to, ethyl cellulose, polyvinyl acetate (PVA), cellulose acetate (CA), and cellulose acetate butyrate (CAB). Each possibility represents a separate embodiment.

In some embodiments, the coating comprising a reverse enteric polymer further comprises one or more pharmaceutically acceptable excipients, such as a glidant or colorant described herein.

In some embodiments, this coating layer further provides taste masking properties, which may reduce the taste sensation of active ingredients characterized by bitter or unpleasant taste. However, this coating layer can also be applied where a taste-masking effect is not required due to its unexpected effect of increasing the compressibility of the orally disintegrating tablets described herein.

In further embodiments, the coating comprising a reverse enteric polymer is in a range of from about 0.5% to about 20% (w/w) of a total weight of the tablet. In certain embodiments the reverse enteric polymer is in amount of about 0.5%, about 3%, about 3.5%, about 4%, about 7%, about 10%, about 15%, about 20% (w/w) of a total weight of the tablet.

In one embodiment, the reverse enteric coating layer is in an amount of from about 2.5 % to about 25% (w/w) of a total weight of the tablet. In certain embodiments the reverse enteric polymer is in

amount of about 2.5%, about 3%, about 3.5%, about 5%, about 10%, about 15%, about 20%, about 25% (w/w) of a total weight of the tablet.

In another embodiment, the present specification relates to solid oral dosage forms of Rabeprazole or its pharmaceutically acceptable salts, a disintegrant comprising one or more of crospovidone, crospovidone XL-10, croscarmellose sodium, a cellulose derivative, cross-linked derivatives of starch, pregelatinized starch, crosslinked sodium carboxymethyl cellulose, low substituted hydroxypropyl cellulose or a mixture or combination thereof.

Exemplary and non-limiting plasticizers include but not limited to glycerol, polyethylene glycol and derivatives thereof, citric acid esters, such as triethyl citrate, and tributyl citrate, fatty alcohol derivatives such as cetyl alcohol, stearyl alcohol or phthalate derivatives, such as diethyl phthalate, dipropyl phthalate, dibutyl phthalate, and dioctyl phthalate, or dibutyl sebacate, or a mixture or combination thereof. In certain embodiments, the plasticizer comprises triethyl citrate, cetyl alcohol or a mixture thereof.

The solid oral dosage forms of the present invention further comprise a disintegrant comprising one or more of crospovidone, croscarmellose sodium, a cellulose derivative, cross-linked derivatives of starch, pregelatinized starch, crosslinked sodium carboxymethyl cellulose, low substituted hydroxypropyl cellulose or a mixture or combination thereof. Disintegrants can include one or more of crospovidone, croscarmellose, such as croscarmellose sodium, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, such as hydroxypropyl methyl cellulose and hydroxypropyl ethyl cellulose, starch, pregelatinised starch, sodium alginate, and sodium starch glycolate, for example, sodium starch glycolate.

In some embodiments, the one or more disintegrants are in an amount of about 2% to about 50%, of the total weight of the orally disintegrating tablet composition mass, including each integer within the specified range. In other embodiments, the one or more disintegrants are in an amount of about 2% to about 40%, about 2% to about 30%, about 2% to about 25% of the total weight of the orally disintegrating tablet composition mass, including each integer within the specified range. In additional embodiments, the one or more disintegrants are in an amount of about 2%, about 4%, about 6%, about 8%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, or about 50% of the total weight of the orally disintegrating tablet composition mass.

Exemplary and non-limiting binders include povidone (PVP: polyvinylpyrrolidone), copovidone, hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC), carboxymethyl cellulose (CMC), hydroxyethyl cellulose, gelatin, polyethylene oxide, poly ethylene glycol (PEG), poly vinyl alcohol (PVA), acacia, dextrin, magnesium aluminum silicate, starch, and
5 polymethacrylates or a mixture or combination thereof. Also includes any one or more of saccharides, such as sucrose, lactose, mannose, trehalose, fructose, starches, cellulose, microcrystalline cellulose, methyl cellulose, ethyl cellulose, and the like, gelatin, polyvinylpyrrolidone, and the like.

Exemplary and non-limiting fillers include lactose, glucose, fructose, sucrose, dicalcium
10 phosphate, sugar alcohols also known as "sugar polyol" such as sorbitol, mannitol, maltitol, lactitol, xylitol, isomalt, erythritol, and hydrogenated starch hydrolysates (a blend of several sugar alcohols), corn starch, potato starch, sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate, cellulose, microcrystalline cellulose, dibasic calcium phosphate, monobasic calcium phosphate, lactose, sucrose, glucose, mannitol, sorbitol, calcium carbonate, and the like or a
15 mixture or combination thereof.

Exemplary and non-limiting diluents include dicalcium phosphate dihydrate, sugars, lactose, calcium phosphate, cellulose, kaolin, mannitol, sodium chloride, and dry starch or a mixture or combination thereof. Each possibility represents a separate embodiment.

Exemplary and non-limiting surfactants include non-ionic, zwitterionic, anionic or cationic
20 compounds. Generally, surfactants have a lipophilic and a hydrophilic moiety within the molecule. The surfactant may optionally comprise one or more of soaps, detergents, emulsifiers, and dispersing agents. Suitable surfactants include, but are not limited to, Stearic acid and its salts like sodium, potassium, glyceryl monostearate, lanolin alcohols, lecithin, mono- and di-glycerides, monoethanolamine, oleic acid, oleyl alcohol, poloxamer, poly oxy ethylene 50 stearate, polyoxyl
25 35 castor oil, polyoxyl 40 hydrogenated castor oil, polyoxyl 10 oleyl ether, polyoxyl 20 cetostearyl ether, polyoxyl 40 stearate, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, propylene glycol diacetate, propylene glycol monostearate, sodium lauryl sulfate, sodium stearate, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, sorbitan monostearate, stearic acid, trolamine, and emulsifying wax or a mixture or combination thereof.

30 Exemplary and non-limiting glidant includes silicon dioxide, corn starch, and talc.

Exemplary and non-limiting lubricants include sodium stearyl fumarate, stearic acid, polyethylene glycol or stearates, such as magnesium stearate or a mixture or combination thereof.

Exemplary and non-limiting anti-tacking agents include magnesium stearate, calcium stearate, stearic acid, talc, colloidal silicon or a mixture or combination thereof.

- 5 Exemplary and non-limiting alkalizing agents substances include organic and inorganic alkaline substances. Suitable organic alkaline substances include, but are not limited to, basic amino acids such as arginine and lysine, amine derivatives and salts, amino sugars such as meglumine, salts of stearic acid such as sodium stearate and the like, with each possibility representing a separate embodiment. Suitable inorganic alkaline agents include, but are not limited to, hydroxides such as
10 sodium or potassium hydroxide, carbonates such as calcium, magnesium or zinc carbonate, oxides such as magnesium oxide, Sodium oxide, Lithium oxide, potassium oxide and the like.

- Exemplary and non-limiting tonicity enhancing agents include ionic and non-ionic agents. For example, ionic compounds include, but are not limited to, alkali metal or alkaline earth metal halides, such as, for example, CaCl_2 KBr, KCl, LiCl, NaI, NaBr or NaCl, and boric acid or a
15 mixture or combination thereof. Each possibility represents a separate embodiment. Non-ionic tonicity enhancing agents are, for example, urea, glycerol, sorbitol, mannitol, propylene glycol, and dextrose or a mixture or combination thereof.

Exemplary and non-limiting wetting agents include glycerin, starches or a mixture or combination thereof.

- 20 Exemplary and non-limiting buffering substances include acidic buffering agents such as short chain fatty acids, citric acid, acetic acid, hydrochloric acid, sulfuric acid and fumaric acid; and basic buffering agents such as tris, sodium carbonate, sodium hydroxide, sodium bicarbonate, sodium hydroxide, potassium hydroxide and magnesium hydroxide or a mixture or combination thereof.

- 25 Exemplary and non-limiting preservatives include quaternary ammonium salts such as benzalkonium chloride, benzoxonium chloride or polymeric quaternary ammonium salts; alkyl-mercury salts of thiosalicylic acid, such as, for example, thiomersal, phenylmercuric nitrate, phenylmercuric acetate or phenylmercuric borate; parabens, such as, for example, methylparaben or propylparaben; alcohols, such as, for example, chlorobutanol, benzyl alcohol or phenyl ethanol;
30 guanidine derivatives, such as, for example, chlorohexidine or polyhexamethylene biguanide; sorbic acid and ascorbic acid or a mixture or combination thereof.

Exemplary and non-limiting flavoring agents include, but are not limited to, sweeteners such as sucralose, and synthetic flavor oils and flavoring aromatics, natural oils, extracts from plants, leaves, flowers, and fruits, or a mixture or combinations thereof. Each possibility represents a separate embodiment. Exemplary flavoring agents include cinnamon oils, oil of wintergreen, peppermint oils, clover oil, hay oil, anise oil, eucalyptus, vanilla, citrus oil such as lemon oil, orange oil, grape and grapefruit oil, and fruit essences including apple, peach, pear, strawberry, raspberry, cherry, plum, pineapple, and apricot or a mixture or combination thereof.

Exemplary and non-limiting opacifiers include titanium dioxide.

Exemplary and non-limiting colorants include alumina (dried aluminum hydroxide), annatto extract, calcium carbonate, canthaxanthin, caramel, β -carotene, cochineal extract, carmine, potassium sodium copper chlorophyllin (chlorophyllin-copper complex), dihydroxyacetone, bismuth oxychloride, synthetic iron oxide, ferric ammonium ferrocyanide, ferric ferrocyanide, chromium hydroxide green, chromium oxide greens, guanine, mica-based pearlescent pigments, pyrophyllite, mica, dentifrices, talc, titanium dioxide, aluminum powder, bronze powder, copper powder, and zinc oxide or a mixture thereof.

Exemplary and non-limiting anti-oxidants include tocopherols (e.g., alpha-tocopherol, beta-tocopherol, gamma-tocopherol, or delta-tocopherol), butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), citric acid, ascorbic acid, phenolic diterpenes (e.g., carnosic acid, carnosol, rosmanol, epirosmanol, isorosmanol, or methyl carnosate), rosmarinic acid, eugenol, eugenyl acetate, clove bud extract, methanolic extract, tea catechins (e.g., epigallocatechin gallate, epicatechin gallate, epigallocatechin, or epicatechin), or a mixture thereof.

In another aspect, the present specification relates to processes for preparing the dosage forms as disclosed herein.

One embodiment of the present specification relates to a process of manufacturing the compressed orally disintegrating tablet described herein, the process comprising:

- a) generating seal coating layer with sugar spheres
- b) generating a plurality of cores or multiple units/pellets comprising a therapeutically effective amount of a proton pump inhibitor stabilized with an alkalizing agent;
- c) applying a barrier coating or sub coating around the drug layer comprising Ethyl cellulose and hypromellose polymer and its derivatives in all grades like phthalate, acetate, HPC SSL, HPC LF to the units/ pellets of step (b) obtaining a plurality of subcoated pellets;

- d) applying a solution or dispersion comprising an enteric polymer to the plurality of cores of step (c) thereby obtaining a plurality of enteric coated cores/ pellets;
- e) applying a solution or dispersion comprising a reverse enteric polymer to the enteric coated cores of step (d) thereby obtaining a plurality of units/ reverse enteric coated pellets;
- 5 f) blending the plurality of units/ pellets obtained in step (e) with one or more pharmaceutically acceptable excipients selected from the group consisting of a binder, a filler, a diluent, a surfactant, a glidant, a lubricant, a plasticizer, an anti-tacking agent, an alkaline substance, a tonicity enhancing agent, a wetting agent, a buffering substance, a preservative, a flavoring agent, an opacifier, a colorant, an anti-oxidant or a mixture or combination thereof; and
- 10 g) compressing the blend of step (f) thereby obtaining the compressed orally disintegrating tablet.

Another embodiment of the present invention is a method of preparing the modified release dosage form is described herein. The method comprises the following steps:

- i. preparing the core material in the form of pellets containing Rabeprazole as the active drug
15 by any conventional method;
- ii. coating the pellet core from step i) with the barrier coat;
- iii. coating the pellet core formed with the barrier layer from step ii) with an enteric coat layer;
- iv. optionally coating the pellets obtained from step iii) with an optional pulse coating layer;
and
- 20 v. Formulating the multi-coated pellet obtained from step iv) into a capsule, or multi-unit pellet tablet.

In yet another aspect, the present specification relates to solid oral dosage forms of Rabeprazole or its pharmaceutically acceptable salts thereof, as described herein are useful in treating a gastric
25 disorder. In one aspect, the gastric disorder comprises gastric reflux, gastroesophageal reflux disease, laryngopharyngeal reflux, laryngitis, dyspepsia, Barrett's esophagus, eosinophilic esophagitis, gastritis, gastrinomas, Zollinger-Ellison syndrome, peptic ulcers, or excessive helicobacter pylori or combinations thereof.

The following examples will further describe certain specific aspects and embodiments of the
30 invention in greater detail but are not intended to limit the scope of invention.

EXAMPLES**Example 1: Oral disintegrating compositions of Rabeprazole sodium**

	Example 1a	Example 1b	Example 1c	Example 1d
Ingredients	(% W/W)	(% W/W)	(% W/W)	(% W/W)
Seal Coating				
Sugar sphere	3.8	3.6	3.6	3.6
HPMC	0.1	0.1	0.1	0.1
Talc	0.1	0.1	0.1	0.1
Drug Layering				
Rabeprazole Sodium	4.4	4.3	4.3	4.3
Sodium hydroxide	0.7	1.0	1.0	1.0
HPMC	2.2	2.1	2.1	2.1
Barrier coating				
HPC LF	2.4	-	2.3	-
HPC SSL	0.0	2.8	-	2.3
Magnesium Oxide	2.2	2.6	2.2	2.2
Talc	0.4	0.3	0.3	0.3
Ethyl cellulose	0.8	0.9	0.8	0.8
Ethanol	QS	QS	QS	
Enteric Coating				
Hypromellose Phthalate	11.7	12.0	-	-
Eudragit L 100	-	-	11.3	11.3
Eudragit L 100 - 55	-	-	2.0	2.0
Triethyl citrate	1.0	1.0	6.7	6.7
Cetyl alcohol	2.5	2.6	-	-
Talc	1.2	1.2	6.7	6.7
Titanium dioxide	0.2	0.3	-	-
Acetone + Methanol	QS	QS	-	-
IPA +Water+Acetone	-	-	QS	QS
Top Coating/Reverse Enteric Coating				
Eudragit	6.8	6.0	3.7	3.7
Talc	1.7	3.0	1.9	1.9
Stearic acid	1.0	0.9	0.6	0.6
Sodium Lauryl Sulfate	0.7	0.6	0.4	0.4
Water	QS	QS	QS	QS
Extra granular material				
Mannitol	30.4	29.9	27.6	27.6
Crospovidone XL-10	5.7	5.9	5.5	5.5
Sucralose IP	2.4	2.5	2.3	2.3
Sodium Stearyl Fumarate NF	2.0	1.7	1.5	1.5
Silicified MCC	14.6	14.2	12.8	12.8
Colloidal Silicon Dioxide	0.5	0.5	0.4	0.4

Brief manufacturing process:

- 5 1. All the ingredients were dispensed and sifted
2. Seal coating layer was prepared by mixing the ingredients in seal coating in a solvent

3. Then the units or pellets of step (2) were sub coated/ barrier coated using the subcoated polymer solution prepared by dissolving the polymer (HPC SSL, HPC LF), alkali (Magnesium oxide), anti-tacking agent (Talc) in a solvent (ethanol)
4. The units or pellets of step (3) were enteric coated by enteric coating layer, which is prepared by dissolving enteric polymer (Hypermellose phthalate/ Eudragit), and all ingredients in enteric coated layer mentioned in above examples.
5. The pellets or units of step 4 were then reverse enteric coated with a reverse enteric coating layer which is prepared by dissolving reverse enteric polymer and all other ingredients as mentioned in above reverse enteric coated layer section.
6. The extra material was prepared by mixing the Mannitol, Crospovidone XL-10, Sucralose IP, Sodium Stearyl Fumarate NF, Silicified MCC, Colloidal Silicon Dioxide.
7. Finally the units of step 5 and extragranular material of step 6 were compressed to form a tablet

Example 2:

Optimisation of Drug: NaOH ratio for stabilization of drug Layer:

The amount of NaOH in the drug layer is important for the stabilization of the drug i.e., Rabeprazole sodium in the drug layer. The ratio of Drug: NaOH in the drug layer of the examples disclosed in example 1 is optimized to be in the ratio of 4:1 to 6:1. The compositions of Example 1a and Example 1b which is having Rabeprazole sodium: NaOH in the ratio of 6.6: 1, 4.4: 1 respectively when subjected to stability study at 30°C/ 75%RH for 1M showed that Example 1b showed better impurity profile compared to Example 1a. Table 1 represents the stability study data

Table 1: Stability study of Example 1a and 1b for selection of Drug: NaOH ratio

Stability Condition (30°C/75%RH)	Interval	Related Substances			
		Single Max unknown	Sulphone	Sulphide	Total Imp
Example 1b	Initial	0.06	0.33	ND	0.40
	1M	0.43	0.61	0.09	1.14
Example 1a	Initial	0.65	0.17	0.13	1.3
	1M	0.58	0.3	1.13	3.2

Example 3:**In-vitro dissolution study:**

The release profile of the oral disintegrating compositions of Rabeprazole sodium as per the present specification was evaluated through *in vitro* dissolution studies by comparing the dissolution profile of Rabeprazole sodium compositions of the present invention with that of commercially available Rabeprazole sodium tablets under the brand name Pariet® DR tablets. The compositions were prepared according to the formula and process of example 1 (Example 1a, 1b, 1c, 1d), and pariet 20mg tablets were subjected to an *in vitro* dissolution study in a changeover dissolution medium at 100 rpm, 37°C by using USP type II apparatus. Table 2 represents the dissolution results data.

Table 2: Dissolution study of Example 1b, 1d

Time (min)	Pariet® DR Tab 20 mg	Example 1b	Example 1d
0	0	0	0
5	12	83	90
10	36	88	88
15	64	91	87
20	82	91	85
30	90	88	82
45	86	84	78

Example 4:**Selection of HPC-SSL / HPC-LF in the Barrier coating:**

The compositions of present specification as exemplified in the above examples (1a, 1b) were subjected to stability study at 30°C/75% RH and 40°C/75% RH for 3M. The compositions comprising HPC-SSL showed better impurity profile (40% lesser) as compared to HPC-LF formulation.

Table 3: Selection of HPC-SSL Vs HPC-LF

Examples	Condition	Interval	Single max.	Sulphone	Sulphide	Total impurities
Example 1a	30°C/75%RH	Initial	0.06	0.33	ND	0.40
		1M	ND	0.49	ND	0.49
	40°C/75%RH	1M	0.34	0.61	0.14	1.21
		3M	0.8	0.7	0.3	3.75
Example 1b	30°C/75%RH	Initial	ND	0.36	0.12	0.48
		1M	0.07	0.38	0.06	0.51
	40°C/75%RH	1M	0.1	0.45	0.06	0.71
		3M	0.09	0.49	ND	0.77

Example 5

Stability Study:

The compositions of present specification as exemplified in the above examples were be subjected to stability study at 30°C/75% RH and 40°C/75% RH for 3M. The compositions was found to be stable at accelerated conditions. Table 4 and table 5 represents the study result data.

Table 4: Stability study of Example 1d

Condition	Interval	Related substances						
		SMU	Sulphone	Sulphide	Total impurities	Assay	Dissolution (pH 8.0)	Water content
30°C/75% RH	Initial	ND	0.33	0.05	0.38	100.49	90 (89-91)	4.00
	1M	ND	0.35	ND	0.35	100	88 (84-90)	3.12
	3M	0.05	0.41	ND	0.50	97.20	83 (82-86)	3.55
40°C/75% RH	1M	0.04	0.42	ND	0.46	100	90 (88-92)	4.15
	2M	0.06	0.40	0.05	0.52	103.9	88 (83-91)	4.19
	3M	0.06	0.48	ND	0.65	97.2	85.2 (84-87)	3.97

Table 5: Acid resistance of Example 1d unit compositions:

Condition/Time period	Unit 1	Unit 2	Unit 3	Unit 4	Unit 5	Unit 6
Initial	7	7	7	7	8	4
30°C/75% RH (3M)	3	3	3	4	3	3
40°C/75% RH (3M)	9	6	9	6	9	6

Example 6:**Pharmacokinetic Study:**

A Single dose, three-treatment, three-period, six-sequence cross-over, bioequivalence study was conducted in healthy subjects using administration of the Rabeprazole compositions of the present invention as test formulations (T) and Pariet 20mg tablets as reference product. Pharmacokinetic data is shown in table 6 below. Tmax of the test formulation is reduced to 2.33 (1.33 – 3.67) hr compared to reference formulation 4.17 (2.67 – 10.00) hr.

Table 6: Pharmacokinetic data

Parameters	Pilot study Results	
	Test (Arit. Mean $\pm$ SD)	Reference (Arit. Mean $\pm$ SD)
T _{max} (Hours)	2.33 (1.33 – 3.67) ^b	4.17 (2.67 – 10.00) ^b
C _{max} (ng/mL)	746.3909 $\pm$ 258.33251	853.2686 $\pm$ 372.49570
AUC _{0-t} (ng.hr/mL)	1782.3497 $\pm$ 687.56890	1793.2760 $\pm$ 756.70636
AUC _{0-inf} (ng.hr/mL)	1843.6854 $\pm$ 724.60247	1926.6697 $\pm$ 741.61962
t _{1/2} (hr)	2.485 $\pm$ 0.5316	1.814 $\pm$ 0.5167
T _{lag} (hr)	0.458 $\pm$ 0.490	2.640 $\pm$ 0.822
K _{el} (hr ⁻¹)	0.29255 $\pm$ 0.068385	0.40928 $\pm$ 0.104477
AUC _{%Extrap}	3.127 $\pm$ 1.9417	3.651 $\pm$ 2.9131

^b expressed as median (minimum – maximum)

Example 7: Modified release compositions of Rabeprazole sodium

Ingredients	Example 7(a) (mg/pellet)	Example 7(b) (mg/capsule)
Core		
Rabeprazole Sodium	10.00	40.00
Mannitol	100.00	104.00
Crospovidone	64.00	64.00
Sodium Starch Glycolate	-	60.00
Sodium Hydroxide	4.00	4.00
Hydroxypropyl Cellulose	6.00	6.00
Magnesium Oxide	60.00	60.00
Colloidal Silicon Dioxide	6.00	6.00
Sodium Stearyl Fumarate	4.00	4.00
Dehydrated Ethanol	q.s.	q.s.
Barrier Coating		
Ethyl Cellulose 4cps	33.60	4.08

Magnesium oxide	3.36	4.08
Hydroxypropyl cellulose	5.04	2.04
Dehydrated Ethanol	q.s.	q.s.
Enteric Release Coating		
HPMC Phthalate	34.08	34.08
Diacetylated Monoglycerides	3.40	3.4
Talc	5.12	5.12
Methanol	q.s.	q.s.
Acetone	q.s.	q.s.
Tablet Weight (Enteric Coated Tablet)	3.72	5.19
Pulsed Release Coating		
Eudragit L-100	2.75	4.12
Ethyl Cellulose 4 Cps	0.43	0.64
Calcium Stearate	1.92	2.88
Triethyl Citrate	0.59	0.88
Talc	0.51	0.76
Methanol	q.s.	q.s.

Brief manufacturing process:

- i) Mannitol and crospovidone were added to and mixed with Rabeprazole sodium.
- ii) Ethanol having hydroxypropyl cellulose, sodium hydroxide and magnesium oxide dissolved
5 therein was added, and granulation was carried out.
- iii) The granules obtained in step ii) were dried and sieved.
- iv) Sodium stearyl fumarate and colloidal silicon dioxide was then added to the granules obtained in step iii) and mixed in, and pellet formation was carried out.
- v) The barrier coating solution was obtained by dissolving ethyl cellulose, hydroxypropyl
10 cellulose and magnesium oxide in ethanol.
- vi) The uncoated pellets obtained in step iv) were made to flow in a fluidized bed coating apparatus and the barrier coating solution was sprayed on.
- vii) Separately, an enteric coating solution was prepared by dissolving hydroxypropyl methyl cellulose phthalate and diacetylated monoglycerides in methanol and adding a suspension
15 obtained by uniformly dispersing talc in acetone solution.
- viii) The enteric coating solution was sprayed onto the barrier coated pellets obtained in step vi) in the fluidized bed coating apparatus.
- ix) The enteric coated pellets were further coated with a solution containing the components of the pulse coating dissolved in methanol.

- x) The multi-coated modified release pellets obtained in step ix) were filled into HPMC capsule and vacuum dried.

Example 8:

5 Pharmacokinetic Study:

A Single dose, three-treatment, three-period, six-sequence cross-over, bioequivalence study was conducted in healthy subjects using administration of the Rabeprazole compositions of Example 7(b) as Test formulation and Pariet 2 x 20mg tablets as Reference product (administered as BID with 12 hr interval). Means are expressed as geometric means (AUC_{0-t}, C_{max}) or arithmetic means (T_{max}, T_{last}, C_{last}). Pharmacokinetic data is shown in table 7 below.

Table 7: Pharmacokinetic data

Parameters	Fasting study Results		Fed study Results	
	Test Arit. Mean $\pm$ SD	Reference Arit. Mean $\pm$ SD	Test Arit. Mean $\pm$ SD	Reference Arit. Mean $\pm$ SD
T _{max} (Hours)	5.00 (3.50 – 8.00) ^b	14.50 (3.00 – 17.00)	7.50 (3.00 – 10.00)	6.50 (3.00 – 22.00)
C _{max} (ng/mL)	823.8652 $\pm$ 446.24279	796.4292 $\pm$ 220.19730	874.9477 $\pm$ 296.89228	783.7663 $\pm$ 233.74677
AUC _{0-t} (ng.hr/mL)	2159.8055 $\pm$ 936.38070	2735.7062 $\pm$ 963.36871	2844.4462 $\pm$ 820.87831	2708.6286 $\pm$ 907.02214
AUC _{0-inf} (ng.hr/mL)	2280.3732 $\pm$ 940.47751	2785.2486 $\pm$ 994.57737	2936.0766 $\pm$ 858.65177	2973.5331 $\pm$ 1243.22031
t _{1/2} (hr)	7.033 $\pm$ 5.3249	2.203 $\pm$ 0.8046	5.222 $\pm$ 3.1524	3.230 $\pm$ 2.3465
K _{el} hr ⁻¹)	0.16567 $\pm$ 0.114023	0.37877 $\pm$ 0.199593	0.18449 $\pm$ 0.105873	0.30464 $\pm$ 0.166408
AUC _{%Extrap}	5.307 $\pm$ 6.1535	1.671 $\pm$ 0.8743	3.000 $\pm$ 2.8292	8.110 $\pm$ 11.6676
C _{Last}	8.1 (0 - 26)	11.2 (0 – 33)	9.8 (0 - 32)	80 (10 – 291)
T _{Last}	20 (10 – 24)	22 (18 – 24)	18 (12 – 24)	24

^b expressed as median (minimum – maximum)

We Claim:

1. A solid oral pharmaceutical composition of Rabeprazole comprising:
 - i) a core comprising a therapeutically effective amount of Rabeprazole stabilized with an alkalizing agent;
 - ii) a barrier coating or sub coating around the drug core comprising one or more polymer, and an alkalizing agent; and
 - iii) an enteric coating comprising enteric polymer having solubility at pH higher than 5.5.
2. An oral disintegrating solid pharmaceutical composition of Rabeprazole comprising a plurality of units comprising:
 - i. an inert core comprising sugar spheres, coated by an optional seal coating layer
 - ii. a drug layer comprising a therapeutically effective amount of a proton pump inhibitor stabilized with an alkalizing agent;
 - iii. a barrier coating or sub coating around the drug layer comprising polymer, an alkalizing agent;
 - iv. an enteric coating comprising enteric polymer having solubility at pH higher than 5.5;
 - v. a reverse enteric coating or top coating comprising reverse enteric polymer, and
 - vi. an extragranular material comprising at least one disintegrant, filler, glidant, lubricant, binder, diluent, surfactant, plasticizer, anti-tacking agent, alkaline substance, tonicity enhancing agent, wetting agent, buffering substance, preservative, flavoring agent, an opacifier, colorant, anti-oxidant or combinations thereof.
3. The composition as claimed in claim 2, wherein drug and alkalizing agent in the drug layer is present in the ratio of about 10:1 to 1:10, preferably in the ratio of about 6:1, about 4:1 and the alkalizing agent is selected from sodium hydroxide, magnesium hydroxide, magnesium oxide, sodium oxide or combinations thereof.
4. The composition as claimed in claim 2, wherein the reverse enteric polymer in the reverse enteric coating or top coating layer is present in an amount of about 2.5 % to about 30% by weight based on total weight of the composition and is selected from one or more of a (a (meth) acrylate polymer or copolymer, methyl methacrylate-butyl methacrylate-

dimethylaminoethyl methacrylate copolymer, dimethyl amino ethyl (meth)acrylate, diethyl amino ethyl (meth)acrylate, piperidine ethyl (meth)acrylate, tertbutyl amino ethyl (meth)acrylate, butyl methacrylate, dimethylaminoethyl methacrylate, methyl methacrylate copolymer or combinations thereof and is present in an amount of about 2.5 % to about 30% (w/w) of a total weight of the tablet.

5. The composition as claimed in claim 2, wherein the disintegrant is present in an amount of about 2% to about 25% by weight based on total weight of the composition and is selected from one or more of crospovidone, crospovidone XL-10, croscarmellose sodium, a cellulose derivative, cross- linked derivatives of starch, pregelatinized starch, crosslinked sodium carboxymethyl cellulose, low substituted hydroxypropyl cellulose or Combinations thereof
6. The composition as claimed in claim 2, wherein the glidant in the extragranular material is selected from one or more of silicon dioxide, corn starch, and talc or mixtures thereof.
7. The composition as claimed in claim 2, wherein the lubricant in the extragranular material is selected from one or more of sodium stearyl fumarate, stearic acid, polyethylene glycol or stearates, such as magnesium stearate or a mixture thereof.
8. The composition as claimed in claim 2, wherein the said composition exhibits a Tmax which is in the range of 2Hrs to 2.5Hrs, a reduced Tmax compared to commercially available Rabeprazole 20mg DR tablets formulation which is 4.17Hrs.
9. A modified release solid oral dosage form of Rabeprazole, suitable for once daily administration, comprising:
 - iv) a core comprising a therapeutically effective amount of Rabeprazole stabilized with an alkalizing agent;
 - v) a barrier coating or sub coating around the drug core comprising one or more polymer, and an alkalizing agent;
 - vi) an enteric coating comprising enteric polymer having solubility at pH higher than 5.5, and
 - vii) optionally, a pulse coating layer comprising water-insoluble polymers, water soluble polymers, enteric polymers, waxes and mixtures thereof.

10. The composition as claimed in claim 9, wherein the alkalizing agent in the drug core is selected from sodium hydroxide, magnesium hydroxide, magnesium oxide, sodium oxide or a combination thereof.
11. The composition as claimed in claim 9, wherein the final dosage form is a pellet or a capsule or a tablet.
12. The composition as claimed in claims 1, 2 and 9, wherein the polymer in the barrier coating or sub coating is present in an amount of about 5% to about 20% by weight based on total weight of the composition and is selected from ethyl cellulose, hydroxypropyl methyl cellulose and its derivatives, hydroxypropyl cellulose polymer and its derivatives and combinations thereof.
13. The composition as claimed in claims 1, 2 and 9, wherein the barrier coating or sub coating comprises ethyl cellulose, hydroxypropyl cellulose polymer and an alkalizing agent.
14. The compositions as claimed in claims 1, 2 and 9, wherein the said compositions the ratio of ethyl cellulose: HPC polymer in the barrier coating/subcoating layer is about 0:100, about 20:80, about 50:50, more preferably is about 25:75 to provide a satisfactory *in vitro* dissolution.
15. The composition as claimed in claims 1, 2 and 9, wherein the enteric polymer in the enteric coating layer is present in an amount of about 15% to about 30% by weight based on total weight of the composition and is selected from one or more of (meth) acrylate polymer or copolymer, methyl methacrylate-butyl methacrylate-dimethylaminoethyl methacrylate copolymer, dimethyl amino ethyl (meth)acrylate, diethyl amino ethyl (meth)acrylate, piperidine ethyl (meth)acrylate, tertbutyl amino ethyl (meth)acrylate, cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), hydroxypropyl methylcellulose acetate succinate (HPMCAS), polyvinyl acetate phthalate, cellulose acetate trimellitate, shellac, polymethacrylic acid, polymethyl methacrylate, polyethyl methacrylate, polyethyl acrylate or combinations thereof

16. The compositions as claimed in claims 1, 2 and 9, wherein said composition when administered exhibits bioequivalence to a commercially available Rabeprazole 20mg DR tablets in a human subject under fasting conditions and is established by:
 - a) a 90% Confidence Interval for mean AUC(0-t), which is between 80% and 125%, and
 - b) a 90% Confidence Interval for mean AUC(0-∞), which is between 80% and 125%.
17. The composition as claimed in claims 1, 2 and 9, wherein the said composition exhibits a Cmax of about 600 ng.hr/mL to about 1200 ng.hr/mL.
18. The composition as claimed in claims 1, 2 and 9, wherein the composition comprises additional one or more pharmaceutically acceptable excipients selected from the group consisting of a binder, a filler, a diluent, a surfactant, a glidant, a lubricant, a plasticizer, an anti-tacking agent, an alkaline substance, a tonicity enhancing agent, a wetting agent, a buffering substance, a preservative, a flavoring agent, an opacifier, a colorant, an anti-oxidant or a mixture or combination thereof.
19. A method of preparing oral disintegrating compositions comprising Rabeprazole or a pharmaceutically acceptable salt thereof, the said method comprising steps of:
 - a) Applying seal coating layer over the inert sugar spheres
 - b) generating a plurality of cores or multiple units/pellets comprising a therapeutically effective amount of Rabeprazole stabilized with an alkalizing agent;
 - c) applying a barrier coating or sub coating around the drug layer comprising Ethyl cellulose and hypromellose polymer and its derivatives in all grades like phthalate, acetate, HPC SSL, HPC LF to the units/ pellets of step (b) obtaining a plurality of subcoated pellets
 - d) applying a solution or dispersion comprising an enteric polymer to the plurality of cores of step (c) thereby obtaining a plurality of enteric coated cores/ pellets
 - e) applying a solution or dispersion comprising a reverse enteric polymer to the enteric coated cores of step (d) thereby obtaining a plurality of units/ reverse enteric coated pellets;
 - f) blending the plurality of units/ pellets obtained in step (e) with one or more pharmaceutically acceptable excipients selected from the group consisting of a binder, a filler, a diluent, a surfactant, a glidant, a lubricant, a plasticizer, an anti-tacking agent,

- an alkaline substance, a tonicity enhancing agent, a wetting agent, a buffering substance, a preservative, a flavoring agent, an opacifier, a colorant, an anti-oxidant or a mixture or combination thereof and
- g) compressing the blend of step (f) thereby obtaining the compressed orally disintegrating tablet.
20. A method of preparing modified release solid oral compositions comprising Rabeprazole or a pharmaceutically acceptable salt thereof, the said method comprising steps of:
- a) generating cores comprising a therapeutically effective amount of Rabeprazole stabilized with an alkalizing agent;
 - b) applying a barrier coating or sub coating around the drug layer comprising polymers and alkalizing agent to the units/ pellets of step (b) obtaining a plurality of subcoated pellets
 - c) applying a solution or dispersion comprising an enteric polymer to the plurality of cores of step (c) thereby obtaining a plurality of enteric coated cores/ pellets
 - d) optionally, applying a layer of pulse release coating to the enteric coated cores of step (d) thereby obtaining a plurality of multi-coated pellets; and
 - e) either, blending the plurality of units/ pellets obtained in step (e) with one or more pharmaceutically acceptable excipients selected from the group consisting of a binder, a filler, a diluent, a surfactant, a glidant, a lubricant, a plasticizer, an anti-tacking agent, an alkaline substance, a tonicity enhancing agent, a wetting agent, a buffering substance, a preservative, a flavoring agent, an opacifier, a colorant, an anti-oxidant or a mixture or combination thereof, and compressing the blend thereby obtaining the compressed orally disintegrating tablet, or
 - f) filling the pre-determined number of multi-coated pellets in to capsules.
21. The use of the compositions as claimed in claim 1, 2 and 9, for the treatment of a gastric disorder selected from gastric reflux, gastroesophageal reflux disease, laryngopharyngeal reflux, laryngitis, dyspepsia, Barrett's esophagus, eosinophilic esophagitis, gastritis, gastrinomas, Zollinger-Ellison syndrome, peptic ulcers, or excessive helicobacter pylori or combinations thereof.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

A61K9/00, A61K9/20, A61P1/04, A61K9/28 Version=2023.01

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K; A61P

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

Electronic database consulted during the international search (name of database and, where practicable, search terms used)

PatSeer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 101507718 A (DENGKE ZHANG [CN]); 19 Aug 2009 Abstract, Example 1, paragraph 1 on page 4, Tables 1-2, Claims 1-10.	1-21



Further documents are listed in the continuation of Box C.



See patent family annex.

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