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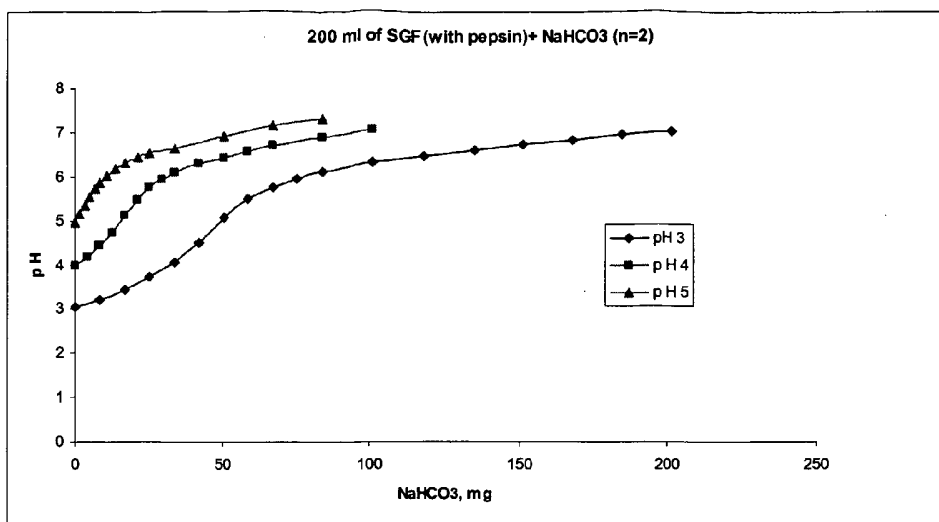
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(54) Title: A KIT FOR INHIBITING GASTRIC ACID SECRETION HAVING AN ADJUSTABLE AMOUNT OF PH REGULATING AGENT



(57) Abstract: The present invention relates to an oral kit for inhibiting gastric acid secretion comprising an immediate-release proton pump inhibitor (PPD) in conjunction with an adjustable amount of one or more pH regulating agents, e.g., pH regulating agents, and optionally a parietal cell activator or gastric acid stimulant. The present invention further relates to a method of using such kit.

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A KIT FOR INHIBITING GASTRIC ACID SECRETION HAVING AN ADJUSTABLE AMOUNT OF pH REGULATING AGENT

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 60/682,808 filed May 20, 2005, the content of which is expressly incorporated herein by reference thereto.

FIELD OF THE INVENTION

The present invention relates to novel oral kit for inhibition of gastric acid secretion comprising an immediate-release proton pump inhibitor (PPI) in conjunction with an adjustable amount of one or more pH regulating agents, *e.g.*, buffering agent, and optionally one or more parietal cell activators or gastric acid stimulants. The present invention further relates to a method of using such kits.

BACKGROUND OF THE INVENTION

A wide number of pathological conditions are characterized by the need to suppress gastric acid secretion. Such conditions include, but are not limited to Zollinger/Ellison syndrome (ZES), gastroesophageal reflux disease (GERD), peptic ulcer disease, duodenal ulcers, esophagitis, and the like. Conditions such as peptic ulcers can have serious complications and represent some of the most prevalent diseases in industrialized nations.

Presently, the main therapies employed in the treatment of GERD and peptic ulcer diseases include agents for reducing the stomach acidity, for example by using the histamine H₂-receptor antagonists or proton pump inhibitors (PPI's). PPI's act by inhibiting the parietal cell H⁺/K⁺ ATPase proton pumps responsible for acid secretion from these cells. PPI's, such as omeprazole, and its pharmaceutically acceptable salts are disclosed for example in EP 05129, EP 124495 and US Patent No. 4,255,431.

PPI agents are acid-labile pro-drugs that are usually administered in enteric-coated delayed release granules. Following their absorption in the small intestine PPIs, which are weak bases, preferentially accumulate within the acid milieu of the acid-secreting parietal cells. The acid environment within the acid milieu of parietal cells causes the conversion of the pro-drugs into the active sulfenamids, which are the active

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agents that bind and inhibit the parietal cell H^+/K^+ ATPase pumps. Thus, pre-activation of parietal cells is required for the conversion of PPI's to its active protonated form. The pre-activation of parietal cells is usually achieved by meal ingestion that initiates gastrin-dependent parietal cell activation. Indeed, patients are instructed to take PPI one hour prior to meal intake in order to ensure that parietal cells are activated when the PPI reaches the parietal cells via blood stream.

Despite their well-documented efficacy, PPIs have notable limitations. The PPI must be taken prior to ingestion of food in order to synchronize between the pre-activation of parietal cells and PPI absorption in blood. Furthermore, PPIs have a relatively slow onset of pharmacological action and may require several days to achieve maximum acid suppression and symptom relief, limiting their usefulness in on-demand GERD therapy (Sachs G, Eur J Gastroenterol Hepatol. 2001;13 Suppl 1:S35-41). Thus, an improvement of PPI-mediated activity is a well-recognized challenge in gastroenterology.

US Patent Nos. 5,840,737; 6,489,346; 6,645,988; and 6,699,885; to Phillips (jointly the "Phillips patents") disclose pharmaceutical compositions and methods of treating acid-caused gastrointestinal disorders using oral compositions consisting of an immediate-release non-enteric-coated PPI, at least one buffering agent and optionally a parietal cell activator. The amount of buffer disclosed in the Phillips patents is in excess in order to obtain a basic environment in the stomach to preserve the acid-labile PPI in the stomach. These excess amounts of buffer can be problematic when used for chronic treatment, for example, when administered to patients suffering from metabolic alkalosis, hypocalcemia, and hypokalemia.

Chronic treatment with a PPI usually leads to average gastric pH values that are above 4.0 (see for example in Tsai et. al., Aliment. Pharmacol. Ther. 2000, 14, 123-127 and in Phillips et. al., Crit. Care Med., 1996, Vol. 24, No. 11, 1793-1800). None of the above prior art disclose or suggest a solution to the problems associated with use of excess buffer during for chronic treatment.

Despite the wide-spread chronic use of PPIs, a need still exist for immediate-release PPI granules exhibiting fast absorption in blood in order to provide fast effect of the PPI without the risk of chronic consumption of high amount of buffer along with the PPI.

SUMMARY OF THE INVENTION

It is the object of the present invention to provide a fast absorption of PPI in the blood without the risk of chronic consumption of high amounts of buffer. The inventors have unexpectedly found that the amount of pH regulating agents, *e.g.*, buffering agents, used to preserve the acid-labile PPI granules in the stomach could be lowered during the continuance stage of treatment while still providing fast anti-secretory onset times during chronic PPI treatment.

The present invention relates to a kit for chronic treatment of gastric-acid secretion-related disorders based on immediate-release benzimidazole H^+/K^+ -ATPase proton pump inhibitor (PPI) and adjustable amounts of one or more pH regulating agents. The kit comprises at least two different doses: an initial dose for the early stage of treatment containing an effective amount of PPI granules combined with one or more pH regulating agents in an amount sufficient to raise the pH in the stomach to a pH of at least 4.5, and a continuance dose containing a comparable amount of PPI granules combined with one or more pH regulating agents in an amount less than in the initial dose, but sufficient to raise the pH in the stomach to a pH of at least 4.5.

In a preferred embodiment, both initial and continuance doses comprise one or more pH regulating agents in an amount sufficient to raise the pH in the stomach to a pH of at least 5.5, more preferably to a pH of at least 6.0.

In another preferred embodiment, the initial dose comprises one or more pH regulating agents in an amount sufficient to raise the pH in the stomach by at least 2.5 to 5.5 pH units and the pH regulating agent in the continuance dose is in an amount sufficient to raise the pH in the stomach by at least 1 to 3 pH units.

In more preferred embodiment, the initial dose comprises one or more pH regulating agents in an amount sufficient to raise the pH in the stomach by at least 4 to 5 pH units and the pH regulating agent in the continuance dose is in an amount sufficient to raise the pH in the stomach by at least 1.5 to 2.5 pH units.

In another embodiment, the kit of the present invention comprises at least two continuance doses, a first and second continuance dose, wherein the amount of pH regulating agent in the second continuance dose is less than the amount of pH regulating agent in the first continuance dose.

The substituted benzimidazole PPIs according to the present invention are compounds that inhibit the activity of the H^+/K^+ -adenosine triphosphatase (ATPase) proton pump in the gastric parietal cells. In its pro-drug form, the PPI is non-ionized and

therefore is capable of passing through the cellular membrane of the parietal cells. Once reaching activated parietal cells, the non-ionized PPI moves into the acid-secreting portion of the cells, the secretory canaliculus. The PPI trapped in the canaliculus becomes protonated, thus converted to the active sulfenamide form that can form disulfide covalent bonds with cysteine residues in the alpha subunit of the proton pump, thereby irreversibly inhibiting the proton pump.

In a preferred embodiment, the kit of the present invention further comprises one or more parietal cell activators or gastric acid stimulants in order to maximize the inhibitory effect of the PPI by pre-activation of parietal cells. Active parietal cells possess acidic pH, which is required for the conversion of the PPI to the active protonated sulfenamide form. Therefore, the synchronized activation of the parietal cells maximizes the inhibition of the pumps by the PPI. The presence of one or more parietal cell activators or gastric acid stimulants in the kit permits the pre-activation of parietal cells in a meal independent manner. In this embodiment of the invention it is possible to take the PPI independent of food consumption.

The kit of the present invention exhibits a significant advantage over the immediate-release PPI-based compositions known in the art since the adjustable amount of pH regulating agent prevents alkalosis following the chronic ingestion of high amounts of buffer. High doses of buffer such sodium bicarbonate is not recommended especially in patients on sodium-restricted diet. Furthermore, high dose of sodium bicarbonate is contradicted in patients with metabolic alkalosis and hypocalcemia, and should be used with caution in patients with hypokalemia and respiratory alkalosis. Thus, the combination kit of the present invention provides an effective solution for patients that would like to use immediate-release PPI-based compositions chronically but are instructed not to ingest high amount of buffer.

The active ingredients of the present invention are PPI and one or more pH regulating agents, and optionally one or more parietal cell activators or gastric acid stimulants. The active ingredients may be formulated in a kit, preferably a kit for oral use, comprising an initial dose for the early stage of treatment and a continuance dose for the chronic stage of treatment. The initial dose containing an effective amount of PPI granules combined with high amount of pH regulating agents. According to various embodiments, the initial dose contains pH regulating agents in an amount sufficient to raise the acidic pH of the stomach to a pH in which the stability of PPI granules is maintained, preferable to a pH above about 5.5-6.0. The continuance dose containing

low amount of pH regulating agent and should be taken only following the ingestion of PPIs for several days and the consequent establishment of more basic pH in the stomach. The amount of pH regulating agent in the continuance dose is sufficient to elevate the pH of the stomach from about pH 4.0-5.0 (the pH in stomach during chronic treatment of PPI) to a pH above about pH 6.0 (the pH sufficient to dissolve the enteric-coating and preserve the stability of the PPI in the stomach). It is also possible to use the continuance dose of the present kit as a continuation treatment of regular delayed-release enteric-coated PPI granules.

Both the initial dose and continuance dose should contain sufficient pH regulating agent to raise the pH of the stomach to at least 4.5, or 4.8, more preferably to at least 5, 5.5 or 5.8, and most preferably to at least 6.0. As discussed above, Applicants discovered that less pH regulating agent is needed in the continuance dose to raise the pH in the stomach to these pHs than is required in the initial dose.

The PPI in the kit of the present invention is formulated either as non-enteric-coated or enteric-coated PPI granules. Both will provide an immediate release profile and fast absorption of PPI in blood due to the basic environment of the stomach. The basic environment rapidly induces the dissolving of the enteric-coating from the PPI granules, thereby permitting immediate release of the PPI from the granules and fast absorption in blood.

The active ingredients in the initial dose and the continuance dose may be formulated in any oral dosage forms such as capsules or tablets. The pH regulating agent in the acute dose is preferably formulated as suspension tablet, effervescent tablet, chewable tablet or powder for suspension for fast relief of heartburn in patients. Both initial and continuance doses may be divided to more than one capsules or tablets. The kit preferably further comprises a parietal cell activator that is aimed to synchronize between the activation of the parietal cells and the absorption of the PPI in blood in order to maximize the inhibition of the pumps by the PPI.

In another embodiment, the present invention is directed to a method of treating a subject suffering from a disorder in which chronic suppression of gastric acid secretion is required or a disorder normally treated by chronic suppression of gastric acid secretion. Such method comprises administering to the subject the kit of the present invention. Preferably, the subject is a human subject.

The kit of the present invention may be used for preventing or treating pathologies in a mammal in which chronic inhibition of gastric acid secretion is required.

The kit of the present invention is effective both in treating the pathologies and in minimizing the risk of development of such pathologies before onset of symptoms.

The kit of the present invention may be used in a wide number of pathological conditions that are treated by suppression of gastric acid secretion. Such conditions include, but are not limited to Zollinger/Ellison syndrome (ZES), gastroesophageal reflux disease (GERD), esophagitis, peptic ulcer diseases, duodenal ulcers, gastritis and gastric erosions, dyspepsia, NSAID- induced gastropathy, and the like.

The kit of the present invention may further comprise any additional components that are active in upper gastrointestinal pathologies, such as antibiotics effective against pathological bacteria residing in the stomach (such as *H. Pylori* bacteria), or agents that support the healing of gastric ulcer such as sucralfate, prokinetics, *etc.*

These and further embodiments will be apparent from the detailed description and examples that follow.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 details the amount of sodium bicarbonate required in order to raise the pH in gastric stimulated fluid to pH 6.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a unique kit of immediate-release PPI and adjustable amounts of pH regulating agents. The kit comprises at least two different doses: an initial dose for the early stage of treatment containing an effective amount of PPI granules combined with high amount of at least one pH regulating agents and a continuance dose containing comparable amount of PPI granules combined with low amount of at least one pH regulating agents. The kit of the present invention provides the advantage of immediate-release PPI-based composition having fast absorption in blood and fast onset of anti-secretory effect with adjustable amount of pH regulating agent in order to minimize the risk of alkalosis.

In one embodiment, the kit of the present invention is formulated as a separate dosage form for the initial stage and the continuance stage of treatment. The initial dose containing an effective amount of either enteric-coated or non-enteric-coated PPI granules with one or more pH regulating agents in an amount sufficient to raise the acidic pH of the stomach to a pH in which the stability of PPI granules is maintained, preferable to a pH above about 5.5-6.0. In a non-limiting example, sodium bicarbonate is used as

the pH regulating agent and the its amount ranges from about 1000 mg to about 2000 mg, more preferable from about 1300mg to about 1800 mg. The continuance dose contains an effective amount of either enteric-coated or non-enteric-coated PPI granules with one or more pH regulating agents in an amount sufficient to raise the gastric pH from about 4-5 to above about 5.5-6.0. When sodium bicarbonate is used as the pH regulating agent, its amount ranges from about 50 mg to about 500 mg, more preferable from about 50 mg to about 300 mg. The pH regulating agents in combination with the PPI and optionally one or more parietal cell activators or gastric acid stimulants of the initial dose may be divided to more than one capsule or tablet for more convenient use. The pH regulating agent in the acute dose is preferably formulated as suspension tablet, effervescent tablet, chewable tablet or powder for suspension.

In one embodiment, the continuance dose may comprise at least 2 doses: a first and second continuance dose, wherein the amount of pH regulating agent of the second continuance dose is less than that in the first continuance dose. In other embodiments the kit advantageously comprises multiple continuance doses wherein each subsequent continuance doses has less pH regulating agent then the prior continuance dose.

The term "pH regulating agent" as used herein, includes any agent used to regulate the pH of the stomach, preferably any weak base or strong base that inhibits or prevents the acid degradation of PPI. Examples include buffering agents, alkaline agents, and antacids, such as, aluminum, calcium and magnesium hydroxides; magnesium oxide or composite substances. The pH regulating agents to be used in the present invention, preferably include, for example: sodium or potassium bicarbonate, magnesium oxide, hydroxide or carbonate, magnesium lactate, magnesium gluconate, aluminum hydroxide, aluminum, calcium, sodium or potassium carbonate, phosphate or citrate, di-sodium carbonate, disodium hydrogen phosphate, a mixture of aluminum glycinate and a buffer, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, and other calcium salts. It is noted that while sodium bicarbonate dissolves easily in water, calcium carbonate is water-insoluble and is slowly soluble only in acidic environment. Therefore, calcium carbonate may be useful when sustained dissolution of the pH regulating agent in the stomach is desired.

Other examples of pH regulating agents or combination thereof that can be used in the present invention include one or more of the following: alumina, calcium carbonate, and sodium bicarbonate; alumina and magnesia; alumina, magnesia, calcium carbonate, and simethicone; alumina, magnesia, and magnesium carbonate; alumina,

magnesia, magnesium carbonate, and simethicone; alumina, magnesia, and simethicone; alumina, magnesium alginate, and magnesium carbonate; alumina and magnesium carbonate; alumina, magnesium carbonate, and simethicone; alumina, magnesium carbonate, and sodium bicarbonate; alumina and magnesium trisilicate; alumina, magnesium trisilicate, and sodium bicarbonate; alumina and simethicone; alumina and sodium bicarbonate; aluminum carbonate, basic ; aluminum carbonate, basic, and simethicone ; aluminum hydroxide; calcium carbonate; calcium carbonate and magnesia; calcium carbonate, magnesia, and simethicone; calcium carbonate and simethicone; calcium and magnesium carbonates; magaldrate; magaldrate and simethicone; magnesium carbonate and sodium bicarbonate; magnesium hydroxide; magnesium oxide.

The kit of the present invention comprises a PPI that acts as an irreversible inhibitor of the gastric H^+/K^+ -ATPase proton pump. The PPI used in the present invention can be any substituted benzimidazole compound having H^+ , K^+ -ATPase inhibiting activity. For the purposes of this invention, the term "PPI" shall mean any substituted benzimidazole or imidazole pyridine backbone compounds possessing pharmacological activity as an inhibitor of H^+, K^+ -ATPase, or any salts and derivatives thereof. This includes, but not limited to, omeprazole, lansoprazole, pantoprazole, rabeprazole, dontoprazole, perprazole (s-omeprazole magnesium), habeprazole, ransoprazole, pariprazole, tenatoprazole and leminoprazole in neutral form or a salt form, a single enantiomer or isomer or other derivative or an alkaline salt of an enantiomer of the same.

Examples of gastric H^+/K^+ -ATPase proton pump inhibitors that may be used in the present invention are disclosed for example in US Patent 6,093,738 that describes novel thiadiazole compounds that are effective as proton pumps inhibitors. European Patent Nos. 322133 and 404322 disclose quinazoline derivatives, European Patent No. 259174 describes quinoline derivatives, and WO 91/13337 and US Patent 5,750,531 disclose pyrimidine derivatives, as proton pump inhibitors. Suitable proton pump inhibitors are also disclosed for example in EP-A1-174726, EP-A1-166287, GB 2 163 747 and W090/06925, W091/19711, W091/19712, W094/27988 and W095/01977.

The kit of the present invention is preferably suitable for oral administration. The PPI particles in the kit according to the present invention may be either enteric-coated or non-enteric-coated. Both non-enteric and enteric PPI granules should permit fast absorption in blood due to the basic environment of the stomach that rapidly induces the dissolving of the enteric-coating from the PPI granules. Non-limiting examples of

suitable enteric-coated (pH-dependent) polymers to be used in the present invention are: cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, polyvinylacetate phthalate, methacrylic acid copolymer, shellac, hydroxypropylmethylcellulose succinate, cellulose acetate trimellitate, and mixtures of any of the foregoing. A suitable commercially available enteric material, for example, is sold under the trademark Eudragit L 100-55. This coating can be spray coated onto the substrate.

In a preferred embodiment, the PPI particles are enteric-coated in order to stabilize the granules during storage. The preparation of enteric-coated particles comprising a PPI such as Omeprazole is disclosed for example in US Patents Nos. 4,786,505 and 4,853,230.

The kit of the present invention comprises a PPI in an effective amount to achieve a pharmacological effect or therapeutic improvement without undue adverse side effects. A therapeutic improvement includes but is not limited to: raising of gastric pH, reduced gastrointestinal bleeding, or improvement or elimination of symptoms. According to a preferred embodiment, the typical daily dose of the PPI varies and will depend on various factors such as the individual requirements of the patients and the disease to be treated. In general, the daily dose of PPI will be in the range of 1-400 mg. A preferred standard approximate amount of a PPI present in the composition is typically about 20-80 mg of omeprazole, about 30 mg lansoprazole, about 40-80 mg pantoprazole, about 20 mg rabeprazole, and the pharmacologically equivalent doses of the following PPIs: habeprazole, pariprazole, dontoprazole, ransoprazole, perprazole (s-omeprazole magnesium), tenatoprazole and leminoprazole.

The kit of the present invention may further comprise one or more parietal cell activators or gastric acid stimulants in order to activate the parietal cells and synchronize between the activation of parietal cells and the absorption of PPI in blood, preferably in a meal-independent manner. The synchronization between the activation of the parietal cells and absorption of PPI in blood maximizes the inhibition of the pumps by the PPI.

The term "gastric acid stimulant" refers to any agent that is capable of stimulating gastric acid secretion via direct or indirect effect on parietal cells. The term "parietal cell activator" refers to any agent that produces an increase in proton pump activity in parietal cells. Any parietal cell activators or gastric acid stimulants or combinations thereof may be used in the kit of the present invention.

Preferred parietal cell activators to be used in the present invention are any gastrin analogs that comprise the C-terminal tetrapeptide of gastrin Trp-Met-Asp-PheNH₂ (SEQ

ID NO:1). Such analogues include, but are not limited to the 34-, 17-, and 14-amino acid species of gastrin, and other truncation variants. Also included are variants of gastrin and/or truncated gastrins where native amino acids are replaced with conservative substitutions. A preferred parietal cell activator is Pentagastrin in an oral dose ranging between 10mg to 100 mg, more preferably between 20mg to 40mg. Other preferred parietal cell activators are one or more acid inducers, preferably a dicarboxylic or tricarboxylic acid molecule. Preferred inducers include small dicarboxylic and tricarboxylic acids such as succinic acid, maleic acid, citric acid and fumaric acid, or the salts thereof. In this embodiment, the dicarboxylic or tricarboxylic acids are in a pharmacological effective amount sufficient to activate parietal cells. In a preferred embodiment, the dicarboxylic or tricarboxylic acids are in an amount ranging from about 50 mg to about 500 mg, more preferable from about 50 mg to about 300 mg. Other parietal cell activators may include chocolate, caffeine, buffering agents such as sodium bicarbonate, calcium (*e.g.*, calcium carbonate, calcium gluconate, calcium hydroxide, calcium acetate and calcium glycerophosphate), peppermint oil, spearmint oil, and amino acids. Such parietal cell activators are administered in an amount sufficient to produce the desired stimulatory effect without causing undesired side effects to the subject.

In a preferred embodiment, the kit comprises a combination of Pentagastrin in an oral dose ranging between 10 mg to 100 mg, more preferably between 20 mg to 40 mg, and succinic acid in an amount ranging from about 10 mg to about 500 mg.

The kit of the present invention may be used for preventing or treating pathologies in a mammal in which inhibition of gastric acid secretion is required. The kit of the present invention is effective both in treating the pathologies and in minimizing the risk of development of such pathologies before onset. Such pathologies include for example: reflux esophagitis, gastritis, duodenitis, gastric ulcer and duodenal ulcer. Furthermore, the compositions of the present invention may be used for treatment or prevention of other gastrointestinal disorders where gastric acid inhibitory effect is desirable, *e.g.* in patients on nonsteroidal anti-inflammatory drugs (NSAID) therapy having gastric ulcers (including low dose aspirin), in patients with Non Ulcer Dyspepsia, in patients with symptomatic gastro-esophageal reflux disease (GERD), and in patients with gastrinomas. The kit may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, in conditions of pre-and postoperatively to prevent aspiration of gastric acid and to prevent and treat stress ulceration. Further, it may be used in the treatment of *Helicobacter* infections and

diseases related to these. Other conditions well suited for treatment include, but are not limited to Zollinger-Ellison syndrome (ZES), Werner's syndrome, and systemic mastocytosis.

The kit of the present invention may be formulated in either solid or liquid form or a mixture thereof. It is noted that solid formulations are preferred in view of the improved stability of solid formulations as compared to liquid formulations. Such solid forms are for example tablets, suspension tablets, effervescent tablets, powder, pellets, granules or capsules. The pH regulating agents are preferably formulated as a suspension tablet, an effervescent tablet, a chewable tablet or powder for suspension. However, tablets or capsules are also possible as a dosage form for the pH regulating agents.

The active ingredients of the present invention may be incorporated within inert pharmaceutically acceptable beads. In this case, the drug(s) may be mixed with further ingredients prior to being coated onto the beads. Ingredients include, but are not limited to, binders, surfactants, suspending agents, fillers, disintegrating agents, alkaline additives or other pharmaceutically acceptable ingredients, alone or in mixtures. Binders include, for example, celluloses such as hydroxypropyl methylcellulose, hydroxypropyl cellulose and carboxymethyl-cellulose sodium, polyvinyl pyrrolidone, sugars, starches and other pharmaceutically acceptable substances with cohesive properties. Suitable surfactants include pharmaceutically acceptable non-ionic or ionic surfactants. An example of a suitable surfactant is sodium lauryl sulfate.

The particles may be formed into a packed mass for ingestion by conventional techniques. For instance, the particles may be encapsulated as a "hard-filled capsule" using known encapsulating procedures and materials. The encapsulating material should be highly soluble in gastric fluid so that the particles are rapidly dispersed in the stomach after the capsule is ingested.

In another embodiment, the active ingredients of the present invention may be packaged in compressed tablets. The term "compressed tablet" generally refers to a plain, uncoated tablet for oral ingestion, prepared by a single compression or by pre-compaction tapping followed by a final compression. Such solid forms can be manufactured as is well known in the art. Tablet forms can include, for example, one or more of lactose, mannitol, corn starch, potato starch, microcrystalline cellulose, acacia, gelatin, colloidal silicon dioxide, croscarmellose sodium, talc, magnesium stearate, stearic acid, and other excipients, colorants, diluents, buffering agents, moistening agents, preservatives, flavoring agents, and pharmaceutically compatible carriers. The manufacturing processes

may employ one, or a combination of, four established methods: (1) dry mixing; (2) direct compression; (3) milling; and (4) non-aqueous granulation. Lachman et al., *The Theory and Practice of Industrial Pharmacy* (1986). Such tablets may also comprise film coatings, which preferably dissolve upon oral ingestion or upon contact with diluent.

In another alternative, the kit of the present invention is formulated in compressed forms, such as suspension tablets and effervescent tablets, such that upon reaction with water or other diluents, the aqueous form of the kit is produced for oral administration. These forms are particularly useful for medicating children and the elderly and others in a way that is much more acceptable than swallowing or chewing a tablet. The present pharmaceutical tablets or other solid dosage forms preferably disintegrate the alkaline agent with minimal shaking or agitation.

The term "suspension tablets" as used herein refers to compressed tablets which rapidly disintegrate after they are placed in water, and are readily dispersible to form a suspension containing a precise dosage of the PPI and the pH regulating agent. To achieve rapid disintegration of the tablet, a disintegrant such as Croscarmellose sodium may be added to the formulation. The disintegrant may be blended in compressed tablet formulations either alone or in combination with microcrystalline cellulose, which is well known for its ability to improve compressibility of difficult to compress tablet materials. Microcrystalline cellulose, alone or co-processed with other ingredients, is also a common additive for compressed tablets and is well known for its ability to improve compressibility of difficult to compress tablet materials. It is commercially available under the Avicel trademark.

The suspension tablet composition may, in addition to the ingredients described above, contain other ingredients often used in pharmaceutical tablets, including flavoring agents, sweetening agents, flow aids, lubricants or other common tablet adjuvants, as will be apparent to those skilled in the art. Other disintegrants, such as crospovidone and sodium starch glycolate may be employed, although croscarmellose sodium is preferred.

In addition to the above ingredients, the oral dosage forms described above may also contain suitable quantities of other materials, *e.g.* diluents, suspending agents, lubricants, binders, granulating aids, colorants, flavorants and glidants that are conventional in the pharmaceutical art. The quantities of these additional materials will be sufficient to provide the desired effect to the desired formulation. Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate oral

dosage forms are described in the Handbook of Pharmaceutical Excipients, American Pharmaceutical Association (1986), incorporated by reference herein.

The following examples are presented in order to more fully illustrate certain embodiments of the invention. They should in no way, however, be construed as limiting the broad scope of the invention. One skilled in the art can readily devise many variations and modifications of the principles disclosed herein without departing from the scope of the invention.

EXAMPLES

Example 1: The effect of increasing amount of sodium bicarbonate on the pH of stimulated gastric fluid

The effect of increasing amount of sodium bicarbonate on the pH of stimulated gastric fluid (SGF) was determined *in vitro* by adding escalated amounts of sodium bicarbonate to artificial gastric fluid in different pre-determined pH. Stimulated gastric fluid was prepared in accordance with U.S. Pharmacopoeia (USP) 2000 Ed., P. 235. For preparing 200 ml of gastric fluid, 0.4 g of NaCl and 0.64 g of Pepsin were dissolved in 16 ml 1M HCl and 184 ml of water (final concentration of HCl is 80mM). Three solutions of 200ml Gastric fluid (containing Pepsin) were prepared at pH -3, pH-4 and pH-5 by adding different amounts of HCL. The Gastric Fluid was titrated with increasing amounts of NaHCO₃. As shown in Figure 1, when the initial pH of the SGF is 4.0, less than 100mg of sodium bicarbonate were needed to raise the pH of modified gastric fluid (initial pH 3, 4 or 5 mimicking chronic PPI treatment conditions) to a pH around 6.

Table 1 below summarizes the results obtained under conditions that simulate chronic PPI administration and continuance acid secretion under PPI treatment (initial gastric pH of 4 and acid secretion rate of approximately 3mmol HCl/hour). As revealed from this table, 336mg of sodium bicarbonate were sufficient to maintain the pH at about 5.7 for at least one hour with simulation of 3mmol HCL secretion per hour. This implies that this amount of sodium bicarbonate may preserve the pH in the stomach above 5.7 for at least one hour.

Table 1: Titration of stimulated gastric fluid solutions starting from pH 4, containing different amounts of NaHCO₃ with HCl

NaHCO ₃ , mg	252	336	420	600	714
Initial pH	4.02	4.02	3.95	4.01	4.05
mM HCl/hour	pH				
0	8.9	8.92	8.92	8.9	8.9
3	4.55	5.77	6.10	6.44	6.55
6	1.56	1.73	2.06	5.6	5.88
9				1.84	2.39

Example 2: Compositions with adjustable amount of pH regulating agent

This example describes a kit for oral delivery containing a start dose (first six days of treatment) and a continuance dose. Both doses comprise omeprazole as a PPI, sodium bicarbonate as a pH regulating agent and Pentagastrin as a parietal cell activator.

Initial dose for the first six days:

Capsule I/effervescent tablet: 1300 mg NaHCO₃

Capsule II: 40mg Pentagastrin

80mg omeprazole

300mg NaHCO₃

Continuance dose for consequent use:

Single capsule: 40mg Pentagastrin

80mg omeprazole

300mg NaHCO₃

Example 3: Compositions with adjustable amount of pH regulating agent

This example describes a kit for oral delivery containing a start dose (first six days of treatment) and a continuance dose. Both doses comprise omeprazole as a PPI, sodium bicarbonate as a pH regulating agent and succinic acid as a gastric acid stimulant.

Initial dose for the first six days:

Capsule I/effervescent tablet: 1300 mg NaHCO_3

Capsule II: 300mg succinic acid

80mg omeprazole

300mg NaHCO_3

Continuance dose for consequent use:

Single capsule: 300mg succinic acid

80mg omeprazole

300mg NaHCO_3

It will be appreciated by a person skilled in the art that the present invention is not limited by what has been particularly shown and described hereinabove. Rather, the scope of the invention is defined by the claims that follow.

THE CLAIMS

What is claimed is:

1. A pharmaceutical kit for oral administration of immediate-release proton pump inhibitor (PPI) comprising:
 - (a) an initial dose for the early stage of PPI treatment comprising a pharmaceutically effective amount of the PPI combined with one or more pH regulating agents, wherein the pH regulating agents are in an amount sufficient to raise the pH in the stomach to a pH of at least 4.5, and
 - (b) a continuance dose for the subsequent stage of PPI treatment comprising an effective amount of PPI combined with one or more pH regulating agents in an amount less than in the initial dose, but sufficient to raise the pH in the stomach to a pH of at least 4.5.
2. The kit of claim 1, wherein the pH regulating agent in the initial dose is sufficient to raise the pH in the stomach by at least 2.5 to 5.5 pH units and the pH regulating agent in the continuance dose is in an amount sufficient to raise the pH in the stomach by at least 1 to 3 pH units.
3. The kit of claim 1, wherein the pH regulating agent in the initial dose is sufficient to raise the pH in the stomach by at least 4 to 5 pH units and the pH regulating agent in the continuance dose is in an amount sufficient to raise the pH in the stomach by at least 1.5 to 2.5 pH unit.
4. The kit of claim 1, wherein the pH regulating agent in the initial dose and the continuance dose is sufficient to raise the pH of the stomach to a pH of at least 5.5.
5. The kit of claim 4, wherein the pH regulating agent in the initial dose and the continuance dose is sufficient to raise the pH of the stomach to a pH of at least 6.
6. The kit of claim 1, wherein the early stage of PPI treatment is sufficient for up to at least 5 days after the initiation of the PPI treatment.
7. The kit of claim 1 further comprising one or more of parietal cell activators or gastric acid stimulants in both the initial dose and the continuance dose.
8. The kit of claim 7, wherein the parietal cell activator or gastric acid stimulants are selected from the group consisting of: a peptide comprising the amino acid sequence of SEQ ID NO. 1, a dicarboxylic acid molecule, tricarboxylic acid molecule, or a combination thereof.
9. The kit of claim 8, wherein the parietal cell activator is pentagastrin.

10. The kit of claim 1, wherein the one or more pH regulating agents are selected from the group consisting of: sodium bicarbonate, potassium bicarbonate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium lactate, magnesium glucomate, aluminum hydroxide, sodium carbonate, potassium carbonate, phosphate carbonate, citrate carbonate, di-sodium carbonate, disodium hydrogen phosphate, aluminum glycinate, calcium hydroxide, calcium lactate, calcium carbonate and calcium bicarbonate, or a mixture thereof.
11. The kit of claim 10, wherein the pH regulating agent is sodium bicarbonate.
12. The kit of claim 1, wherein the amount of the pH regulating agents in the initial dose is between about 1000 mg to about 2000 mg and the amount of the pH regulating agents in the continuance dose is between about 50 mg to about 500 mg.
13. The kit of claim 1, wherein the initial and continuance doses are formulated as solid oral dosage form selected from one or more units of: a double-layered tablet, a press-coat tablet, a multi-particulate capsule, an effervescent tablet, a suspension tablet, a chewable tablet and powder for suspension, or a mixture thereof.
14. The kit of claim 1, wherein the PPI is granulated into beads coated with enteric-coating polymers.
15. The kit of claim 1, wherein the PPI is a substituted benzimidazole derivative selected from the group consisting of: rabeprazole, omeprazole, isomeprazole, lansoprazole, pantoprazole, leminoprazole, tenatoprazole, single enantiomers thereof, any alkaline salts thereof, any derivatives thereof, and mixtures thereof.
16. The kit of claim 1, wherein there are at least two continuance doses, a first and second continuance dose, wherein the amount of pH regulating agent in the second continuance dose is less than the amount of pH regulating agent in the first continuance dose.
17. A method of treatment a disorder in which a reduction of gastric acid secretion is required, comprising administering to a subject in need thereof an effective amount of the pharmaceutical kit of claim 1, thereby-reducing gastric acid secretion in the subject.
18. The method of claim 18, wherein the disorder is selected from the group consisting of: reflux esophagitis, gastritis, duodenitis, gastric ulcer, duodenal ulcer, pathologies associated with nonsteroidal anti-inflammatory drugs (NSAID), non-ulcer Dyspepsia, gastro-esophageal reflux disease, gastrinomas, acute upper gastrointestinal

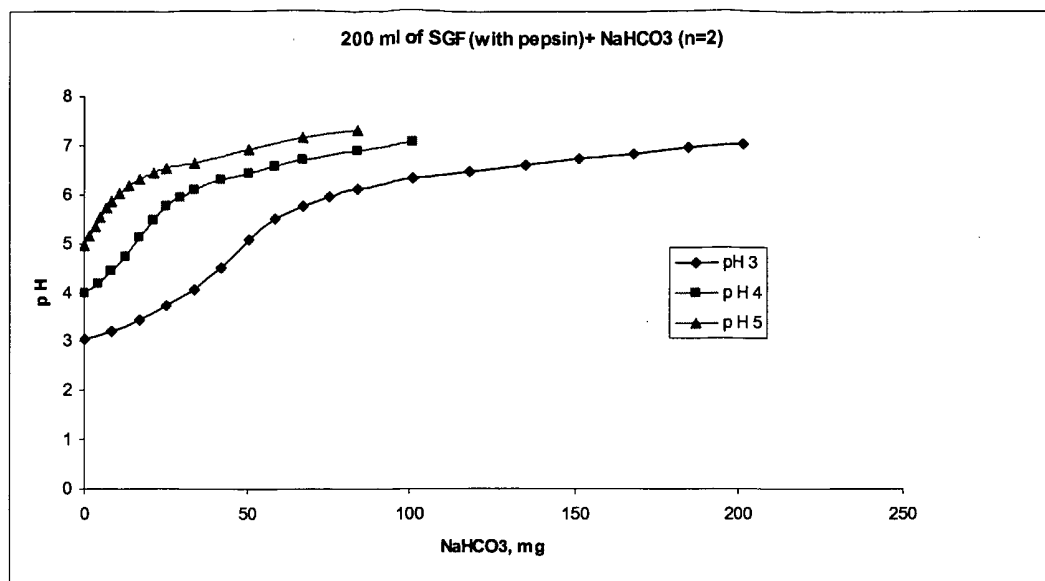
bleeding, stress ulceration, *Helicobacter pylori* infections, Zollinger-Ellison syndrome (ZES), Werner's syndrome, and systemic mastocytosis.

19. The method of claim 17, wherein the subject is a human subject.

20. A pharmaceutical kit for oral administration of enteric coated proton pump inhibitor (PPI) comprising:

(a) an initial dose for the early stage of PPI treatment comprising a pharmaceutically effective amount of enteric-coated PPI, and

(b) a continuance dose for the subsequent stage of PPI treatment comprising an effective amount of immediate-release PPI combined with one or more pH regulating agents in sufficient to raise the pH in the stomach to a pH of at least 4.5.

Figure 1:

15767.007 Sequence (2.8.06).ST25.txt
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