ORAL PHARMACEUTICAL DOSAGE FORMS COMPRISING A PROTON PUMP INHIBITOR AND A PROKINETIC AGENT

REPLACED SHEETS SG
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Field of the invention

The present invention is related to new oral pharmaceutical preparations especially for use in the prevention and treatment of disorders associated with gastro oesophageal reflux. The present preparations comprise a gastric acid suppressing agent, such as a proton pump inhibitor, in combination with one or more prokinetic agents in a new fixed unit dosage form, especially a tablet. Furthermore, the present invention refers to a method for the manufacture of such preparations and the use of such preparations in medicine, especially in the treatment of gastro oesophageal reflux diseases and other gastrointestinal disorders.

Background of the invention

Gastro oesophageal reflux disease (GORD) is among the most common disorders seen by gastroenterologists and general practicians. The wide diversity of symptoms and disease severity produced by acid reflux has led to the need for more individualized treatment strategies. Therapeutic agents effective in the treatment of GORD include gastric acid suppressing agents, such as H_2 receptor antagonists, proton pump inhibitors, other agents of interest are antacids/alginates and prokinetic agents. These agents can be distinguished by their mechanisms of action, safety profile, pharmacokinetics and indications.

Antacids and alginates are still widely used. They have a short duration of action but are seen as inexpensive and safe. They do not provide a layterm symptom resolution of GORD.

H_2 receptor antagonists are widely prescribed for GORD. Their higher cost has been compensated by the clinical results obtained both in terms of symptom relief and healing. These advantages have been related to their mode of action, which offered more potent and longer duration of effect on gastric acidity.

Proton pump inhibitors, such as omeprazole, are rapidly taking share from H_2 receptor antagonists, particularly in reflux oesophagitis. Omeprazole is known to offer significant gain over H_2 receptor antagonists in terms of symptom resolution, healing and prevention of relapse for reflux oesophagitis.

Prokinetic agents of the first generation, e.g. bethanecol, stimulates cholinergic receptors, and of the second generation, e.g. domperidone and metoclopramide, blocks effects of endogenous dopamine in the gut. The results of double-blind placebo controlled trials in GORD patients have been conflicting. The action of the third generation of prokinetic agents, such as substituted benzamides, e.g. cisapride and mosapride derives primarily, but not exclusively, from facilitating acetylcholine release from neurones of the myenteric plexus via stimulation of 5-HT4 receptors. The efficacy of orally administered benzamides, such as cisapride, in patients with GORD and reflux oesophagitis has been studied and a superior effect in alleviating gastro-oesophageal symptoms and healing low grade oesophagitis (non circumferential erosion) has been shown in most studies.

Patients with severe symptoms, severe mucosal damage or both are almost always treated with proton pump inhibitors for profound and long-term control of gastric acid secretion. Patients with mild symptoms and limited mucosal damage respond best to H_2-receptor antagonist, prokinetic agents or proton pump inhibitors.

A combination therapy of a prokinetic agent and a gastric acid lowering compound is rational and was shown more effective than mono therapy apart from full dose of proton pump inhibitors. Administration of cisapride and ranitidine was shown to further lower the exposure of the oesophagus to acid(s) (Inauen W et al. Gut 1993; 34: 1025 - 1031). Such a therapy was also shown to improve healing rates (de Boer WA et al. Aliment Pharmacol Ther 1994; 8: 147 - 157). WO 95/01803 describes a pharmaceutical composition of famitidine, cisapride and optionally simethicone in the treatment of gastrointestinal distress.

Maintenance therapy is often necessary to prevent recurrent symptoms and oesophagitis. Recently a combination therapy combining an acid-suppressing medication with a prokinetic (cisapride) was shown also very effective. Further, Vyneri et al (N. Engl. J Med 1995; 333: 1106 - 1110) found that omeprazole alone or in combination with cisapride was more effective than ranitidine alone or cisapride alone and that omeprazole combined with cisapride was more effective than ranitidine plus cisapride. Such combination therapies might be considered for patients whose predominant symptom is regurgitation; those whose symptoms occur mainly at night; those with respiratory problems such as posterior laryngitis, asthma, chronic bronchitis, or recurrent aspiration; those with cough and hoarseness related to reflux disease.

A combination therapy comprising an acid suppressing agent and a prokinetic agent is attractive, rational and effective. An acid suppressing agent plus a prokinetic agent could be an alternative to each of them separately in case of failure. However, because of the large number of therapeutical tablets/pills that must be taken each day in such a therapy, the compliance of such a treatment may be a problem. It is well known that patient compliance is a main factor in receiving good results in medical treatments. Administration of two, three or even more different tablets to the patient is not convenient or satisfactory to achieve the most optimal results. The present invention now provides new oral dosage forms comprising two or more different active substances combined in one fixed unit dosage form, preferably a tablet.

It is well known that some of the gastric acid suppressing agents, such as proton pump inhibitors are susceptible to degradation/transformation in acid reacting and neutral media. In respect of the stability properties, it is obvious that the one of the active substances being an acid susceptible proton pump inhibitor must be protected from contact with acidic gastric juice by an enteric coating layer. There are different enteric coating layered preparations of proton pump inhibitors described in the prior art, see for example US-A 4,786,505 (AB Hässle) describing a preparation comprising omeprazole.

There are problems to produce a fixed unit dosage form comprising a rather high amount of active substance. Different active substances with differing physical properties in the same preparation give further problems. Preparation of a multiple unit tableted dosage form arises specific problems when enteric coating layered pellets containing acid susceptible proton pump inhibitors as active substance are compressed into tablets. If the enteric coating layer does not withstand the compression of the pellets into a tablet the susceptible active substance will be destroyed by penetrating acidic gastric juice, i.e. the acid resistance of the enteric coating layer of the pellets will not be sufficient in the tablet after compression.

Summary of the invention

The present invention provides oral, fixed unit dosage forms, i.e. a multiple unit tableted dosage forms, multilayered tablets or a capsule filled with more than one pharmaceutically active compound. The active compounds present in the dosage form are preferably an acid susceptible proton pump inhibitor which is protected by an enteric coating layer, and one or more prokinetic agents. These new dosage forms will simplify the regimen and improve the patient compliance.

Brief description of the Figures

Fig. 1 illustrates a cross-section of a multiple unit tableted dosage form comprising an acid susceptible proton pump inhibitor in the form of enteric coating layered pellets (1) in admixture with a prokinetic agent and pharmaceutically acceptable excipients (2). The tablet is covered by a filmcoating layer, i.e. tablet coat (7).

Fig. 2 illustrates a cross-section of a tablet with two separate layers, one of which comprising enteric coating layered pellets (1) in admixture with excipients (3) and the other layer comprising the prokinetic agent in admixture with pharmaceutically acceptable excipients (2). The tablet is covered by a filmcoating layer (7).

Fig. 3 illustrates a cross-section of an enteric coating layered tablet comprising a proton pump inhibitor in admixture with pharmaceutically acceptable excipients in the tablet core (5) surrounded by an enteric coating layer (8) and thereupon a layer of the prokinetic agent(s) in admixture with pharmaceutically acceptable excipients (6). The tablet is covered by a filmcoating layer (7).

Fig. 4 illustrates a cross-section of a multiple unit tableted dosage form comprising an acid susceptible proton pump inhibitor in the form of enteric coating layered pellets (1) in admixture with excipients (3) and on the multiple unit tableted dosage form a layer comprising the prokinetic agent(s) in admixture with pharmaceutically acceptable excipients (6). The tablet is covered by a filmcoating layer (7).

Detailed description of the invention

One object of the invention is to provide an oral, multiple unit tableted dosage form comprising an acid susceptible proton pump inhibitor in the form of individually enteric coating layered units together with one or more prokinetic agents in the form of a powder or granules compressed into a tablet. The enteric coating layer(s) covering the individual units of the proton pump inhibitor has properties such that the compression of the units into a tablet does not significantly affect the acid resistance of the individually enteric coating layered units. Furthermore, the multiple unit tableted dosage form provides a good stability of the active substances during long-term storage.

The new fixed dosage form is preferably in the form of a multiple unit tableted dosage form comprising enteric coating layered units of the one of the active substance which is acid susceptible and granules of the other active substance, i.e. prepared prokinetic granules as shown in Fig. 1.

The proton pump inhibitor, in the form of enteric coating layered units, may also be mixed with pharmaceutically acceptable excipients and compressed into a tablet which is then filmcoated with an aqueous suspension containing the prokinetic substance, see Fig. 4.

Another object of the invention is to provide a tablet preparation comprising a proton pump inhibitor in admixture with tablet excipients in a tablet core and a separate layer surrounding the tablet core, which layer comprises one or more prokinetic agent(s) presscoated onto the tablet core. The tablet core is enteric coating layered before the surrounding layer of prokinetic agents is applied. Optionally a separating layer also is applied on the tablet before the enteric coating layer, see Fig. 3.

Alternatively, the prepared tablet is sectioned in separate layers, each one comprising different active substances. Preferably one layer comprises the proton pump inhibitor in the form of enteric coating layered pellets in admixture with pharmaceutically acceptable excipients and another layer(s) comprises(-e) the prokinetic agent(s) in admixture with pharmaceutically acceptable excipients, respectively, see Fig. 2.

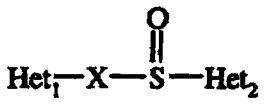
A further object of the invention is to provide a multiple unit tableted dosage form, which is divisible and easy to handle. Such a multiple unit tableted dosage form may be dispersed in an aqueous liquid and can be given to patients with swallowing disorders and in pediatrics. Such a suspension of dispersed units/pellets of appropriate size can be used for oral administration and also for feeding through a naso-gastric tube.

Furthermore, the present invention provides a capsule preparation comprising the proton pump inhibitor in the form of enteric coating layered pellets mixed with one or more prokinetic agents in the form of prepared granules or pellets. The new fixed unit dosage forms comprise as active substances one gastric acid suppressing agent, such as an acid susceptible proton pump inhibitor and one or more prokinetic agents. The different therapeutically active components used in the dosage forms are defined below.

The prokinetic part of the formulation may be formulated in the form of instant release, sustained release or extended release formulations. Alternatively, all the components of the formulation may be formulated in an effervescent formulation.

Active substances

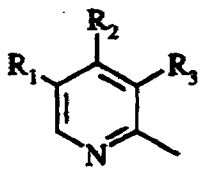
The gastric acid suppressing agent is preferably an acid susceptible proton pump inhibitor. Such proton pump inhibitors are for example compounds of the general formula I



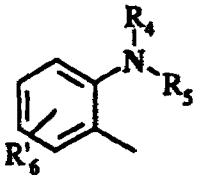
I

wherein

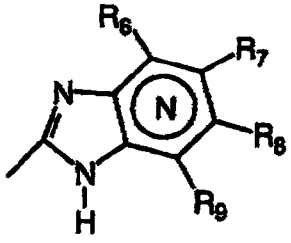
Het_1 is



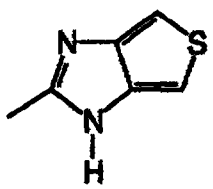
or



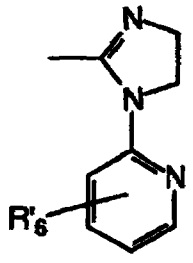
Het_2 is



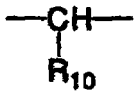
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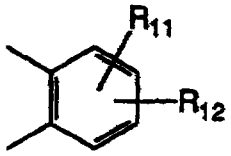
or



X =



or



wherein

N in the benzimidazole moiety means that one of the carbon atoms substituted by R_6-R_9 optionally may be exchanged for a nitrogen atom without any substituents;

R_1, R_2 and R_3 are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R_4 and R_5 are the same or different and selected from hydrogen, alkyl and aralkyl;

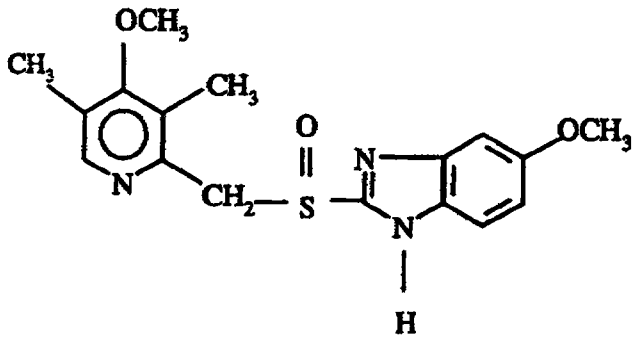
R_6' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

R_6-R_9 are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_6-R_9 form ring structures which may be further substituted;

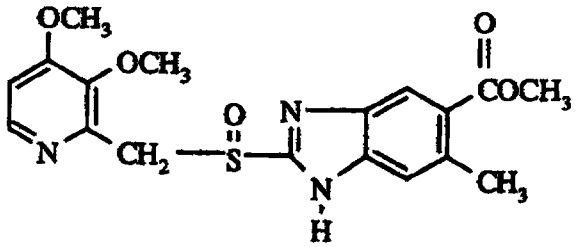
R_{10} is hydrogen or forms an alkylene chain together with R_3 and

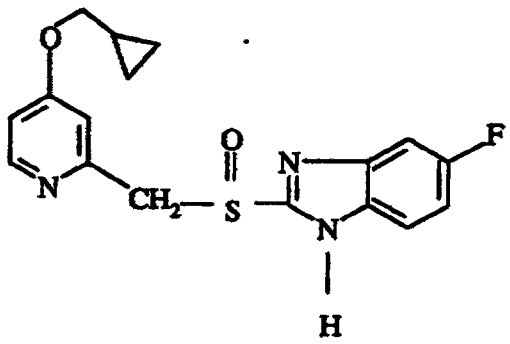
R_{11} and R_{12} are the same or different and selected from hydrogen, halogen or alkyl, alkyl groups, alkoxy groups and moities thereof, they may be branched or straight C_1 - C_9 - chains or comprise cyclic alkyl groups, such as cycloalkylalkyl.

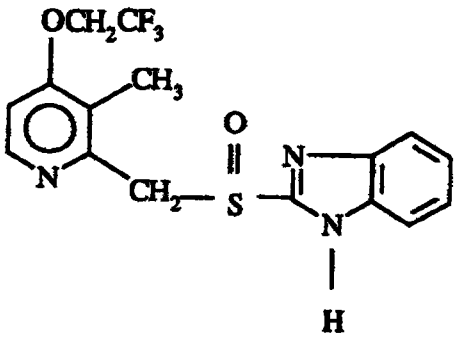
Examples of proton pump inhibitors according to formula I are



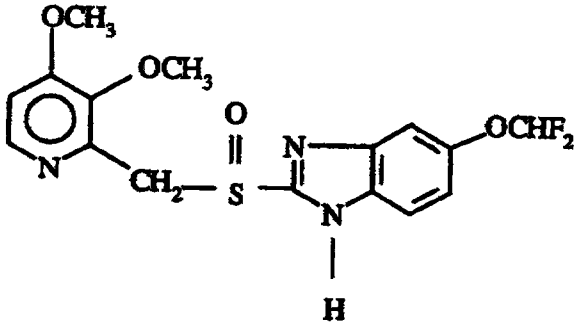
Omeprazole



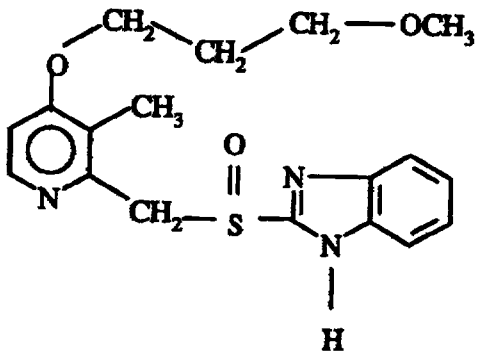




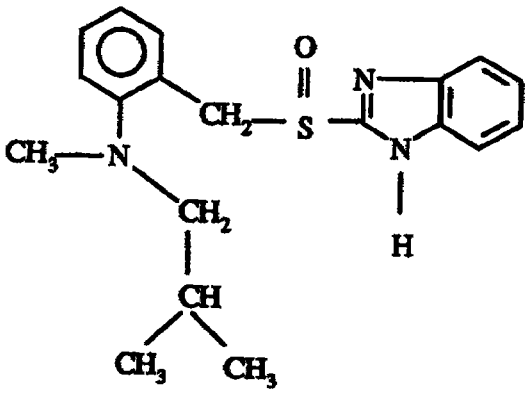
Lansoprazole



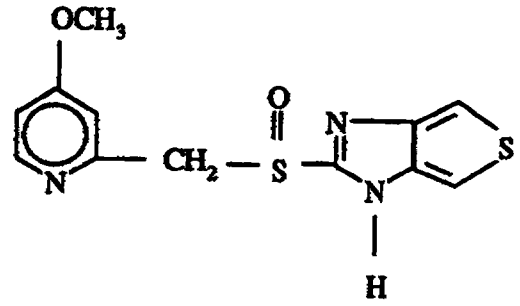
Pantoprazole

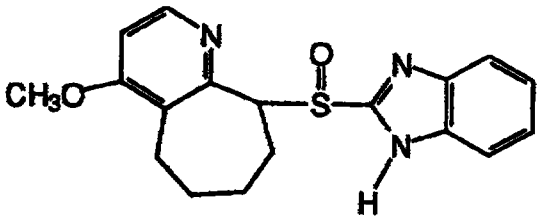


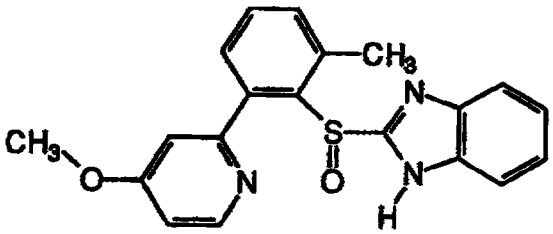
Pariprazole

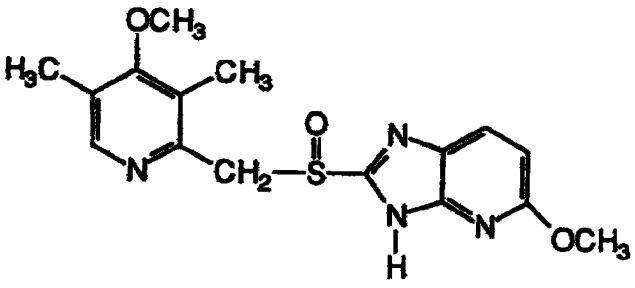


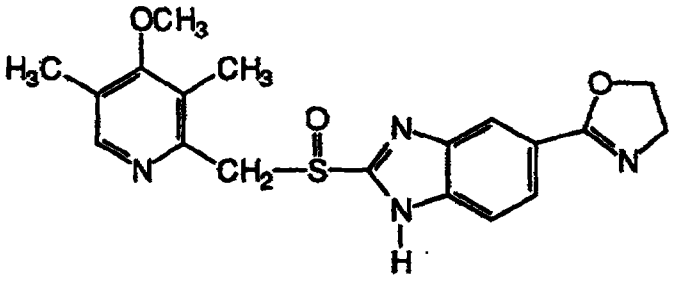
Leminoprazole











The proton pump inhibitors used in the dosage forms of the invention may be used in neutral form or in the form of an alkaline salt, such as for instance the Mg^{2+},Ca^{2+},Na^{+}, K^{+} or Li^{+}salts, preferably the Mg^{2+} salts. Further where applicable, the compounds listed above may be used in racemic form or in the form of a substantially pure enantiomer thereof, or alkaline salts of the single enantiomers.

Suitable proton pump inhibitors are for example disclosed in EP-A1-0005129, EP-A1-174 726, EP-A1-166 287, GB 2 163 747 and WO90/06925, WO91/19711, WO91/19712, and further especially suitable compounds are described in WO95/01977 and WO94/27988.

The gastric acid suppressing agent is preferably an acid susceptible proton pump inhibitor but other gastric acid suppressing agents such as the H_2 receptor antagonists: ranitidine, cimetidine or famotidine, may be used together with a prokinetic agent in the pharmaceutical compositions according to the present invention.

A wide variety of prokinetic compounds may be used in combination with a suitable proton pump inhibitor in the fixed unit dosage form according to the present invention. Such prokinetic agents include for example cisapride, mosapride, metoclopramide, and domperidone. The active prokinetic agents could be in standard forms or used as salts, hydrates, esters etc. A combination of two or more of the above described drugs may be

used. A preferable prokinetic agent for the new fixed dosage form is mosapride or cisapride. Such suitable prokinetic agents are described in EP 0 243 959 and EP 0 076 530.

The preferred multiple unit tableted dosage form comprising a proton pump inhibitor in the form of a racemat, an alkaline salt or one of its single enantiomers in combination with a prokinetic compound, is characterized in the following way. Individually enteric coating layered units (small beads, granules or pellets) containing the proton pump inhibitor and optionally alkaline reacting substances, are mixed with the prokinetic compound and conventionally tablet excipients. The prokinetic compound and tablet excipients may be dry mixed or wet-mixed into granules. The mixture of enteric coating layered units, prokinetic agent(s) and optionally excipients are compressed into the multiple unit tableted dosage forms. With the expression "individual units" is meant small beads, granules or pellets, in the following referred to as pellets of the proton pump inhibitor.

The compaction process (compression) for formulating the multiple unit tableted dosage form must not significantly affect the acid resistance of the enteric coating layered pellets. In other words the mechanical properties, such as the flexibility and hardness as well as the thickness of the enteric coating layer(s), must secure that the requirements on enteric coated articles in the United States Pharmacopeia are accomplished in that the acid resistance does not decrease more than 10% during the compression of the pellets into tablets.

The acid resistance is defined as the amount of proton pump inhibitor in the tablets or pellets after being exposed to simulated gastric fluid USP, or to 0.1 M HCl (aq) relative to that of unexposed tablets and pellets, respectively. The test is accomplished in the following way. Individual tablets or pellets are exposed to stimulated gastric fluid of a temperature of 37°C. The tablets 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).

Further specific components used in the fixed unit dosage forms of the present invention are defined below.

Core material - for enteric coating layered pellets comprising a proton pump inhibitor

The core material for the individually enteric coating layered pellets can be constituted according to different principles. Seeds layered with the proton pump inhibitor, optionally mixed with alkaline substances, can be used as the core material for the further processing.

The seeds which are to be layered with the proton pump inhibitor can be water insoluble seeds comprising different oxides, celluloses, organic polymers and other materials, alone or in mixtures or water-soluble seeds comprising different inorganic salts, sugars, non-pareils and other materials, alone or in mixtures. Further, the seeds may comprise the proton pump inhibitor in the form of crystals, agglomerates, compacts etc. The size of the seeds is not essential for the present invention but may vary between approximately 0.1 and 2 mm. The seeds layered with the proton pump inhibitor are produced either by powder or solution/suspension layering using for instance granulation or spray coating layering equipment.

Before the seeds are layered, the proton pump inhibitor may be mixed with further components. Such components can be binders, surfactants fillers, disintegrating agents, alkaline additives or other and/or pharmaceutically acceptable ingredients alone or in mixtures. The binders are for example polymers such as hydroxypropyl methylcellulose (HPMC), hydroxypropylcellulose (HPC), carboxymethylcellulose sodium, polyvinyl pyrrolidone (PVP), or sugars, starches or other pharmaceutically acceptable substances with cohesive properties. Suitable surfactants are found in the groups of pharmaceutically acceptable non-ionic or ionic surfactants such as for instance sodium lauryl sulfate.

Alternatively, the proton pump inhibitor optionally mixed with alkaline substances and further mixed with suitable constituents can be formulated into a core material. Said core

material may be produced by extrusion/spheronization, balling or compression utilizing conventional process equipment. The size of the formulated core material is approximately between 0.1 and 4 mm and preferably between 0.1 and 2 mm. The manufactured core material can further be layered with additional ingredients comprising the proton pump inhibitor and/or be used for further processing.

The proton pump inhibitor is mixed with pharmaceutical constituents to obtain preferred handling and processing properties and a suitable concentration of the substance in the final mixture. Pharmaceutical constituents such as fillers, binders, lubricants, disintegrating agents, surfactants and other pharmaceutically acceptable additives.

Further, the proton pump inhibitor may also be mixed with an alkaline, pharmaceutically acceptable substance (or substances). Such substances can be chosen among, but are not restricted to substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminium hydroxide/sodium bicarbonate coprecipitate; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $Al_2O_3.6MgO.CO_2.12H_2O$, $(Mg_6Al_2(OH)_{16}CO_3.4H_2O)$, $MgO.Al_2O_3.2SiO_2.nH_2O$ or similar compounds; organic pH-buffering substances such as trihydroxymethyl-aminomethane, basic amino acids and their salts or other similar, pharmaceutically acceptable pH-buffering substances.

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

Enteric coating layer(s)

Before applying the enteric coating layer(s) onto the core material in the form of individual pellets or tablets, the pellets or tablets may optionally be covered with one or more separating layer(s) comprising pharmaceutical excipients optionally including alkaline

compounds such as pH-buffering compounds. This/these separating layer(s), separate(s) the core material from the outer layers being enteric coating layer(s). The separating layer(s) protecting the core material of a proton pump inhibitor should be water soluble or rapidly disintegrating in water.

The separating layer(s) can be applied to the core material by coating or layering procedures in suitable equipments such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating process. As an alternative the separating layer(s) can be applied to the core material by using powder coating technique. The materials for the separating layers are pharmaceutically acceptable compounds such as, for instance, sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethyl-cellulose, hydroxypropyl methyl cellulose, carboxymethylcellulose sodium and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers anti-tacking and anti-static agents, such as for instance magnesium stearate, titanium dioxide, talc and other additives may also be included into the separating layer(s).

When the optional separating layer, is applied to the core material it may constitute a variable thickness. The maximum thickness of the separating layer(s) is normally only limited by processing conditions. The separating layer may serve as a diffusion barrier and may act as a pH-buffering zone. The pH-buffering properties of the separating layer(s) can be further strengthened by introducing into the layer(s) substances chosen from a group of compounds usually used in antacid formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds such as, for instance $Al_2O_3.6MgO.CO_2.12H_2O$, $(Mg_6Al_2(OH)_{16}CO_3.4H_2O)$, $MgO.Al_2O_3.2SiO_2.nH_2O$, aluminium hydroxide/sodium bicarbonate coprecipitate or similar compounds; or other pharmaceutically acceptable pH-buffering compounds such as, for instance the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, carbonic, citric or other suitable, weak, inorganic or organic acids; or suitable organic bases, including basic amino acids and salts thereof. Talc or other

compounds may be added to increase the thickness of the layer(s) and thereby strenghten the diffusion barrier. The optionally applied separating layer(s) is not essential for the invention. However, the separating layer(s) may improve the chemical stability of the active substance and/or the physical properties of the novel multiple unit tableted dosage form.

Alternatively, the separating layer may be formed in situ by a reaction between an enteric coating polymer layer applied on the core material an alkaline reacting compound in the core material. Thus, the separating layer formed comprises a salt formed between the enteric coating layer polymer(s) and an alkaline reacting compound which is in the position to form a salt.

One or more enteric coating layers are applied onto the core material or onto the core material covered with separating layer(s) by using a suitable coating technique. The enteric coating layer material may be dispersed or dissolved in either water or in suitable organic solvents.As enteric coating layer polymers one or more, separately or in combination, of the following can be used, e.g. solutions or dispersions of methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylethylcellulose, shellac or other suitable enteric coating polymer(s).

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

The amount of plasticizer is optimized for each enteric coating layer formula, in relation to selected enteric coating layer polymer(s), selected plasticizer(s) and the applied amount of said polymer(s), in such a way that the mechanical properties, i.e. flexibility and hardness of the enteric coating layer(s), for instance exemplified as Vickers hardness, are adjusted so

that the acid resistance of the pellets covered with enteric coating layer(s) does not decrease significantly during compression of pellets into tablets. The amount of plasticizer is usually above 10 % by weight of the enteric coating layer polymer(s), preferably 15 - 50 % and more preferably 20 - 50 %. Additives such as dispersants, colorants, pigments polymers e.g. poly (ethylacrylat, methylmethacrylat), anti-tacking and anti-foaming agents may also be included into the enteric coating layer(s). Other compounds may be added to increase film thickness and to decrease diffusion of acidic gastric juices into the acid susceptible material.

To protect the acid susceptible substance, the proton pump inhibitor, and to obtain an acceptable acid resistance of the dosage form according to the invention, the enteric coating layer(s) constitutes a thickness of approximately at least 10 µm, preferably more than 20 µm. The maximum thickness of the applied enteric coating is normally limited by processing conditions and the desired dissolution profile.

Alternatively the enteric coating layer described above may be used for enteric coating of conventional tablets comprising an acid susceptible proton pump inhibitor. Said enteric coating layered tablet is thereafter presscoated with a granulation comprising the prokinetic compound.

Over-coating layer

Pellets covered with enteric coating layer(s) may further be covered with one or more over-coating layer(s). The over-coating layer(s) should be water soluble or rapidly disintegrating in water. The over-coating layer(s) can be applied to the enteric coating layered pellets by coating or layering procedures in suitable equipments such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating or layering process. The materials for over-coating layers are chosen among pharmaceutically acceptable compounds such as, for instance sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methyl cellulose, carboxymethylcellulose

sodium and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers, anti-tacking and anti-static agents, such for instance magnesium stearate, titaniumdioxide, talc and other additives may also be included into the over-coating layer(s). Said over-coating layer may further prevent potential agglomeration of enteric coating layered pellets, further protect the enteric coating layer towards cracking during the compaction process and enhance the tableting process. The maximum thickness of the applied over-coating layer(s) is normally limited by processing conditions and the desired dissolution profile.

The above described over-coating layer may also be used as a tablet filmcoat to obtain tablets of good appearance.

Prokinetic preparation

The active substance(s) in form of one or more prokinetic compound(s) is dry mixed with inactive excipients and the mixture is wet massed with a granulation liquid. The wet mass is dried preferably to a loss on drying of less than 3% by weight. Thereafter the dry mass is milled to a suitable size for the granules, such as smaller than 4 mm, and preferably smaller than 1 mm. Suitable inactive excipients for the prokinetic mixture are for instance lactose, corn starch low substituted hydroxypropyl cellulose, microcrystalline cellulose, sodium starch glycolate and crosslinked polyvinyl pyrrolidone. The dry mixture comprising prokinetic compound is wet-mixed with a suitable granulation liquid comprising for instance hydroxy propyl cellulose or polyvinyl pyrrolidone dissolved in purified water or an alcohol or a mixture thereof. Alternatively, the prokinetic agent(s) are dry mixed with pharmaceutically acceptable excipients according to above.

As a further alternative, the prokinetic agent(s) can be applied in a separate layer onto a multiple unit tableted dosage form or surrounding the tablet comprising the proton pump inhibitor. The prokinetic agent(s) is dispersed or dissolved in an aqueous solution optionally comprising binders for suspension layering onto the tablet.

Multiple unit tablets

The enteric coating layered pellets comprising a proton pump inhibitor are mixed with the granules comprising prokinetic compound and tablet excipients such as fillers, binders, disintegrants, lubricants and other pharmaceutically acceptable additives. The mixture is compressed into a multiple unit tableted dosage form. The compressed tablet is optionally covered with a filmforming agent(s) to obtain a smooth surface of the tablet and further enhance the stability of the tablet during packaging and transport. Such a coating layer may further comprise additives such as anti-tacking agents, colorants and pigments or other additives to obtain a tablet of good appearance.

Alternatively the enteric coated pellets may be dry mixed with the prokinetic compound and pharmaceutically acceptable tablet excipients according to above, and compressed into tablets (direct compression).

Suitable lubricants for the tableting process are for instance sodium stearyl fumarate, magnesium stearate and talc.

Further, the different active substances may be formulated into different layers, wherein the layer comprising the proton pump inhibitor is in the form of a multiple unit tableted dosage form layered with prepared prokinetic granules. The two layers may be separated by an anti-tacking layer.

As a further alternative the proton pump inhibitor is dry mixed with inactive excipients and compressed into a conventional tablet which is coating layered with an enteric coating and optionally a separating layer is applied before the enteric coating. Thereafter the enteric coated tablet is presscoated with a prokinetic preparation. The tablet core may also be formulated as a multiple unit tableted dosage form comprising the proton pump inhibitor, the tablet is spray coating layered by a suspension comprising the prokinetic agent(s).

The fraction of enteric coating layered pellets constitutes less than 75 % by weight of the total tablet weight and preferably less than 60 %. By increasing the amount of the granules comprising the prokinetic agent the fraction of enteric coating layered pellets of the proton pump inhibitor may be reduced in the multiple unit tableted dosage form. By choosing small enteric coating layered pellets in the formulation according to the present invention, the number of pellets in each tablet can be held high which in turn makes the tablet divisible with retained dosing accuracy.

Thus, the preferred multiple unit tablet formulation consists of enteric coating layered pellets containing one active substance in the form of a proton pump inhibitor, optionally admixed with alkaline reacting compound(s), compressed into tablets together with the prepared prokinetic mixture and optionally tablet excipients. The addition of an alkaline reacting material to the proton pump inhibitor is not necessary, in any sense but such a substance may further enhance the stability of the proton pump inhibitor or some of the alkaline reacting compounds may react in situ with the enteric coating material to form a separating layer. The enteric coating layer(s) is making the pellets of the dosage form insoluble in acidic media, but disintegrating/dissolving in near neutral to alkaline media such as, for instance the liquids present in the proximal part of the small intestine, where dissolution of the proton pump inhibitor is desired. The prokinetic agent(s) may be released in the stomach. The enteric coating layered pellets may further be covered with an overcoating layer before being formulated into the tablet and they may also contain one or more separating layer(s) optionally containing alkaline substance(s).

Process

The process for the manufacture of the dosage form represents a further aspect of the invention. After formulation of the pellets by spray coating or layering of the proton pump inhibitor onto seeds, or by extrusion/spheronization or granulation, e.g. rotor granulation of homogeneous pellets, the pellets are first optionally covered with the separating layer(s) and

then with the enteric coating layer(s) or a separating layer is spontaneously developed in situ between the alkaline core material and the enteric coating layer material. The coating is carried out as described above and in the accompanying examples. The preparation of the prokinetic mixture is also described above and in the examples. The pharmaceutical processes can preferably be completely water-based.

The enteric coating layered pellets, with or without an over-coat, are mixed with the prepared prokinetic mixture, optionally tablet excipients and other pharmaceutically acceptable additives and compressed into tablets. Alternatively, the enteric coating layered pellets may be intimately mixed with tablet excipients and precompressed and further layered with the prepared prokinetic mixture and finally compressed into a tablet. As a further alternative the proton pump inhibitor in form of the active substance may be mixed with tablet excipients and compressed into a tablet which is optionally layered with a separating layer and thereafter enteric coating layered. Said tablet is then presscoated with the prepared prokinetic mixture. Alternatively, a multiple unit tableted dosage form of the proton pump inhibitor is manufactured as describes above. The multiple unit dosage form is spray coating layered by an aqueous suspension comprising the prokinetic agent(s). The suspension may optionally comprise binders; such as hydroxypropyl methylcellulose, and an alcohol to solve the binder. The proton pump inhibitor in the form of enteric coating layered pellets may also be filled into a capsule together with the prokinetic substance in the form of a granulation optionally mixed with pharmaceutical excipients.

Use of the preparation

The dosage forms according to the invention are especially advantageous in the treatment of gastro oesophageal reflux disease and other gastrointestinal disorder. They are administered one to several times a day, preferably once or twice daily. The typical daily dose of the active substances varies and will depend on various factors such as the individual requirements of the patients, the mode of administration and disease. In general each dosage form will comprise 0.1-200 mg of the proton pump inhibitor and 0.1-100 mg of the

prokinetic compound. Preferably, each dosage form will comprise 10-80 mg of the proton pump inhibitor and 3-80 mg of the prokinetic compound, and more preferably 10-40 mg of proton pump inhibitor and 15 - 40 mg of the prokinetic compound, respectively.

The multiple unit tablet preparation is also suitable for dispersion in an aqueous liquid with slightly acidic pH-value before being orally administered or fed through a naso-gastric tube.

The invention is illustrated more in detail in the following examples.

Examples

Example 1:

Multiple unit dosage form comprising magnesium omeprazole and mosapride (batch size 500 tablets).

Core material	
Magnesium omeprazole	5 kg
Sugar sphere seeds	10 kg
Hydroxypropyl methylcellulose	0.75 kg
Water purified	20.7 kg
Separating layer	
Core material (acc. to above)	10.2 kg
Hydroxypropyl cellulose	1.02 kg
Talc	1.75 kg
Magnesium stearate	0.146kg
Water purified	21.4 kg

Enteric coating layer		
Pellets covered with separating layer (acc. to above)	11.9	kg
Methacrylic acid copolymer (30 % suspension)	19.8	kg
Triethyl citrate	1.79	kg
Mono- and diglycerides (NF)	0.297	kg
Polysorbate 80	0.03	kg
Water purified	11.64	kg
Over-coating layer		
Enteric coating layered pellets (acc. to above)	20	kg
Hydroxypropyl methylcellulose	0.238	kg
Magnesium stearate	0.007	kg
Water purified	6.56	kg
Tablets		
Prepared pellets comprising omeprazole (acc. to above)	41.2	g
Mosapride citrate dihydrate	23.4	g
Microcrystalline cellulose	138.1	g
Polyvinyl pyrrolidone crosslinked	2.9	g
Sodium stearyl fumarate	0.29	g
Tablet coating solution (for 10 kg tablets)		
Hydroxypropyl methylcellulose	250	g
Polyethylene glycol 6000	62.5	g
Titanium dioxide	62.5	g
Water purified	2125	g
Hydrogen pyroxide	0.75	g

Suspension layering was performed in a fluid bed apparatus. Magnesium omeprazole was sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder. The size of sugar sphere seeds were in the range of 0.25 to 0.35 mm.

The prepared core material was covered with a separating layer in a fluid bed apparatus with a hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides, triethyl citrate and polysorbate was sprayed onto the pellets covered with a separating layer in a fluid bed apparatus. In a fluid bed apparatus enteric coating layered pellets were coated with a hydroxypropyl methylcellulose solution containing magnesium stearate. The over-coating layered pellets were classified by sieving.

The enteric coating layered pellets with an over-coating layer, mosapride citrate dihydrate, microcrystalline cellulose, polyvinyl pyrrolidone crosslinked and sodium stearyl fumarate were dry mixed and compressed into tablets using an excenter tableting machine equipped with 12 mm punches. The amount of omeprazole in each tablet was approx. 10 mg and the amount of mosapride was approx. 30 mg. The tablet hardness was measured to 70-80 N.

The obtained tablets are covered with a conventional tablet filmcoating layer.

Example 2:

Multiple unit dosage form comprising magnesium omeprazole and mosapride (batch size 500 tablets).

Mosapride granulation

Mosapride citrate dihydrate	46.8 g
Lactose monohydrate	350 g
Corn starch	184 g
Hydroxy propyl cellulose LF	25 g

Water purified	225	g
Hydroxypropyl cellulose (L-HPC)	152	g
Magnesium stearate	7.4	g

Tablets

Enteric coating layered pellets with an over-coating layer (manufacturing and composition as in example 1)	41.2	g
Mosapride granulation	190	g

Tablet coating solution (for 10 kg tablets)

Hydroxypropyl methyl cellulose	250	g
Polyethylene glycol 6000	62.5	g
Titaniumdioxid	62.5	g
Water purified	2125	g
Hydrogen peroxide	0.75	g

Hydroxypropyl cellulose was dissolved in purified water to form the granulation liquid. Mosapride citrate dihydrate, lactose monohydrate and corn starch were dry mixed. The granulation liquid was added to the powder mixture and the mass was wet-mixed. The wet mass was dried in a steam-oven and milled through sive 1 mm in an oscillating mill equipment. The prepared granulation was mixed with low substituted hydroxypropyl cellulose and magnesium stearate.

The enteric coating layered pellets with an over-coat and prepared granules were mixed and compressed into tablets using an excenter tableting machine equipped with 11 mm punches. The amount of omeprazole in each tablet was approx. 10 mg and the amount of mosapride was approx. 15 mg. Tablet hardness was measured to 30 - 40 N.

The obtained tablets are covered with a conventional tablet filmcoating layer.

Example 3:

Multiple unit dosage form comprising magnesium omeprazole and mosapride (batch size 500 tablets).

Core material	
Magnesium omeprazole	10 kg
Sugar sphere seeds	10 kg
Hydroxypropyl methylcellulose	1.5 kg
Water purified	29.9 kg
Separating layer	
Core material (acc. to above)	20 kg
Hydroxypropyl cellulose	2 kg
Talc	3.43 kg
Magnesium stearate	0.287kg
Water purified	41 kg
Enteric coating layer	
Pellets covered with separating layer (acc. to above)	24.5 kg
Methacrylic acid copolymer (30 % suspension)	32.7 kg
Triethyl citrate	2.94 kg
Mono- and diglycerides (NF)	0.49 kg
Polysorbate 80	0.049kg
Water purified	19.19 kg
Over-coating layer	
Enteric coating layered pellets (acc. to above)	37.8 kg
Hydroxypropyl methylcellulose	0.49 kg
Magnesium stearate	0.0245kg

Water purified	11.6	kg

Tablets

Prepared pellets comprising omeprazole (acc. to above)	47.45	g
Mosapride citrate dihydrate	23.4	g
Microcrystalline cellulose	163	g
Polyvinyl pyrrolidone crosslinked	3.3	g
Sodium stearyl fumarate	0.3	g

Tablet coating solution (for 10 kg tablets)

Hydroxypropyl methyl cellulose	250	g
Polyethylene glycol 6000	62.5	g
Titanium dioxid	62.5	g
Water purified	2125	g
Hydrogen peroxide	0.75	g

The enteric coating layered pellets with an over-coating layer prepared as described in Example 1, mosapride citrate dihydrate, microcrystalline cellulose, polyvinyl pyrrolidone crosslinked and sodium stearyl fumarate were dry mixed and compressed into tablets using an excenter tableting machine equipped with 12 mm punches.
The amount of omeprazole in each tablet was approx. 20 mg and the amount of mosapride was approx. 30 mg. The tablet hardness was measured to 70 N.

The tablets are covered with a conventional tablet filmcoating layer.

Example 4:

Multiple unit dosage form comprising S-omeprazole magnesium salt and mosapride (batch size 300 tablets).

Core material		
S-omeprazole magnesium salt	120	g
Sugar sphere seeds	150	g
Hydroxypropyl methylcellulose	18	g
Polysorbate 80	2.4	g
Water purified	562	g

Separating layer		
Core material (acc. to above)	200	g
Hydroxypropyl cellulose	30	g
Talc	51.4	g
Magnesium stearate	4.3	g
Water purified	600	g

Enteric coating layer		
Pellets covered with separating layer (acc. to above)	250	g
Methacrylic acid copolymer (30% suspension)	333.7	g
Triethyl citrate	30	g
Mono- and diglycerides (NF)	5	g
Polysorbate 80	0.5	g
Water purified	196	g

Tablets		
Prepared pellets comprising (s)-omeprazole Mg-salt (acc. to above)	38.2	g
Mosapride citrate dihydrate	14	g
Microcrystalline cellulose	98.3	g
Polyvinyl pyrrolidone crosslinked	2.1	g
Sodium stearyl fumarate	0.2	g

Tablet coating solution (for 10 kg tablets)		
Hydroxypropyl methyl cellulose	250	g
Polyethylene glycol 6000	62.5	g
Titaniumdioxid	62.5	g
Water purified	2125	g
Hydrogen peroxide	0.75	g

Suspension layering was performed in a fluid bed apparatus. S-Omeprazole magnesium salt was sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder and polysorbate 80. The size of sugar sphere seedes were in the range of 0.25 to 0.35 mm.

The prepared core material was covered with a separating layer in a fluid bed apparatus with hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer consisting of methacrylic acid copolymer, mono-and diglycerides, triethyl citrate and polysorbate was sprayed onto the pellets covered with a separating layer in a fluid bed apparatus. The enteric coating layered pellets were classified by sieving.

The enteric coating layered pellets, mosapride citrate dihydrate, microcrystalline cellulose, polyvinyl pyrrolidone crosslinked and sodium stearyl fumarate were mixed and compressed into tablets using an excenter tableting machine equipped with 12mm punches.
The amount of S-omeprazole in each tablet was approx. 20 mg and the amount of mosapride was approx. 30 mg. The tablet hardness was measured to 65 N.

The tablets are covered with a conventional tablet filmcoating layer.

"Acid resistance" i.e. % left after exposure to 0.1 N HCl for 2 hrs	
	Tablets
Ex 1	97%
Ex 2	90%
Ex 3	102%
Ex 4	104%

Example 5:

Multiple unit dosage form comprising lanzoprazole and mosapride (batch size 500 tablets).

Core material	
Lanzoprazole	400 g
Sugar sphere seeds	400 g
Hydroxypropyl methylcellulose	80 g
Sodium laurylsulfate	3 g
Water purified	1500 g
Separating layer	
Core material (acc. to above)	400 g
Hydroxypropyl cellulose	40 g
Talc	69 g
Magnesium stearate	6 g
Water purified	800 g

Enteric coating layer

Pellets covered with a separating layer (acc. to above)	400 g
Methacrylic acid copolymer (30 % suspension)	667 g
Triethyl citrate	60 g
Mono- and diglycerides (NF)	10 g
Polysorbate 80	1 g
Water purified	420 g

Tablets

Prepared pellets comprising lanzoprazole (acc. to above)	47 g
Mosapride citrate dihydrate	46.8 g
Microcrystalline cellulose	261 g
Polyvinyl pyrrolidone crosslinked	5 g
Sodium stearyl fumarate	0.5 g

Tablet coating solution (for 10 kg tablets)

Hydroxypropyl methylcellulose	250 g
Polyethylene glycol 6000	62.5 g
Titanium dioxid	62.5 g
Water purified	2125 g
Hydrogen peroxide	0.75 g

Suspension layering was performed in a fluid bed apparatus. Lansoprazole was sprayed onto the sugar sphere seeds from a suspension containing the dissolved binder in a water solution. Pellets covered with separating layer and enteric coating layer were produced as in example 1.

The enteric coating layered pellets, mosapride citrate dihydrate, microcrystalline cellulose, polyvinyl pyrrolidone crosslinked and sodium stearyl fumarate were dry mixed and compressed into tablets using an excenter tableting machine equipped with 10 mm punches.

The amount of lanzoprazole in each tablet was approx. 10 mg and the amount of mosapride was approx. 30 mg. The tablet hardness was measured to 70 N.

The tablets are covered with a conventional tablet filmcoating layer.

Example 6:

Magnesium omeprazole and mosapride presscoated tablets (batch size 10.000 tablets).

Omeprazole tablets	
Mg-omeprazole	112.5 g
Mannitol	287 g
Microcrystalline cellulose	94 g
Sodium starch glycolate	30 g
Hydroxypropyl methylcellulose	30 g
Talc	25 g
Microcrystalline cellulose	31 g
Sodium stearyl fumarate	12.5 g
Water purified	200 g

Solution for separating layer (for 10 kg tablets)	
Hydroxypropyl methylcellulose	300 g
Hydrogen peroxide (30%)	0.003 g
Water purified	2700 g

Solution for enteric coating layer (for 10 kg tablets)	
Methacrylic acid copolymer dispersion (30%)	2450 g
Polyethylene glycol 400	80 g
Titanium dioxide Colour	100 g
Water purified	1960 g

Presscoated tablet	
Mg-Omeprazole tablets	10.000 tabl
Mosapride granulation	
(manufacturing and composition as in example 2)	3800 g

Tablet coating solution (for 10 kg tablets)	
Hydroxypropyl methylcellulose	250 g
Polyethylene glycol 6000	62.5 g
Titaniumdioxid	62.5 g
Water purified	2125 g
Hydrogen peroxide	0.75 g

Magnesium omeprazole, mannitol, microcrystalline cellulose, sodium starch glycolate and hydroxypropyl methyl cellulose are dry mixed. The powder mixture is moistened with water purified. The granulation is dried and milled through sive 1 mm in a suitable mill. The prepared granules comprising proton pump inhibitor is mixed with talc, microcrystalline cellulose and sodium stearyl fumarate and compressed into tablets using a rotary tableting machine equipped with 5 mm punches.

The obtained tablets are coated layered with a separating layer and an enteric coating layer. Said tablets are then presscoated with mosapride granulation using a presscoating machine equipped with 11 mm punched.

The tablets are covered with a conventional tablet filmcoating layer.

Example 7:

A capsule formulation comprising magnesium omeprazole and mosapride (batch size 100 capsules).

Capsules	
Enteric coating layered pellets with an over-coating layer (manufacturing and composition as in example 3)	9.49 g
Mosapride granulation (manufacturing and composition as in example 2)	38 g

Enteric coating layered pellets and mosapride granulation are filled into capsules, size 00. The amount of omeprazole in each capsule is approx. 20 mg and the amount of mosapride is approx. 15 mg.

Example 8:

Multiple unit dosage form comprising magnesium omeprazole with a tablet coating layer comprising mosapride (batch size 1 000 tablets).

Tablets	
Enteric coating layered pellets with an overcoat (manufacturing and composition as in example 1)	82.4 g
Microcrystalline cellulose	179.2 g
Polyvinyl pyrrolidone crosslinked	3.7 g
Sodium stearyl fumarate	0.4 g

Mosapride coating layer suspension	
Mosapride citrate dihydrate	23.4 g
Hydroxypropyl methyl cellulose	13.4 g

Ethanol 99 %	132.5 g
Water purified	132.5 g

Tablet coating solution (for 10 kg tablets)

Hydroxypropyl methylcellulose	250 g
Polyethylene glycol 6000	62.5 g
Titanium dioxid	62.5 g
Water purified	2125 g
Hydrogen peroxide	0.75g

The enteric coating layered pellets are mixed with microcrystalline cellulose, polyvidone and sodium stearyl fumarate and compressed into tablets using an excenter tableting machine equipped with 9 mm punches. The tablets are then coated layered in a fluid bed apparatus with the suspension comprising mosapride. The amount of omeprazole in each tablet is approx. 10 mg and the amount of mosapride is approx. 15 mg.

Finally the tablets are covered with a conventional tablet filmcoating layer.

The best mode to practise the invention is according to compositions described in Examples 1 and 4.

The enteric coating layered pellets comprising a proton pump inhibitor may also be prepared as described in the following examples.

Example 9:

Preparation of enteric coating layered pellets by extrusion/spheronization.

Core material	
Magnesium omeprazole	600 g
Mannitol	1000 g
Microcrystalline cellulose	300 g
Hydroxypropyl cellulose	100 g
Sodium lauryl sulphate	6 g
Water purified	802 g

Separating layer	
Core material	400 g
Hydroxypropyl methylcellulose	48 g
Water purified	960 g

Enteric coating layer	
Pellets covered with separating layer	200 g
Methacrylic acid copolymer	100 g
Triethyl citrate	30 g
Mono- and diglycerides (NF)	5 g
Polysorbate 80	0.5 g
Water purified	309 g

Sodium lauryl sulphate is dissolved in purified water to form the granulation liquid. Magnesium omeprazole, mannitol, microcrystalline cellulose and hydroxypropyl cellulose are dry-mixed. The granulation liquid is added to the powder mixture and the mass is wet-mixed.

The wet mass is forced through an extruder equipped with screens of size 0.5 mm. The extrudate is spheronized on a friction plate in a spheronizing apparatus. The core material is dried in a fluid bed dryer and classified. The prepared core material is covered by a

separating layer in a fluid bed apparatus with a hydroxypropyl methylcellulose/water solution.

The enteric coating layer is applied to the pellets covered with separating layer from an aqueous dispersion of methacrylic acid copolymer plasticized with triethyl citrate to which a mono- and diglycerides/polysorbate dispersion has been added. The pellets are dried in a fluid bed apparatus.

Example 10:

Preparation of enteric coating layered pellets by powder.

Core material	
Magnesium omeprazole	1 500 g
Sugar sphere seeds	1 500 g
Hydroxypropyl methylcellulose	420 g
Aerosil®	8 g
Water purified	4 230 g

Separating layer	
Core material	500 g
Hydroxypropyl cellulose	40 g
Talc	67 g
Magnesium stearate	6 g
Water purified	800 g

Enteric coating layer	
Pellets covered with separating layer	500 g
Methacrylic acid copolymer	200 g

Triethyl citrate	60 g
Water purified	392 g

Magnesium omeprazole, part of the hydroxypropyl methylcellulose and Aerosil® are dry-mixed forming a powder. Sugar sphere seeds (0.25-0.40 mm) are layered with the powder in a centrifugal fluidized coating granulator while spraying a hydroxypropyl methylcellulose solution (6 %, w/w).

The prepared core material is dried and covered by a separating layer in a centrifugal fluidized coating-granulator. A fluid bed apparatus is used for enteric coating layereing.

Example 11:

Preparation of enteric coating layered pellets with of silicon dioxide seeds.

Core material

Magnesium omeprazole	8.00 kg
Silicon dioxide	8.00 kg
Hydroxypropyl methylcellulose	1.41 kg
Sodium lauryl sulphate	0.08 kg
Water purified	28.00 kg

Separating layer

Core material	10.00 kg
Hydroxypropyl methylcellulose	0.80 kg
Water purified	10.00 kg

Enteric coating layer

Pellets covered with separating layer	300 g
Methacrylic acid copolymer	124 g

Polyethylene glycol 400	25 g
Mono- and diglycerides (NF)	3 g
Polysorbate 80	1 g
Water purified	463 g

Suspension layering is performed in a fluid bed apparatus. Magnesium omeprazole is sprayed onto the silicon dioxide seeds from a water suspension containing the dissolved binder and a surface active ingredient.

The prepared core material is covered with a separating layer in a fluid bed apparatus with a hydroxypropyl methylcellulose solution. The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides, polyethylene glycol 400 and polysorbate is sprayed onto the pellets covered with separating layer in a fluid bed apparatus.

Example 12:

Preparation of enteric coating layered pellets.

Enteric coating layer

Pellets covered with separating layer (manufacturing and composition as in example 10)	500 g
Methacrylic acid copolymer	250 g
Polyethylene glycol 6000	75 g
Mono- and diglycerides (NF)	12.5 g
Polysorbate 80	1.2 g
Water purified	490 g

Example 13:

Preparation of enteric coating layered pellets.

Enteric coating	
Pellets covered with separating layer	500 g
(manufacturing and composition as in example 1)	
Hydroxypropyl methylcellulose phthalate	250 g
Cetanol	50 g
Ethanol (95%)	1000 g
Acetone	2500 g

Example 14:

Preparation of enteric coating layered pellets.

Core material	
Omeprazole	225 g
Mannitol	1425 g
Hydroxypropyl cellulose	60 g
Microcrystalline cellulose	40 g
Lactose anhydrous	80 g
Sodium lauryl sulphate	5 g
Disodium hydrogen phosphate dihydrate	8 g
Water purified	350 g

Separating layer	
Core material	300 g
Hydroxypropyl cellulose	30 g
Talc	51 g

Magnesium stearate	4	g

Enteric coating layer

Pellets covered with separating layer	300	g
Methacrylic acid copolymer	140	g
Triethyl citrate	42	g
Mono- and diglycerides (NF)	7	g
Polysorbate 80	0.7	g

The dry ingredients for producing the core material are well mixed in a mixer. Addition of granulation liquid is made and the mixture is kneeded and granulated to a proper consistency. The wet mass is pressed through an extruder screen and the granules are converted into a spherical form in a spheronizer. The core material is dried in a fluid bed apparatus and classified into a suitable particle size range, e.g. 0.5 - 1.0 mm.The prepared core material is covered with a separating layer and enteric coating layered as described in previous examples.

Preparation of active substance

Magnesium omeprazole used in some of the examples is produced according to the process described in WO95/01977, the single enantiomers of omeprazole salts are prepared as described in WO94/27988 and omeprazole is produced according to the process disclosed in EP-A1 0005129. These documents are hereby incorporated in a whole by reference.

CLAIMS

1. An oral pharmaceutical dosage form comprising an acid susceptible proton pump inhibitor together with at least one prokinetic agent and optionally pharmaceutically acceptable excipients, characterized in that the dosage form is in the form of a fixed unit dosage form comprising at least two pharmaceutically active components, and wherein the proton pump inhibitor is protected by an enteric coating layer.

2. A dosage form according to claim 1, wherein the dosage form is a tablet formulation.

3. A dosage form according to claim 1, wherein the dosage form is a capsule formulation.

4. A dosage form according to claim 1, wherein the proton pump inhibitor is protected by two layers, an enteric coating layer and a layer separating the enteric coating from the proton pump inhibitor.

5. A dosage form according to claim 1, wherein the dosage form comprises a proton pump inhibitor and one prokinetic agent.

6. A dosage form according to claim 1, wherein the proton pump inhibitor is omeprazole, one of its single enantiomer or an alkaline salt thereof.

7. A dosage form according to claim 6, wherein the proton pump inhibitor is S-omeprazole magnesium salt.

8. A dosage form according to claim 1, wherein the proton pump inhibitor is lansoprazole, one of its single enantiomer or an alkaline salt thereof.

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9. A dosage form according to one of claims 6 - 8, wherein the prokinetic agent is mosapride.

10. A dosage form according to one of claims 6 - 8, wherein the prokinetic agent is cisapride.

11. A dosage form according to claim 1, wherein the amount of proton pump inhibitor is in the range of 10-80 mg and the amount of prokinetic agent(s) is in the range of 3-80 mg.

12. A dosage form according to claim 1, wherein the amount of proton pump inhibitor is in the range of 10-40 mg and the amount of prokinetic agent(s) is in the range of 15-40 mg.

13. A tableted dosage form according to claim 2, wherein the dosage form consists of two separate layers, one layer comprising a proton pump inhibitor and the other layer comprising one or more prokinetic agents.

14. A tableted dosage form according to claim 2, wherein the tablet formulation is a multiple unit tableted dosage form comprising the proton pump inhibitor in the form of enteric coating layered pellets compressed together with a prokinetic preparation into a tablet, whereby the enteric coating layer covering the pellets has mechanical properties such that the tableting of the pellets together with the prokinetic granulation and optionally pharmaceutically acceptable excipients does not significantly affect the acid resistance of the enteric coating layered pellets.

15. A tableted dosage form according to claim 14, wherein the acid resistance of the enteric coating layered pellets is in coherence with the requirements on enteric coating layered articles defined in the United States Pharmacopeia.

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16. A tableted dosage form according to 14, wherein the acid resistance of the enteric coating layered pellets does not decrease more than 10 % during the compression of the pellets into the multiple unit tableted dosage form.

17. A tableted dosage form according to claim 14, wherein the enteric coating of the pellets comprises a plasticized enteric coating layer material.

18. A tableted dosage form according to claim 14, wherein the enteric coating layered pellets are further covered with an over-coating layer comprising pharmaceutically acceptable excipients.

19. A tableted dosage form according to claim 14, wherein the tablet is divisible.

20. A tableted dosage form according to claim 19, wherein the tablet is dispersible to a slightly acidic aqueous suspension comprising a prokinetic agent and enteric coating pellets of a proton pump inhibitor.

21. A tableted dosage form according to claim 2, wherein the tablet is an enteric coating layered tablet comprising the proton pump inhibitor surrounded by a layer comprising the prokinetic agent.

22. A tableted dosage form according to claim 14, wherein a multiple unit tableted dosage form comprising the proton pump inhibitor is layered with a separate layer comprising the prokinetic agent, or the multiple unit tableted dosage form is surrounded by a layer comprising the prokinetic agent.

23. A process for the manufacture of a fixed dosage form comprising a proton pump inhibitor and one or more prokinetic agents in a capsule, characterized in that the proton pump inhibitor is prepared in the form of enteric coating layered pellets and the pellets are

filled into a capsule together with the prokinetic agent(s) optionally mixed with pharmaceutically acceptable excipients.

24. A process for the manufacture of a fixed dosage form comprising a proton pump inhibitor and one or more prokinetic agents in a multiple unit tableted dosage form, characterized in that the proton pump inhibitor is prepared in the form of enteric coating layered pellets and these pellets are mixed with prepared prokinetic mixture and optionally pharmaceutically acceptable tablets excipients whereafter the mixture is compressed into a multiple unit tablet without giving any significant change of the acid resistance of the enteric coating layer.

25. A process for the manufacture of a fixed dosage form comprising a proton pump inhibitor and one or more prokinetic agent(s) in an enteric coating layered tablet characterized in that the proton pump inhibitor is admixed with tablet excipients and pre-compressed into a tablet, whereafter tablet is covered with an enteric coating layer and that optionally a separating layer is applied before the enteric coating layer, and the prokinetic agent(s) mixed with pharmaceutically acceptable excipients are thereafter presscoated onto the enteric coating layered tablet.

26. A process for the manufacture of a fixed dosage form comprising a proton pump inhibitor and one or more prokinetic agents in a multiple unit tableted dosage form, characterized in that the proton pump inhibitor is prepared in the form of enteric coating layered pellets and these pellets are mixed with pharmaceutically acceptable tablet excipients and the dry mixture is compressed into a multiple unit tablet without giving any significant change of the acid resistance of the enteric coating layer and whereafter the multiple unit tableted dosage form is spray coating layered by an aqueous suspension of the prokinetic agent(s), or the multiple unit tableted dosage form is layered with a separate layer comprising the prokinetic agent(s) in admixture with pharmaceutically acceptable excipients.

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27. A method for the treatment of disorders associated with gastro oesophageal reflux diseases in mammals and man by administering to a host in need thereof a therapeutically effective dose of a multiple unit tableted dosage form according to any of claims 1 to 22.

28. A method according to claim 27, wherein the disorder is a gastric disorder associated with gastro oesophageal reflux diseases.

29. Use of a dosage form according to any of claims 1 to 22 for the manufacture of a medicament for treating disorders associated with gastro oesophageal reflux deseases.

30. Use according to claim 29 wherein the disorder is a gastric disorder associated with gastro oesophageal reflux diseases.

Fig. 1

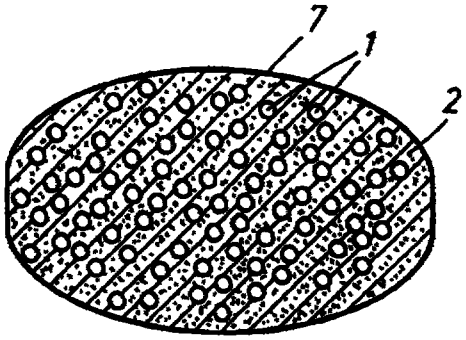


Fig. 2

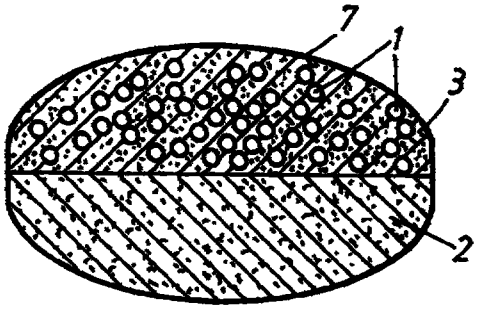


Fig. 3

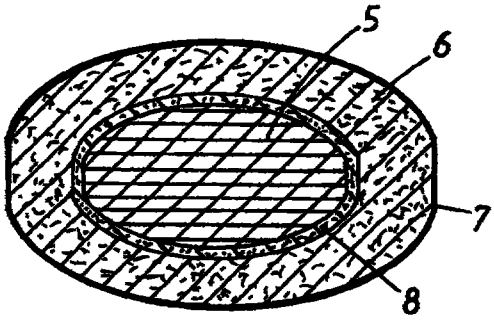
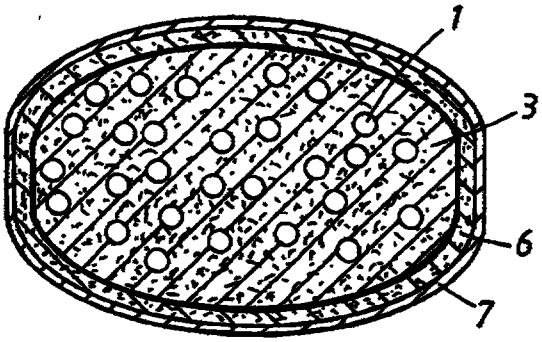


Fig. 4



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☑ Claim(s) : paged 43 to paged 46
☐ Drawing(s) : paged ..... to paged .....
☐ Abstract : paged ..... to paged .....

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CLAIMS

1. A multiple unit tableted dosage form comprising an acid susceptible proton pump inhibitor compound at least one prokinetic agent and optionally pharmaceutically acceptable tablet excipients, characterized in that the dosage form comprises the proton pump inhibitor in the form of a multitude of enteric coating layered pellets which are compressed with the prokinetic preparation and optional excipients into a tablet, and the enteric coating layer covering the pellets has mechanical properties such that the tableting of the pellets together with the prokinetic granulation and optionally pharmaceutically acceptable excipients does not significantly affect the acid resistance of the enteric coating layered pellets..

2. A tableted dosage form according to claim 1, wherein the proton pump inhibitor pellets are protected by two layers, an enteric coating layer and a layer separating the enteric coating from the proton pump inhibitor compound.

3. A tableted dosage form according to claim 1, wherein the dosage form comprises a proton pump inhibitor compound and one prokinetic agent.

4. A tableted dosage form according to claim 1, wherein the proton pump inhibitor compound is omeprazole, one of its single enantiomer or an alkaline salt thereof.

5. A tableted dosage form according to claim 4, wherein the proton pump inhibitor compound is S-omeprazole magnesium salt.

6. A tableted dosage form according to claim 1, wherein the proton pump inhibitor compound is lansoprazole, one of its single enantiomer or an alkaline salt thereof.

7. A tableted dosage form according to one of claims 4 - 6, wherein the prokinetic agent is mosapride.

8. A tableted dosage form according to one of claims 4 - 6, wherein the prokinetic agent is cisapride.

9. A tableted dosage form according to claim 1, wherein the amount of the proton pump inhibitor is in the range of 10-80 mg and the amount of the prokinetic agent(s) is in the range of 3-80 mg.

10. A tableted dosage form according to claim 1, wherein the amount of the proton pump inhibitor is in the range of 10-40 mg and the amount of the prokinetic agent(s) is in the range of 15-40 mg.

11. A tableted dosage form according to claim 1, wherein the acid resistance of the enteric coating layered pellets is in coherence with the requirements on enteric coating layered articles defined in the United States Pharmacopeia.

12. A tableted dosage form according to 1, wherein the acid resistance of the enteric coating layered pellets does not decrease more than 10 % during the compression of the pellets, the prokinetic preparation and optional excipients into the multiple unit tableted dosage form.

13. A tableted dosage form according to claim 1, wherein the enteric coating of the pellets comprises a plasticized enteric coating layer material.

14. A tableted dosage form according to claim 1, wherein the enteric coating layered pellets are further covered with an over-coating layer comprising pharmaceutically acceptable excipients.

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15. A tableted dosage form according to claim 1, wherein the tablet is divisible.

16. A tableted dosage form according to claim 15, wherein the tablet is dispersible to a slightly acidic aqueous suspension comprising the prokinetic agent and enteric coating pellets comprising the proton pump inhibitor.

17. A tableted dosage form according to claim 1, wherein a multiple unit tableted dosage form comprising enteric coating layered pellets of the proton pump inhibitor, is layered with a separate layer comprising the prokinetic agent, or the multiple unit tableted dosage form is surrounded by a layer comprising the prokinetic agent.

18. A process for the manufacture of a multiple unit tableted dosage form, comprising a proton pump inhibitor compound at least one prokinetic agent and optionally pharmaceutically acceptable tablet excipients characterized in that the proton pump inhibitor is prepared in the form of enteric coating layered pellets and these pellets are mixed with a prepared prokinetic mixture and optionally pharmaceutically acceptable tablets excipients whereafter the mixture is compressed into a multiple unit tablet without giving any significant change of the acid resistance of the enteric coating layer.

19. A process for the manufacture of a multiple unit tableted dosage form, comprising a proton pump inhibitor, at least one prokinetic agent and pharmaceutically acceptable tablet excipients characterized in that the proton pump inhibitor is prepared in the form of enteric coating layered pellets and these pellets are mixed with the pharmaceutically acceptable tablet excipients and the dry mixture is compressed into a multiple unit tablet without giving any significant change of the acid resistance of the enteric coating layer and whereafter the multiple unit tableted dosage form is spray coating layered by an aqueous suspension of the prokinetic agent(s), or the multiple unit tableted dosage form is layered with a separate layer comprising the prokinetic agent(s) in admixture with pharmaceutically acceptable excipients.

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* C L M S *

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20. Use of a dosage form according to any of claims 1 to 17 for the manufacture of a medicament for treating disorders associated with gastro oesophageal reflux deseases.

21. Use according to claim 20 wherein the disorder is a gastric disorder associated with gastro oesophageal reflux diseases.

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(54) Title: ORAL PHARMACEUTICAL DOSAGE FORMS COMPRISING A PROTON PUMP INHIBITOR AND A PROKINETIC AGENT

(57) Abstract

An oral pharmaceutical dosage form comprising a proton pump inhibitor and one or more prokinetic agents in a fixed formulation, wherein the proton pump inhibitor is protected by an enteric coating layer. The fixed formulation is in the form of multilayered tablets, capsules or multiple unit tableted dosage forms. The multiple unit dosage forms are most preferred. The new fixed formulation is especially useful in the treatment of disorders associated with gastro oesophageal reflux diseases.

