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(54) Titre : COMPOSITION PHARMACEUTIQUE DE TOLTERODINE ENROBEE OU SEL DE CELLE-CI PRESENTANT UNE DISSOLUTION RAPIDE DANS DES CONDITIONS ACIDES ET UNE DISSOLUTION LENTE A DES VALEURS DE PH PLUSELEVEES

(54) Title: COATED PHARMACEUTICAL COMPOSITION OF TOLTERODINE OR A SALT THEREOF HAVING RAPID DISSOLUTION AT ACIDIC CONDITIONS AND SLOW DISSOLUTION AT HIGHER PH VALUES

(57) Abrégé/Abstract:
A pharmaceutical composition of a drug which may have increased plasma concentrations due to the concomitant use of antacids has been developed which comprises coating with the pH-dependent dissolution, characterized by the rapid dissolution at acidic conditions (pH < 5.5) and very slow dissolution at higher pH values.

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(54) Title: COATED FORMULATIONS

(57) Abstract: A pharmaceutical composition of a drug which may have increased plasma concentrations due to the concomitant use of antacids has been developed which comprises coating with the pH-dependent dissolution, characterized by the rapid dissolution at acidic conditions (pH < 5.5) and very slow dissolution at higher pH values.

COATED PHARMACEUTICAL COMPOSITION OF TOLTERODINE OR A SALT THEREOF HAVING RAPID DISSOLUTION AT ACIDIC CONDITIONS AND SLOW DISSOLUTION AT HIGHER pH VALUES

FIELD OF THE INVENTION

The present invention relates to the field of pharmaceutics, and specifically to pharmaceutical formulation comprising a coating exhibiting a pH-dependent dissolution, characterized by the rapid dissolution at acidic conditions (which means at pH < 5.5, preferably < 5, more preferably at pH in stomach) and very slow dissolution at higher (meaning more alkaline than 5,5, preferably 6) pH values.

BACKGROUND OF THE INVENTION

Many active pharmaceutical ingredients (drugs thereon) exhibit pH-dependent dissolution and/or pH-dependent stability. For these drugs and formulations thereof the change of the gastric pH can significantly affect the release of the drug from the formulation, which results in the altered pharmacokinetics and consequently altered pharmacodynamics of the drug. In the case of the increased plasma concentration of the drug the patient may experience enhanced side effects, while decreased plasma concentrations could result in the lack of the efficacy of the drug.

One of the most frequent change of the gastric pH is the elevation of the gastric pH caused by antacids. Antacids, including specifically group consisting of: magnesium carbonate, calcium carbonate, sodium bicarbonate, magnesium hydroxide, magnesium oxide, aluminum carbonate, aluminum hydroxide, aluminum phosphate, magnesium trisilicate, megaldrate, almagate, dihydroxyaluminum aminoacetate, and dihydroxyaluminum sodium carbonate (or mixtures thereof) work by neutralizing the excess of the stomach acid. For example, it was demonstrated that orally taken almagate (magnesium carbonate-aluminium hydroxide) increased gastric pH from about 1.2 to about 6.0 in about 5.5 minutes (Aliment. Pharmacol. Ther., 20, 683-688, 2004). Antacids are widely used for the relief of the gastro-oesopahageal reflux symptoms which show a high prevalence in general population (30-60%), antacids are also used for the treatment of duodenal ulcers, gastric ulcers, stress gastritis, bile acid mediated diarrhea, biliary reflux, constipation (Drugs, 57, 855-870, 1999) thus one can expect frequent concomitant use of antacids with other medications, including drugs

and pharmaceutical formulations with pH-dependent dissolution and or pH-dependent stability.

A condition that is very frequently connected to the concomitant use of antacids with other medications is for example stress. It is noted that stress contributes to the etiology of between 30 % and 65 % of peptic ulcer cases (Psychosom. Med., 62, 176-185, 2000), and antacids are commonly used for the treatment of upper gastrointestinal ulcers (Drugs, 57, 855-870, 1999). It is also noted that stress is related to several diseases, including urinary incontinence (Int. J. Gynaecol. Obstet., 82, 327-338, 2003), heart and coronary diseases (Curr. Opin. Cardio.l, 19, 494-499, 2004), hypertension (Metabolism, 51, 40-45, 2002), Alzheimer's disease, Parkinson's disease, cancer, chronic renal disease, chronic locomotor system diseases, chronic intestinal diseases, chronic liver disease, gallbladder disease, polycystic ovary syndrome, prostatic hyperplasia, type 2 diabetes, infections (Clin. Nutr, 23, 1256-1266, 2004).

Drugs with the decreased plasma concentrations defined by the decreased peak plasma concentration (C_{MAX}) and/or area under the curve (AUC) due to increase of the gastric pH and consequently impaired *in vivo* dissolution are for example poorly-water soluble weakly basic drugs. Specifically: antifungal agent ketoconazole, anti-emetic agent cinnarizine, antibacterial agents enoxacin and cefpodoxime proxetil, antianxiety agent diazepam. Additionally, calcium salts and zinc salts also exhibit impaired *in vivo* dissolution due to elevated gastric pH. On the other hand a drug with the increased plasma concentrations defined by the increased C_{MAX} due to the concomitant use of antacids and consequently the increased *in vivo* dissolution of the drug is for example an urinary antispasmodic agent tolterodine in its tartrate salt form, thereon term tolterodin will comprise tolterodin or any salt or metabolite thereof, preferably tolterodine tartrate.

Decreased or increased as used above relates to values compared to the ones obtained by administering the drugs to patients having normal stomach and gastrointestinal pH.

Elevated gastric pH may also afford the enhanced absorption of the acid-labile drugs, which may be preferably: penicillins, erythromycin, used as antiinfectives or digoxin

used to treat congestive heart failure or proton pump inhibitors such as omeprazole, lansoprazole, pantoprazole, enantiomers and salts thereof.

Elevated gastric pH might also change the pharmacokinetic properties of the coated formulations (i.e. enteric coated ketoprofen tablets), because the pH in the stomach increase as a result of the concomitant use of the antacids to the values that are characteristic for the small intestine, thus the release of the drug may begin already in the stomach, resulting in shorter T_{MAX} (time to reach maximum concentration) and increased C_{MAX}.

The high probability of impaired gastric pH associated with diseases and conditions selected form the above-mentioned groups, particularly urinary diseases, thus requires that drugs used for the manufacturing of the medicament for treatment of above diseases and/or conditions are formulated into a pharmaceutical composition exhibiting predictable pH dependant dissolution characteristics; especially if they are to be used concomitantly.

DISCLOSURE OF THE INVENTION

The aspect of the invention are summarized as:

A coated pharmaceutical composition, characterized by the rapid dissolution at acidic conditions (pH < 5.5) and slow dissolution at higher pH values.

The pharmaceutical composition as above comprising an active pharmaceutical ingredient which has increased plasma concentrations if administered concomitantly with an antacid.

The pharmaceutical composition as above wherein the active pharmaceutical ingredient is tolterodine or salt thereof.

A pharmaceutical composition, characterized by the rapid dissolution at acidic conditions (pH < 5.5) and slow dissolution at higher pH values, wherein said

composition comprises tolterodine or a salt thereof and a pharmaceutically acceptable carrier.

A pharmaceutical composition comprising tolterodine tartrate, said composition having a coating with the pH-dependent dissolution, characterized by the rapid dissolution at pH < 5.5 and slow dissolution at higher pH values.

A pharmaceutical composition, characterized by the rapid dissolution at acidic conditions (pH < 5.5) and slow dissolution at higher pH values, wherein said composition comprises tolterodine or a salt thereof and a coating comprising (i) a polymer or copolymer of acrylate, methacrylate, or both, with quarternary ammonium group, (ii) chitosan or chitosan derivatives, or (iii) any combination thereof.

The pharmaceutical composition as above wherein the coating comprises a polymer or copolymer of acrylate and/or methacrylate with quarternary ammonium group.

The pharmaceutical composition as above wherein the coating comprises a polymer or copolymer of dimethylaminoethyl methacrylate

The pharmaceutical composition as above wherein the rapid dissolution at pH < 5.5 is defined by that at pH 2.0 the coating is completely dissolved in less than 30 minutes if subjected to the dissolution test in apparatus 2 in accordance with USP 28.

The pharmaceutical composition as above wherein slow dissolution at pH values above 5.5 is defined by that at pH 6.8 the coating is substantially not dissolved after 180 minutes if subjected to the dissolution test in apparatus 2 in accordance with USP 28.

The pharmaceutical composition as above characterized in that that less than 20% by weight of active pharmaceutical ingredient is released at pH = 6,8 within 3 h if subjected to the dissolution test in apparatus 2 in accordance with USP 28.

The pharmaceutical composition as above characterized in that that in the solution or the suspension less than 20% by weight of the amount of polymer used in coating is detected after 3 h, when subjecting the composition to dissolution test in apparatus 2 in accordance with USP 28.

The pharmaceutical composition as above, wherein the amount of polymer is detected by HPLC in solution or dispersion after subjecting the composition to dissolution test in apparatus 2 in accordance with USP 28.

The pharmaceutical composition as above, characterized in that it consists of cores coated with a first coating wherein cores comprise an active

pharmaceutical ingredient, and a second separating coating and a third coating comprising copolymer of acrylate and methacrylate with quarternary ammonium group.

The pharmaceutical composition as above wherein the second coating comprises hydroxypropyl cellulose

The pharmaceutical composition as above where the cores are pellets.

The pharmaceutical composition as above where the cores are inert cores coated with film comprising active pharmaceutical ingredient.

A pharmaceutical composition, characterized in that it consists of pellets which comprise tolterodine tartrate which are coated by one or optionally more coatings and at least one of said coatings comprises a polymer or copolymer of acrylate and/or methacrylate with quarternary ammonium group.

A pharmaceutical composition, characterized in that it consists of pellets which comprise tolterodine tartrate which are coated by one or more coatings and at least one of said coatings comprises a polymer or copolymer of acrylate, methacrylate, or both, with quarternary ammonium groups.

The pharmaceutical composition as above wherein said a polymer or copolymer is Eudragit E PO or Eudragit E 100.

A pharmaceutical composition comprising cores wherein cores comprise tolterodine tartrate,
and first coating which comprises
6-12% of coating agent;
0,5-1,5% of surfactant;
0,5-1,5 of plasticizer; and
2- 5 % of glidant;

and separating coating which comprises

2-5% of coating agent;

0,2-0,5% of plasticizer; and

0,5-1% of glidant;

and third coating comprising

6-12% of coating agent;

0,5-1,5% of surfactant;

0,5- 1,5% of plasticizer; and

2-5% of glidant;

whereby the amounts mean by weight to the finished composition.

A pharmaceutical composition which is a finished dosage form comprising the pharmaceutical composition as above filled into gelatine or HPMC capsules.

A pharmaceutical composition, characterized in that it consists of pellet cores comprising tolterodine tartrate coated with a first coating, a second coating and a third coating comprising Eudragit E PO, sodium lauryl sulfate, stearic acid, and magnesium stearate.

The pharmaceutical composition as above characterized in that a second coating comprises ethylcellulose, and hydroxypropyl cellulose, while first coating may be enteric coating.

Use of the coating characterized by the pH-dependent dissolution which is rapid at acidic conditions (pH < 5.5) and very slow at higher pH values for neutralizing the effect of the elevated pH on the release and/or stability of the drug and/or formulations that exhibit pH-dependent dissolution and/or stability, caused by the concomitant use of the antacids.

Use of a coating characterized by the pH-dependent dissolution which is rapid at acidic conditions (pH < 5.5) and very slow at higher pH values, for neutralizing the effect of the elevated pH on the release, stability, or both, of tolterodine tartrate, a formulation compirising tolterodine tartrate, or both, that exhibits pH-dependent dissolution, stability, or both, caused by concomitant use of an antacid.

Use of a coating comprising (i) a polymer or copolymer of acrylate, methacrylate, or both, with quarternary ammonium group, (ii) chitosan or chitosan derivatives, or (iii) a combination of (i) and (ii), characterized by a pH-dependent dissolution which is rapid at acidic conditions (pH < 5.5) and very slow at higher pH values, for neutralizing the effect of the elevated pH on the release, stability, or both, of a drug, a drug formulation, or both, that exhibits pH-dependent dissolution, stability, or both, caused by concomitant use of an antacid, wherein the drug is tolterodine or a salt thereof.

Use of coating as above in manufacturing a medicament exhibiting increased Cmax if administered concomitantly with an antacids.

Use of coating as above in manufacturing a medicament for treating urinary or gastrointestinal disease or hypertension.

Use of coating as above in manufacturing a medicament comprising tolterodine tartrate.

Use of a copolymer of acrylate and methacrylate with quarternary ammonium group for coating a pharmaceutical composition comprising tolterodine.

A process for manufacturing a pharmaceutical composition characterized in that it consists of following steps:

a) preparing cores comprising an active pharmaceutical ingredient; (wherein said active pharmaceutical ingredient may be in or on cores)

b) applying a coating to said cores, characterized in that the coating layer provides for the rapid dissolution at pH < 5.5 and slow dissolution at higher pH values.

A process as above, wherein active pharmaceutical ingredient is tolterodine or tolterodine tartrate and the coating applied in step b) comprises aminoylkyl methacrylate copolymers and/or chitosan or chitosan derivatives.

A process for manufacturing a pharmaceutical composition characterized in that it consists of following steps:

a) preparing cores comprising tolterodine or tolterodine tartrate;

b) applying a coating to said cores, characterized in that the coating layer provides for the rapid dissolution at pH < 5.5 and slow dissolution at higher pH values, wherein the coating comprises aminoylkyl methacrylate copolymers, chitosan, chitosan derivatives, or any combination thereof.

A process for manufacturing a pharmaceutical composition characterized in that it consists of following steps:

a) preparing cores comprising an active pharmaceutical ingredient; (wherein said active pharmaceutical ingredient may be in or on cores); the cores may be prepared by mixing active pharmaceutical ingredient with inactive ingredients and granulating or extrusion or spheronization or may be prepared by applying a film containing active pharmaceutical ingredient into inert cores;

b) applying an enteric coating or release controlling agent to said cores;

c) applying second separating coating to said first coated cores, giving second cores;

d) applying third coating to said second cores, characterized in that third coating layer provides for the rapid dissolution at pH < 5.5 and slow dissolution at higher pH values.

A process for manufacturing a pharmaceutical composition characterized in that it consists of following steps:

a) preparing cores comprising tolterodin or a salt thereof;

b) applying a coating to said cores, characterized in that the coating layer provides for the rapid dissolution at pH < 5.5 and slow dissolution at higher pH values, wherein the coating comprises (i) a polymer or copolymer of acrylate, methacrylate, or both, with quarternary ammonium group, (ii) chitosan or chitosan derivatives, or (iii) any combination thereof.

A process for manufacturing a pharmaceutical composition characterized in that it consists of following steps:

a) preparing cores comprising an active pharmaceutical ingredient, wherein the active pharmaceutical ingredient is tolterodine or a salt thereof;

b) applying an enteric coating or release controlling agent to said cores;

c) applying a second separating coating to said first coated cores, giving second cores; and

d) applying a third coating to said second cores, wherein said coating comprises (i) a polymer or copolymer of acrylate, methacrylate, or both, with quarternary ammonium group, (ii) chitosan or chitosan derivatives, or (iii) any combination thereof, characterized in that the third coating provides for the rapid dissolution at pH < 5.5 and slow dissolution at higher pH values.

A process in as above where the coating in step d) comprises a polymer selected from aminoalkyl methacrylate copolymers, chitosan of chitosan derivatives.

A process in as above wherein the aminoalkyl methacrylate copolymer is a copolymer of acrylate and methacrylate with quarternary ammonium group.

A process in as above where the coating in step c) comprises hydroxypropyl cellulose.

A process in as above wherein the active pharmaceutical ingredient is tolterodine tartrate.

Use of a composition as above for treatment of patient who is being concomitantly treated with antacid.

Use of coating with the pH-dependent dissolution, characterized by the rapid dissolution at acidic conditions (pH < 5.5) and very slow dissolution at higher pH values for manufacturing a medicament.

Use as above, wherein the medicament comprises tolterodine or salt thereof.

Use as above for manufacturing a medicament for treating an urinary difficulty.

Use as above where urinary difficulty is frequent urination and/or inability to control urination.

Method of treating urinary diseases by administering a composition as described or exemplified above.

Method as above, wherein the urinary disease is an urinary difficulty.

Method as above, wherein the urinary difficulty is frequent urination and/or inability to control urination.

Method of administering urinary antispasmodic medicament by using a composition as described or exemplified above wherein the administration is performed concomitantly with administration of an antacid.

The present invention is in a broad sense a pharmaceutical composition, characterized by the rapid dissolution at acidic conditions (pH < 5.5) and slow dissolution at higher pH values, in particular it will comprise an active pharmaceutical ingredient which has increased plasma concentrations if administered concomitantly with an antacid, more particularly the active pharmaceutical ingredient is tolterodine, more particularly salt thereof.

In a specific aspect the invention is a pharmaceutical composition (in a specific embodiment comprising tolterodine tartrate), said composition having a coating providing for the pH-dependent dissolution, characterized by the rapid dissolution at pH < 5.5 and slow dissolution at higher pH values, in particular the formulations and coating thereof which comprises a polymer or copolymer of acrylate and/or methacrylate with quarternary ammonium group, such as dimethylaminoethyl methacrylate (Eudragit E PO).

In one embodiment of the invention the pharmaceutical composition the rapid dissolution at pH < 5.5 is defined by that at pH 2.0 the coating is completely dissolved in less than 30 minutes if subjected to the dissolution test in apparatus 2 in accordance with USP 28 and/or the slow dissolution at pH values above 5.5 is defined by that at pH 6.8 the coating is substantially not dissolved after 180 minutes if subjected to the dissolution test in apparatus 2 in accordance with USP 28. Specifically this can be detected by fact that that in the solution or the suspension less than 20% by weight of

the amount of polymer used in coating is detected, (which can be performed by HPLC analysis) after 3 h from the start of dissolution test, when subjecting the composition to dissolution test in apparatus 2 in accordance with USP 28.

In an alternative embodiment the dissolution characteristics of said composition are characterized in that that less than 20% by weight of active pharmaceutical ingredient is released into solution at pH = 6,8 within 3 h (from the start of dissolution test) if subjected to the dissolution test in apparatus 2 in accordance with USP 28.

The pharmaceutical composition of our invention is one structural aspect consists of cores coated with a first coating wherein cores comprise an active pharmaceutical ingredient, and a second separating coating and a third coating comprising copolymer of acrylate and methacrylate with quarternary ammonium group, preferably wherein the second coating comprises hydroxypropyl cellulose, more preferably where the active pharmaceutical ingredient is tolterodine, or salt thereof, more preferably where the coated cores are pellets, which are filled into capsule or compressed into tablets.

In a specific aspect the invention is a pharmaceutical composition, characterized in that it consists of pellet which comprise tolterodine tartrate which are coated by one or optionally more coatings and at least one of said coatings comprises a polymer or copolymer of acrylate and/or methacrylate with quarternary ammonium group, preferably Eudragit E PO or Eudragit E 100.

In yet more specific aspect the invention is a pharmaceutical composition, characterized in that it consists of pellet cores comprising active pharmaceutical ingredient for treating a stress related disease, which may be urinarly disease, gastrointestinal disease, hypertension, (in particular tolterodine tartrate for treating urinary disease), (in another embodiment omeprazole or another proton pump inhibitor for treating gastrointestinal disease,) coated with a first coating, a second coating and a third coating comprising Eudragit E PO, sodium lauryl sulfate, stearic acid, and magnesium stearate, preferably where second coating comprises ethylcellulose, and/or hydroxypropyl cellulose, while first coating (which may be in certain embodiments optional) may comprise an anionic polymer containing alkaline functional groups.

In another specific structural embodiment the cores may be inert cores such as sugar spheres onto which active pharmaceutical ingredient is applied as film.

In the particular embodiment our invention is a finished dosage form (that is a pharmaceutical composition in a form suitable for the administration to patients) comprising the pharmaceutical composition according to any of the previous claims filled into capsules, where in case gelatine or HPMC capsules are used it has been found those have no effect on pH dependant release

Skilled person will appreciate different structural approaches in order to achieve desired pH dependant dissolution. Such structures may be for example pellets providing for controlled release which are incorporated into multiple units tablet coated with a coating which provides the effect in accordance with our invention or such pellets or a structurally different reservoir devices incorporated into a releasing device which releases said reservoir device or active ingredient contained therein in controlled pH dependant matter.

Use of the coating characterized by the pH-dependent dissolution which is rapid at acidic conditions (pH < 5.5) and very slow at higher pH values for neutralizing the effect of the elevated pH on the release and/or stability of the drug and/or formulations that exhibit pH-dependent dissolution and/or stability, caused by the concomitant use of the antacids is contemplated within the scope of the invention, in particular the use of a copolymer of acrylate and methacrylate with quarternary ammonium group for coating a pharmaceutical composition comprising tolterodine.

The invention is for example embodied in a process for manufacturing a pharmaceutical composition characterized in that it consists of following steps:

a) preparing cores comprising an active pharmaceutical ingredient;

b) applying a coating to said cores, characterized in that the coating layer provides for the rapid dissolution at pH < 5.5 and slow dissolution at higher pH values. In particular the coating applied in step b) comprises aminoylkyl methacrylate copolymers and/or chitosan or chitosan derivatives.

More specifically the invention is embodied in a process for manufacturing a pharmaceutical composition characterized in that it consists of following steps:

a) Preparing cores comprising an active pharmaceutical ingredient;

b) applying an enteric coating or release controlling agent to said cores;

c) applying second separating coating to said first coated cores, giving second cores;

d) applying third coating to said second cores, characterized in that third coating layer provides for the rapid dissolution at pH < 5.5 and slow dissolution at higher pH values. In particular the coating applied in step d) comprises a polymer selected from aminoalkyl methacrylate copolymers, (preferably a copolymer of acrylate and methacrylate with quarternary ammonium group), chitosan or chitosan derivatives, in particular also the coating in step c) comprises a cellulose derivative such as and preferably hydroxypropyl cellulose.

The aspect of the invention are also the use of the above described composition for treatment of patient who is being concomitantly treated with antacid.

In summary the general aspect of the invention is thus the use of coating with the pH-dependent dissolution, characterized by the rapid dissolution at acidic conditions (pH < 5.5) and very slow dissolution at higher pH values for manufacturing a medicament.

Although any active pharmaceutical ingredient may be formulated according to our invention it has been exemplified for drugs which are used for stress related diseases in particular urinary disease. In particular in our invention the medicament comprises tolterodine and the use of so coated compositions for manufacturing a medicament for treating an urinary difficulty, which is preferably a frequent urination and/or inability to control urination.

The method of treatment aspects of the invention are the treating urinary diseases by administering above described compositions in particular treating urinary difficulty.

Yet another aspect of the invention is a method of administering urinay antispasmodic medicament, by using a described composition wherein the administration is performed concomitantly with administration of an antacid.

DETAILED DESCRIPTION OF THE INVENTION

The present invention describes the use of the coating in the manufacturing of a pharmaceutical composition with the pH-dependent dissolution, characterized by the rapid dissolution thereof at acidic conditions, that is at pH < 5.5; which means that at pH 2.0 the coating comprising a coating agent is completely dissolved in less than 30 minutes, preferably in less than 20 minutes, more preferably in less than 15 minutes (if coating dissolution is measured under sink conditions in an USP 28 dissolution apparatus 2) and slow dissolution at pH values higher than 5.5 that is at pH 6.8 the coating is substantially not dissolved even after 180 minutes (if coating dissolution is measured under sink conditions in an USP 28 dissolution apparatus 2). The fact that coating is substantially not dissolved may be characterized in one embodiment by measuring the release active pharmaceutical ingredient (API) wherein the release of API is not a limited or modified factor, in that at pH = 6,8 (0.1 M phosphate buffer, USP 28 apparatus 2) less than 30% of API is released within 3 h, preferably less than 20% after 1 h; more preferably less than 10% after 2 h. In the other embodiment it may be characterized by the fact that in the solution or the suspension (when subjecting the coated composition to dissolution test in apparatus 2 in accordance with USP 28) less than 20% by weight of the amount of polymer (coating agent) used in coating is detected after 3 h, preferably less than 10% after 1 h, more preferably less than 10% after 2 h, still more preferably less than 10 after 3 h; which can be conveniently measured spectrofotometricaly or alternatively by HPLC or MS or other analytical technique.

It is assumed that the dissolution of API is not a limiting factor. The invention is thus particularly suitable for relatively good soluble drugs such as those in form of salts.

This coating is intended to neutralize the effect of the elevated pH on the release/stability of the drugs and formulations that exhibit pH-dependent dissolution and/or stability, in particular caused by the concomitant use of the antacids and is applied in the pharmaceutical composition in a manner that it comes in the contact with the gastric content sooner then the drug. It is contemplated that the coating primarily influences the pH dependence of the dissolution and/or stability characteristics of the

drugs and/or pharmaceutical compositions, however the cores being coated may be also formulated (manufactured) in a way to provide modified release after the coating has dissolved or disintegrated.

Coating preferably contains a polymer or combination of polymers which contain alkaline functional groups. Polymers are selected from the purely synthetic materials such as aminoalkyl methacrylate copolymers or from the natural polymers such as chitosan and chitosan derivatives. Under the normal acidic conditions in the stomach this coating is rapidly dissolved without affecting the drug release from the pharmaceutical formulation. If antacids are concomitantly used with the drugs and pharmaceutical formulation that exhibit pH-dependent dissolution and/or stability the above mentioned coating prevents the release of the drug from the pharmaceutical formulation and thus neutralize the effect of elevated pH on the drug release/stability. When pH in the stomach falls under the pH at which the above mentioned coating is dissolved (i.e. in the case of orally taken almagate the gastric pH, after being increased to about 6.0 in about 5.5 minutes, decreased under 5.5 in about 10 minutes (Aliment. Pharmacol. Ther., 20, 683-688, 2004)) as a result of the ceasing of the antacid activity, the coating is dissolved and the drug or pharmaceutical formulation is exposed to more normal acidic conditions in the stomach, enabling the more predictive pharmacokinetic and consequently more predictive efficacy of the drug.

Formulation to avoid enhanced absorption of drugs

In the case of the acid-labile drugs elevated gastric pH may result in enhanced absorption and subsequently enhanced adverse effects. This undesired effect can be circumvented by coating the cores, with a coating layer of a coating agent, preferably an anionic polymer containing alkaline functional groups, more preferably an acrylate polymer, most preferably copolymer of acrylate and methacrylates with quarternary ammonium group, such as Eudragit E PO.

The cores may be either crystals, granules, pellets, tablets or capsules comprising above mentioned drug and suitable pharmaceutical excipients. Specifically the cores may be pellets or granules comprising API therein or alternatively inert cores, such as sugar spheres onto which API is applied as a film.

The following table shows a typical weight (relative to finished composition) composition of a coating to be applied to the cores of the pharmaceutical composition, whereas the coating amounts to 10 – 20 % by weight to the finished composition.

coating agent	polymer (preferably: Eudragit E PO)	6,0-12,0
surfactant	sodium lauryl sulfate, polysorbate 80	0,5-1,5
plasticizer	stearic acid, dibutyl sebacate, acetyltributyl citrate	0,5-1,5
glidant	magnesium stearate, talc	2,0-5,0

Cores, preferably pellets are prepared, preferably by extrusion and spheronisation of wet mass consisting of API, sufficient amount of spheronising agent (i. e. microcrystalline cellulose), optionally release controlling agent and granulation fluid (i.e. water, ethanol). Dry cores are coated with the coating dispersion prepared in following steps. First, surfactant, preferably a sodium lauryl sulfate, is dissolved in purified water and plasticizer. preferably containing stearic acid and/or dibutyl sebacate and/or acetyltributyl citrate or similar excipient, preferably stearic acid, added while stirring (e.g. by propeller mixer). Then, coating agent is dispersed into prepared liquid and mixed (e.g. with high shear mixer) until clear, yellowish dispersion is formed. Separately, suspension of glidant in water is prepared, added to polymer dispersion and mixed. The resulting dispersion is used for coating of the cores in a fluid-bed device.

Formulation to avoid premature release of coated composition

Due to elevated gastric fluid pH changes in the pharmacokinetic properties of coated , preferably enteric coated, formulations may occur and the release of the drug may begin already in the stomach. Additional coating layer comprising of polymer with cationic properties is able to prevent this undesired effect. Due to possible interactions between anionic polymer for first coating and cationic polymer for protective coating additional inert separating coating layer may be required. First coated material may be in the form of coated crystals, granules, pellets, tablets or capsules.

The following table shows a typical weight (relative to finished composition) composition of a separating (second) coating to be applied to the preferably enteric

coated cores of the pharmaceutical composition, whereas the coating amounts to 3 -30 % by weight to the finished composition. Composition will depend on the first and third coating.

coating agent	hydroxypropyl cellulose	preferably 2-5
plasticizer	polyethylene glycol	preferably 0,2-0,5
glidant	talc	preferably 0,5-1,0

Bellow is a typical weight (relative to finished composition) composition of a (third) coating to be applied to the cores of the pharmaceutical composition, whereas the coating amounts to 10 - 20 % by weight to the finished composition.

coating agent	polymer (preferably: Eudragit E PO)	6,0-12,0
surfactant	sodium lauryl sulfate	0,5-1,5
plasticizer	stearic acid	0,5-1,5
glidant	magnesium stearate	2,0-5,0

Cores, preferably pellets are prepared by extrusion and spheronisation of wet mass consisting of active substance, sufficient amount of spheronising agent (e.g. microcrystalline cellulose), optionally release controlling agent and granulation fluid (i.e. water, ethanol).

Dry cores are first coated with separating layer, prepared in following steps: (a) coating agent, preferably powdered hydroxypropyl cellulose, but also hydroxypropylmethylcellulose or methylcellulose is slowly added to well-agitated liquid, preferably water at room temperature and stirred until a gel-free solution is obtained, (b) plasticizer, preferably polyethylene glycol, but also glycerol, propylene glycol, triacetin is stirred into solution, (c) glidant, preferably talc suspension in suitable liquid, preferably water, is prepared separately (e.g. with high-shear mixing) and (d) combined with above solution. Cores are coated and preferably dried in a fluid bed device.

Finally, the protective coating is applied on coated cores. The coating dispersion is prepared in following steps: (a) surfactant, preferably sodium lauryl sulphate but also a poloxamer, is dissolved (e.g. in purified water) and a plasticizer, preferably stearic acid,

is added while stirring (e.g. with propeller mixer), (b) coating agent (a polymer) is dispersed into prepared liquid and mixed (e.g. with high shear mixer) until clear dispersion is formed. Separately, suspension of glidant, preferably magnesium stearate or also talc or glycerol monostearat, (e.g. in water) is prepared (c), added to above dispersion and mixed. The resulting dispersion (d) is used for coating of the cores in a fluid-bed device.

Working Example 1

Pellet cores (weight per capsule = 160 mg)		
Tolterodine tartrate	4.00	mg
Microcrystalline cellulose	156.00	mg
Purified water	180.00	mg
Coating (15 % application, based on coated pellets weight)		
Eudragit E PO	15,00	mg
Sodium lauryl sulfate	1,50	mg
Stearic acid	2,00	mg
Magnesium stearate	6,00	mg
Purified water	140,0	mg

Tolterodine tartrate (API) and microcrystalline cellulose are mixed and granulated with water. Granulate is coated by a dispersion prepared as follows: sodium lauryl sulphate is dissolved in purified water and stearic acid is added while stirring, thereto a polymer is dispersed and mixed dispersion is formed. Thereto separately prepared suspension of magnesium stearate in water is added to polymer and the resulting dispersion is used for coating.

Working Example 2

Pellet cores (weight per capsule = 160 mg)		
Tolterodine tartrate	4.000	mg
Microcrystalline cellulose	156.000	mg
Purified water	180.000	mg
Separating coating (15 % application based on core weight)		
Ethylcellulose	26,253	mg
Hypromellose	2,172	mg

Purified water	110,769	mg
Coating (10 % application, based on coated pellets weight)		
Eudragit E PO	13,07	mg
Sodium lauryl sulfate	1,31	mg
Stearic acid	1,96	mg
Magnesium stearate	4,57	mg
Purified water	118,52	mg

Tolterodine tartrate and microcrystalline cellulose are mixed. Demineralised water is added and mixed. From the homogeneous blend, pellet cores are made using the method of extrusion and spheronization. Coating dispersion is prepared in following steps. First, ethylcellulose polymer dispersions with purified water is prepared. Separately, hypromellose is dissolved in water, added to ethylcellulose dispersion and mixed. The resulting dispersion is used for coating of the pellet cores in a fluid-bed device.

Subsequently the protective coating is applied on dry coated pellets. The coating dispersion is prepared in following steps: (a) sodium lauryl sulphate is dissolved in purified water and stearic acid is added while stirring with propeller mixer, (b) polymer is dispersed into prepared liquid and mixed with high shear mixer until clear, yellowish dispersion is formed. Separately, suspension of magnesium stearate in water is prepared (c), added to polymer dispersion and mixed. The resulting dispersion (d) is used for coating of the pellet cores in a fluid-bed device.

Working Example 3

Pellet cores (weight per capsule = 160 mg)		
Tolterodine tartrate	4.00	mg
Microcrystalline cellulose	156.00	mg
Purified water	180.00	mg
Coating (20 % application, based on coated pellets weight)		
Dimethylaminoethyl methacrylate (Eudragit E 100)	32,40	mg
Polyethylene glycol 6000	2,00	mg
Talc	7,60	mg
Isopropyl alcohol	212,40	mg
Acetone	141,60	mg
Purified water	4,00	mg

Tolterodine tartrate and microcrystalline cellulose are mixed. Demineralised water is added and mixed. From the homogeneous blend, pellet cores are made using the method of extrusion and spheronization. Coating dispersion is prepared in following steps. One part (2/3) of Isopropyl alcohol and acetone are introduced first and then Eudragit E 100 is added while stirring with a propeller stirrer for aprox. 30-60 minutes until a clear solution is formed. Separately, polyethylene glycol 6000 is dissolved in water and slowly added to remaining isopropyl alcohol. Then talc is added and suspension is homogenized for 20 minutes. Finally, the talc suspension is added to the polymer solution with gentle stirring.

The coating suspension is applied to the pellet cores in fluid bed device.

Working Example 4

Pellet cores (weight per capsule = 160 mg)		
Tolterodine tartrate	4.000	mg
Microcrystalline cellulose	156.000	mg
Purified water	180.000	mg
Separating coating (15 % application based on core weight)		
Ethylcellulose	26,253	mg
Hypromellose	2,172	mg
Purified water	110,769	mg
Coating (20 % application, based on coated pellets weight)		
Eudragit E PO	29,41	mg
Sodium lauryl sulfate	2,94	mg
Stearic acid	4,42	mg
Magnesium stearate	10,33	mg
Purified water	247,01	mg

Tolterodine tartrate and microcrystalline cellulose are mixed. Demineralised water is added and mixed. From the homogeneous blend, pellet cores are made using the method of extrusion and spheronization. Coating dispersion is prepared in following steps. First, ethylcellulose polymer dispersions with purified water is prepared. Separately, hypromellose is dissolved in water, added to ethylcellulose dispersion and

mixed. The resulting dispersion is used for coating of the pellet cores in a fluid-bed device.

Subsequently the protective coating is applied on dry coated pellets. The coating dispersion is prepared in following steps: (a) sodium lauryl sulphate is dissolved in purified water and stearic acid is added while stirring with propeller mixer, (b) polymer is dispersed into prepared liquid and mixed with high shear mixer until clear, yellowish dispersion is formed. Separately, suspension of magnesium stearate in water is prepared (c), added to polymer dispersion and mixed. The resulting dispersion (d) is used for coating of the pellet cores in a fluid-bed device.

Working Example 5

Pellet cores of Example 4 are replaced by sugar spheres onto which a film containing active pharmaceutical ingredient as disclosed below is applied in fluid bed device. The resulting cores are after drying to form and cure film coated with separating and final coating as in Example 4.

Film applied to sugar spheres (weight per capsule = 160 mg)		
Tolterodine tartrate	4.000	mg
Polyvinylpyrrolidone	20.000	mg
Dibutylsebacate	2.000	mg
Polysorbate 80	0.100	mg
Water		

Working Example 6

Sugar spheres of Example 5 are coated by a suspension containing

Film applied to sugar spheres (weight per capsule = 160 mg)		
Omeprazole	4.000	mg
Polyvinylpyrrolidone	20.000	mg
Dibutylsebacate	2.000	mg
Polysorbate 80	0.100	mg
Absolute ethanol		

As omeprazole is sensitive to moisture the aqueous liquid has been replaced by absolute ethanol and further the ethanol is used also in separating and (optionally) final coating. The amount of liquid is thus increased twofold compared to that used in Example 4.

Claims:

1. A pharmaceutical composition, characterized by the rapid dissolution at acidic conditions (pH < 5.5) and slow dissolution at higher pH values, wherein said composition comprises tolterodine or a salt thereof and a coating comprising (i) a polymer or copolymer of acrylate, methacrylate, or both, with quarternary ammonium group, (ii) chitosan or chitosan derivatives, or (iii) any combination thereof.

2. The pharmaceutical composition according to claim 1, comprising tolterodine tartrate.

3. The pharmaceutical composition according to claim 1 or 2, wherein the coating comprises a polymer or copolymer of acrylate and/or methacrylate with quarternary ammonium group.

4. The pharmaceutical composition according to claim 3, wherein the coating comprises a polymer or copolymer of dimethylaminoethyl methacrylate.

5. The pharmaceutical composition according to any one of claims 1 to 4, wherein the rapid dissolution at pH < 5.5 is defined by that at pH 2.0 the coating is completely dissolved in less than 30 minutes if subjected to the dissolution test in apparatus 2 in accordance with USP 28.

6. The pharmaceutical composition according to any one of claims 1 to 4, wherein slow dissolution at pH values above 5.5 is defined by that at pH 6.8 the coating is substantially not dissolved after 180 minutes if subjected to the dissolution test in apparatus 2 in accordance with USP 28.

7. The pharmaceutical composition according to any one of claims 1 to 6, wherein less than 20% by weight of the tolterodine or salt thereof is released at pH = 6,8 within 3 h if subjected to the dissolution test in apparatus 2 in accordance with USP 28.

8. The pharmaceutical composition according to any one of claims 1 to 7, wherein in the solution or the suspension less than 20% by weight of the amount of polymer, copolymer, chitosan, chitosan derivatives or combination thereof used in coating is detected after 3 h, when subjecting the composition to dissolution test in apparatus 2 in accordance with USP 28.

9. The pharmaceutical composition according to claim 8, wherein the amount of polymer, copolymer, chitosan, chitosan derivatives or combination thereof is detected by HPLC in solution or dispersion after subjecting the composition to dissolution test in apparatus 2 in accordance with USP 28.

10. The pharmaceutical composition according to any one of claims 1 to 9, wherein it consists of cores coated with a first coating, wherein the cores comprise the tolterodine or salt thereof, and a second separating coating and a third coating comprising copolymer of acrylate and methacrylate with quarternary ammonium group.

11. The pharmaceutical composition according to claim 10, wherein the second coating comprises hydroxypropyl cellulose.

12. The pharmaceutical composition according to claim 10 or 11, where the cores are pellets.

13. The pharmaceutical composition according to claim 10 or 11, where the cores are inert cores coated with film comprising the tolterodine or salt thereof.

14. The pharmaceutical composition according to any one of claims 1 to 9, wherein it consists of pellets which comprise tolterodine tartrate which are coated by one or more coatings and at least one of said coatings comprises a polymer or copolymer of acrylate, methacrylate, or both, with quarternary ammonium groups.

15. The pharmaceutical composition according to claim 14, wherein said polymer or copolymer is Eudragit E PO or Eudragit E 100.

16. The pharmaceutical composition according to claim 14 or 15, wherein it consists of pellet cores comprising tolterodine tartrate coated with a first coating, a second coating and a third coating comprising Eudragit E PO, sodium lauryl sulfate, stearic acid, and magnesium stearate.

17. The pharmaceutical composition according to claim 16, wherein said second coating comprises ethylcellulose, hydroxypropyl cellulose, or both.

18. The pharmaceutical composition according to any one of claims 1 to 9, said pharmaceutical composition comprising cores, wherein cores comprise tolterodine tartrate, and

a first coating which comprises

6-12% of coating agent;

0,5-1,5% of surfactant;

0,5-1,5 of plasticizer; and

2-5 % of glidant;

a second separating coating which comprises

2-5% of coating agent;

0,2-0,5% of plasticizer; and

0,5-1% of glidant; and

a third coating which comprises

6-12% of coating agent, which is a polymer or copolymer of acrylate, methacrylate, or both, with quarternary ammonium groups;

0,5-1,5% of surfactant;

0,5-1,5% of plasticizer; and

2-5% of glidant;

whereby the amounts mean by weight to the finished composition.

19. The pharmaceutical composition according to claim 18, wherein the coating agent comprised in the first coating is a polymer or copolymer of acrylate, methacrylate, or both, with quarternary ammonium groups.

20. The pharmaceutical composition according to claim 18 or 19, wherein the surfactant comprised in the first coating is sodium lauryl sulfate or polysorbate 80.

21. The pharmaceutical composition according to any one of claims 18 to 20, wherein the plasticizer comprised in the first coating is stearic acid, dibutyl sebacate or acetyltributyl citrate.

22. The pharmaceutical composition according to any one of claims 18 to 21, wherein the glidant comprised in the first coating is magnesium stearate or talc.

23. The pharmaceutical composition according to any one of claims 18 to 22, wherein the coating agent comprised in the separating coating is hydroxypropyl cellulose.

24. The pharmaceutical composition according to any one of claims 18 to 23, wherein the plasticizer comprised in the separating coating is polyethylene glycol.

25. The pharmaceutical composition according to any one of claims 18 to 24, wherein the glidant comprised in the separating coating is talc.

26. The pharmaceutical composition according to any one of claims 18 to 25, wherein the surfactant comprised in the third coating is sodium lauryl sulfate.

27. The pharmaceutical composition according to any one of claims 18 to 26, wherein the plasticizer comprised in the third coating is stearic acid.

28. The pharmaceutical composition according to any one of claims 18 to 27, wherein the glidant comprised in the third coating is magnesium stearate.

29. A pharmaceutical composition which is a finished dosage form comprising the pharmaceutical composition according to any one of claims 1 to 28 filled into gelatine or HPMC capsules.

30. Use of a coating comprising (i) a polymer or copolymer of acrylate, methacrylate, or both, with quarternary ammonium group, (ii) chitosan or chitosan derivatives, or (iii) a combination of (i) and (ii), characterized by a pH-dependent

dissolution which is rapid at acidic conditions (pH < 5.5) and very slow at higher pH values, for neutralizing the effect of the elevated pH on the release, stability, or both, of a drug, a drug formulation, or both, that exhibits pH-dependent dissolution, stability, or both, caused by concomitant use of an antacid, wherein the drug is tolterodine or a salt thereof.

31. The use of a coating according to claim 30 in manufacturing a medicament exhibiting increased Cmax if administered concomitantly with an antacid.

32. The use of a coating in accordance with claim 30 or 31 in manufacturing a medicament for treating urinary or gastrointestinal disease or hypertension.

33. The use of a coating in accordance with any one of claims 30 to 32, wherein the drug is tolterodine tartrate.

34. A process for manufacturing a pharmaceutical composition characterized in that it consists of following steps:

a) preparing cores comprising tolterodin or a salt thereof;
b) applying a coating to said cores, characterized in that the coating layer provides for the rapid dissolution at pH < 5.5 and slow dissolution at higher pH values, wherein the coating comprises (i) a polymer or copolymer of acrylate, methacrylate, or both, with quarternary ammonium group, (ii) chitosan or chitosan derivatives, or (iii) any combination thereof.

35. The process according to claim 34 wherein the tolterodine or salt thereof is tolterodine tartrate.

36. The process according to claim 34 or 35, wherein the coating applied in step b) comprises (i) aminoalkyl methacrylate copolymers, (ii) chitosan or chitosan derivatives, or (iii) any combination thereof.

37. A process for manufacturing a pharmaceutical composition characterized in that it consists of following steps:

a) preparing cores comprising an active pharmaceutical ingredient, wherein the active pharmaceutical ingredient is tolterodine or a salt thereof;
b) applying an enteric coating or release controlling agent to said cores;
c) applying a second separating coating to said first coated cores, giving second cores; and
d) applying a third coating to said second cores, wherein said coating comprises (i) a polymer or copolymer of acrylate, methacrylate, or both, with quarternary ammonium group, (ii) chitosan or chitosan derivatives, or (iii) any combination thereof, characterized in that the third coating provides for the rapid dissolution at pH < 5.5 and slow dissolution at higher pH values.

38. The process in accordance with claim 37, wherein the coating in step d) comprises a copolymer of acrylate and methacrylate with quarternary ammonium group.

39. The process in accordance with claim 37 or 38, wherein the coating in step c) comprises hydroxypropyl cellulose.

40. The process in accordance with any one of claims 37 to 39, wherein the active pharmaceutical ingredient is tolterodine tartrate.

41. Use of the pharmaceutical composition according to any one of claims 1 to 29 for the treatment of patient who is being concomitantly treated with antacid.

42. The use according to claim 41, wherein the pharmaceutical composition is for treating a urinary difficulty.

43. The use according to claim 43, wherein the urinary difficulty is frequent urination, inability to control urination, or both.

44. Use of the pharmaceutical composition according to any one of claims 1 to 29 for the treatment of a urinary disease.

45. The use according to claim 44, wherein the urinary disease is urinary difficulty.

46. The use according to claim 45, wherein the urinary difficulty is frequent urination, inability to control urination, or both.

47. The pharmaceutical composition according to any one of claims 1 to 29 for the treatment of patient who is being concomitantly treated with antacid.

48. The pharmaceutical composition according to claim 47, for treating a urinary difficulty.

49. The pharmaceutical composition according to claim 48, wherein the urinary difficulty is frequent urination, inability to control urination, or both.

50. The pharmaceutical composition according to any one of claims 1 to 29 for the treatment of a urinary disease.

51. The pharmaceutical composition according to claim 50, wherein the urinary disease is urinary difficulty.

52. The pharmaceutical composition according to claim 51, wherein the urinary difficulty is frequent urination, inability to control urination, or both.