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(54) **Title:** CONTROLLED RELEASE PHARMACEUTICAL COMPOSITIONS OF TOLTERODINE

(57) **Abstract:** A controlled release pharmaceutical composition containing a core comprising tolterodine or pharmaceutically acceptable salts and auxiliary excipients and a single coating layer comprising rate controlling agents(s). A controlled release pharmaceutical composition comprising tolterodine or pharmaceutically acceptable salts thereof wherein the core comprises tolterodine or pharmaceutically acceptable salts thereof and auxiliary excipients and a single coating layer comprising rate controlling agents(s) wherein said composition further comprises dissolution enhancing agent(s).

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CONTROLLED RELEASE PHARMACEUTICAL COMPOSITIONS OF TOLTERODINE

Field of the Invention

The present invention relates to controlled release pharmaceutical compositions comprising tolterodine or pharmaceutically acceptable salts thereof.

Back ground of the Invention

A substantial part (5-10%) of the adult population suffers from urinary incontinence, and the prevalence, particularly of so-called urge incontinence, increases with age. The symptoms of an unstable or overactive bladder comprise urge incontinence, urgency and urinary frequency. It is assumed that unstable or overactive bladder is caused by uncontrolled contractions of the bundles of smooth muscle fibres forming the muscular coat of the urinary bladder (the detrusor muscle) during the filling phase of the bladder. These contractions are mainly controlled by cholinergic muscarinic receptors, and the pharmacological treatment of unstable or overactive bladder has been based on muscarinic receptor antagonists.

Tolterodine is well-known antimuscarinic agent specifically developed for treatment of patients with overactive bladder. It was disclosed in US Patent 5,382,600. Tolterodine is marketed under the brand name Detrol ®film-coated tablets containing 1 mg or 2 mg of tolterodine L-tartrate for immediate release in the gastrointestinal tract. Additionally it is marketed under the brand name Detrol LA ® long acting capsules These capsules contain either 2 or 4 mg of the active ingredient.

US patent 6,911,217 relates to a controlled release bead comprising: (i) a core unit of a substantially water-soluble or water-swellable inert material; (ii) a first layer on the core unit of a substantially water-insoluble polymer; (iii) a second layer covering the first layer and containing an active ingredient; and (iv) a third layer of polymer on the second layer effective for controlled release of the active ingredient, wherein the first layer is adapted to control water penetration into the core. However it is both time and cost intensive manufacturing technique.

WO 2004/105735 discloses controlled release pharmaceutical composition of tolterodine that includes one or more coated units. Each coated unit includes a core, a first layer, and a second layer. The first layer surrounds at least a portion of the core and includes tolterodine and one or more hydrophilic polymers. The second layer surrounds at least a portion of the first layer and includes one or more polymers that are effective for controlled release of the tolterodine from the first layer. The above patent application. involved fewer layering steps.

WO 2005/079748 discloses a pharmaceutical preparation for sustained release of a pharmaceutically active ingredient(s), which preparation comprises particles having an inner core (1) and a first coating (2) provided thereon, wherein said coating (2) contains a mixture of (a) copolymer of ethyl acrylate, methylmethacrylate and trimethylamminoethyl methacrylate chloride (b) copolymer of ethylacrylate and methacrylic acid (c) between 1 % and 40% by weight of the pharmaceutically active ingredient.

WO 2005/016321 discloses a mucoadhesive delivery system for the local or systemic administration of a pharmaceutical agent. The delivery system of the invention effectively and facilely enables transport of the pharmaceutical agent through mucosal membranes and into the vasculature of the mucosa. The delivery system includes an at least partially water-soluble bioadhesive layer and an at least partially water-soluble backing layer. Incorporated within either or both of these layers are the pharmaceutical agent and a mucosal penetration enhancing agent.

WO 2005/048979 discloses a modified release pharmaceutical composition consists of casing comprising at least two micro tablets, which are coated with rate controlling agent(s) optionally in combination with auxiliary pharmaceutical excepient(s), wherein each micro tablet comprises core particles comprising pharmaceutical active ingredient and rate controlling agent(s), the said core particles optionally coated with rate controlling agent(s).

Although above mentioned patents and patent applications provide controlled release dosage forms, but production of dosage forms of these references is lengthy, expensive process or requires specialized equipments or techniques.

Thus there still exists a need to develop a controlled release pharmaceutical composition comprising tolterodine or pharmaceutically acceptable salts, wherein the release rate controlling agent is in the coating.

There exists a need to develop a controlled release pharmaceutical composition comprising tolterodine or pharmaceutically acceptable salts, wherein the release rate controlling agent is in the coating which offers advantages like simple manufacturing process, compact dosage form, use of conventional manufacturing equipment, high throughput, easy scale-up, economic, etc.

Thus the present invention proposes controlled release pharmaceutical compositions of tolterodine or pharmaceutically acceptable salts thereof comprising immediate release core and a single coating layer comprising rate controlling agent(s).

Additionally there is a need to provide a controlled release pharmaceutical composition comprising tolterodine or pharmaceutically acceptable salts thereof, wherein composition provides a dissolution profile having a reduced dependency from the pH- value and/or the ionic strength of the dissolving medium of the controlled release composition.

Object of the Invention

Tolterodine for the purpose of the present invention may be selected from tolterodine base, i. e., (R)-N, N-diisopropyl-3- (2-hydroxy-5-methylphenyl)-3 phenylpropanamine, as well as the corresponding (S)-enantiomer, the racemate and the active 5-hydroxymethyl metabolites, prodrug forms and pharmaceutically acceptable salts thereof. The preferred salt of tolterodine is tartrate.

Therefore, the first object of the present invention provides controlled release pharmaceutical compositions comprising tolterodine or pharmaceutically acceptable salts thereof wherein the

core comprises tolterodine and auxiliary excipients and a single coating layer comprising rate controlling agent(s).

Yet another object of the invention provides controlled release pharmaceutical compositions comprising tolterodine or pharmaceutically acceptable salts thereof comprising an immediate release core wherein said core comprises tolterodine and pharmaceutically acceptable salts thereof, water insoluble inert material with one or more auxiliary pharmaceutical excipients and a single coating layer comprising rate controlling hydrophobic and/or hydrophilic agents(s).

Yet another object of the present invention provides controlled release pharmaceutical compositions of tolterodine or pharmaceutically acceptable salts thereof wherein additionally a composition contains dissolution enhancing agents comprising organic acids.

Detail description of the Invention

The dosage forms of the invention typically contain 1 to 20 mg tolterodine as base. The dosage forms of the invention optionally may comprise salts of tolterodine, preferably tolterodine tartrate.

The term “immediate release core” herein refers to core comprising tolterodine or pharmaceutically acceptable salts thereof devoid of any release-controlling agent(s).

The term "controlled release compositions" herein refers to any composition or dosage form which comprises an active drug and which is formulated to provide a longer duration of pharmacological response after administration of the dosage form than is ordinarily experienced after administration of a corresponding immediate release composition comprising the same drug in the same amount. Controlled release compositions include, inter alia, those compositions described elsewhere as "extended release", "delayed release",

"sustained release", "prolonged release", "programmed release", "time release" and/or "rate controlled" compositions or dosage forms.

The hydrophilic release controlling agents are selected from but are not limited to hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC) polyethylene oxide, polyvinyl alcohol, polyvinylpyrrolidone, xanthan gum, guar gum, chitosan and its derivatives, carbomer, carrageenan, carboxymethyl cellulose, sodium alginate, polyglycolized glycerides, polyethylenglycol, or mixture thereof.

The hydrophobic release controlling agents are selected from but are not limited to polyvinyl acetate dispersion, ethyl cellulose, cellulose acetate, cellulose propionate (lower, medium or higher molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, poly (methyl methacrylate), poly (ethyl methacrylate), poly (butyl methacrylate), poly (isobutyl methacrylate), and poly (hexyl methacrylate), poly (isodecyl methacrylate), poly (lauryl methacrylate), poly (phenyl methacrylate), poly (methyl acrylate), poly (isopropyl acrylate), poly (isobutyl acrylate), poly (octadecyl acrylate), waxes such as beeswax, carnauba wax, paraffin wax, microcrystalline wax, and. ozokerite; fatty alcohols such as cetostearyl alcohol, stearyl alcohol, cetyl alcohol and myristyl alcohol, and fatty acid esters such as glyceryl monostearate; glycerol monooleate, acetylated monoglycerides, tristearin, tripalmitin, cetyl esters wax, glyceryl palmitostearate, glyceryl behenate, and hydrogenated vegetable oils.

The term “controlled release pharmaceutical compositions” includes a pharmaceutical composition that encompasses one or more individual coated units. The coated units may be a capsule or tablet or may be in form of granules, pellets, minitablets or beads.

The compositions of the present invention can also include other materials such as dissolution enhancing agents, binders, diluents, anti-adherents, glidants and lubricants.

Dissolution enhancing agents include pharmaceutically acceptable organic acids. Examples include but not limited to ascorbic acid, succinic acid, malonic acid, oxalic acid, tartaric acid, fumaric acid, adipic acid, glucono delta-lactone and malic acid.

Diluents may be, for example, any pharmaceutically acceptable, non-toxic diluent. Particular examples include lactose, dextrose, sucrose, maltose, microcrystalline cellulose, starch, calcium hydrogen phosphate, mannitol and the like.

Binders may be, for example, starch, sugars, gums, low molecular weight hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxyethyl cellulose or the like.

Lubricants may be, for example, talc, magnesium stearate, calcium stearate, stearic acid, sodium stearyl fumarate, sodium benzoate or the like.

Antiadherents and Glidants may be, for example, colloidal silicon dioxide, talc or the like.

Solid oral dosage forms of the present invention may be prepared by any conventional techniques for example dry granulation, direct compression, wet granulation, and extrusion-spheronization. Wet granulation and extrusion-spheronization are the preferred techniques.

In the wet granulation method, tolterodine or pharmaceutically acceptable salt thereof and other auxiliary pharmaceutical ingredients are granulated with a granulating fluid (e.g., isopropyl alcohol, ethyl alcohol, and water) in a planetary mixer, high shear mixer, or fluidized bed granulator. The binder and organic acid solution is prepared in suitable vehicles, both can be mixed. Only binder or mixed solution of binder and organic acid can be used to granulate the powder mass. The wet granules are dried in an oven or fluidized bed dryer, and then sieved through a suitable screen to obtain free flowing granules. The resulting granules are blended with a suitable lubricant and glidant. These granules are compressed into solid dosage from of suitable size. These are further coated with the one or more hydrophobic and/or hydrophilic controlling agent(s) effective for the controlled release of tolterotidine or pharmaceutical acceptable salts thereof.

In extrusion-spheronization method, tolterodine and pharmaceutically acceptable salts is geometrically mixed with water insoluble inert material. The binder and organic acid solution is prepared in suitable vehicles, both can be mixed. Only binder or mixed solution of binder and organic acid is used to granulate the blend of active material with water insoluble inert material. Then wet mass is extrudated using suitable extruder and spheronized using spheronizer. Pellets or spheroids thus obtained are dried and coated with release controlling hydrophilic and/or hydrophobic controlling agent(s). The so-formed multiple units may be filled into hard shell capsules or compressed into a tablet.

The following examples illustrate various aspects of the present invention. These examples should not be construed as limiting the scope of the invention.

Example: 1

Sr. No.	Ingredient	Mg/Capsule
CORE		
1.	Tolterodine Tartarate	4.00
2.	Microcrystalline Cellulose	133.20
3.	HPMC	2.80
4.	Purified Water	Q.S.
	Total:	140.00
CONTROLLED RELEASE COATING		
1.	Ethyl Cellulose	9.80
2.	HPMC	4.20
3.	Triethyl Citrate	Q.S.
4.	Talc	4.60
5.	Isopropyl Alcohol	Q.S.
6.	Dichloromethane	Q.S.

Brief Manufacturing Procedure:

1. Mix Tolterodine Tartarate geometrically with Microcrystalline Cellulose (sifted through 40 mesh) and load in RMG.
2. Prepare HPMC solution in suitable quantity of water.

3. Granulate the powder mass of step 1 with binder solution of step 2.
4. Extrudate the wet mass through 1 mm sieve using extruder and spheronized using spheronizer.
5. Dry the pellets at temperature of 60°C in FBD. Sized to suitable fraction.
6. Prepare the controlled release solution in the organic solvents.
7. Coat pellets with sustained release coating in FBP to get the desired build up.

Example 2:

Sr. No.	Ingredient	Mg/Capsule
	CORE	
1.	Tolterodine Tartarate	4.00
2.	Microcrystalline Cellulose	128.70
3	Tartaric acid	4.5
4	HPMC	2.80
5	Purified Water	Q.S.
	Total:	140.00
	CONTROLLED RELEASE COATING	
1.	Ethyl Cellulose	9.80
2.	HPMC	4.20
3.	Triethyl Citrate	Q.S.
4.	Talc	4.60
5.	Isopropyl Alcohol	Q.S.
6.	Dichloromethane	Q.S.

Brief Manufacturing Procedure:

1 Mix Tolterodine Tartarate geometrically with Microcrystalline Cellulose (sifted through 40 mesh) and load in RMG.

2 Prepare HPMC solution in suitable quantity of water.

3 Tartaric acid was dissolved in suitable quantity of water.

4 Mix Solution of step 2 and 3

5 Granulate the powder mass of step 1 with solution of step 4

6 Extrudate the wet mass through 1 mm sieve using extruder and spheronized using spheronizer.

7 Dry the pellets at temperature of 60°C in FBD. Sized to suitable fraction.

8 Prepare the controlled release solution in the organic solvents.

9 Coat pellets with sustained release coating in FBP to get the desired build up.

Example 3:

Sr. No.	Ingredient	Mg/Capsule
	CORE	
1.	Tolterodine	4.00
2.	Microcrystalline Cellulose	133.20
3.	HPMC	2.80
4.	Purified Water	Q.S.
	Total:	140.00
	CONTROLLED RELEASE COATING	
1.	Ethyl cellulose	168.00
2.	HPMC	3.80
3.	Triacetin	QS
4.	Water	QS

1 Mix Tolterodine geometrically with Microcrystalline Cellulose and HPMC (sifted through 40 mesh) and load in RMG.

2 Granulate the powder mass of step 1 with purified water.

3 Dry the granules of step 2 in a suitable dryer

4 Lubricate the granules and compressed into solid dosage form

5 Prepare the controlled release solution in the suitable solvents.

6 Coat solid dosage form with controlled release coating to get desired the build up.

CLAIMS

1. A controlled release pharmaceutical composition containing a core comprising tolterodine or pharmaceutically acceptable salts and auxiliary excipients and a single coating layer comprising rate controlling agents(s).

2. A controlled release pharmaceutical composition of claim 1, containing an immediate release core wherein the said core comprises tolterodine or pharmaceutically acceptable salts thereof, water insoluble inert material with one or more auxiliary pharmaceutical excipients and a single coating layer comprising rate controlling hydrophobic and/or hydrophilic agents(s).

3. A controlled release pharmaceutical composition of claim 2, wherein water insoluble inert material comprises cellulose or its derivatives.

4. A controlled release pharmaceutical composition of claim 3, wherein the cellulose derivative is microcrystalline cellulose.

5. A controlled release pharmaceutical composition of claim 2, wherein auxiliary pharmaceutical excipients further comprise a binder.

6. A controlled release pharmaceutical composition of claim 5, wherein the binder is a cellulose or its derivative.

7. A controlled release pharmaceutical composition of claim 6, wherein said binder is selected from the group consisting of hydroxypropyl methyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose or mixtures thereof.

8. A controlled release pharmaceutical composition of claim 2, wherein the hydrophobic release controlling agent(s) employed for coating comprise(s) of polyvinyl acetate dispersion, ethyl cellulose, cellulose acetate, cellulose propionate (lower, medium or higher molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, poly (methyl methacrylate), poly (ethyl methacrylate), poly (butyl methacrylate), poly (isobutyl methacrylate), and poly (hexyl methacrylate), poly (isodecyl methacrylate), poly (lauryl methacrylate), poly (phenyl methacrylate), poly (methyl acrylate), poly (isopropyl acrylate), poly (isobutyl acrylate), poly (octadecyl acrylate), waxes such as beeswax, carnauba wax, paraffin wax, microcrystalline wax, and. ozokerite; fatty alcohols such as cetostearyl alcohol, stearyl alcohol, cetyl alcohol and myristyl alcohol, and fatty acid esters such as glyceryl monostearate; glycerol monooleate, acetylated monoglycerides, tristearin, tripalmitin, cetyl esters wax, glyceryl palmitostearate, glyceryl behenate, and hydrogenated vegetable oils.

9. A controlled release pharmaceutical composition of claim 2, wherein the hydrophilic release controlling agent(s) for coating is selected from the group comprising of hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), polyethylene oxide, polyvinyl alcohol, polyvinylpyrrolidone, xanthan gum, guar gum, chitosan and its derivatives, carbomer, carrageenan, carboxymethyl cellulose, sodium alginate, polyglycolized glycerides, polyethylene glycol, or mixtures thereof.

10. A controlled release pharmaceutical composition comprising tolterodine or pharmaceutically acceptable salts thereof wherein the core comprises tolterodine or pharmaceutically acceptable salts thereof and auxiliary excipients and a single coating layer comprising rate controlling agents(s). wherein said composition further comprises dissolution enhancing agent(s).

11. A controlled release pharmaceutical composition of claim 10, wherein dissolution enhancing agent(s) is an organic acid.

12. A controlled release pharmaceutical composition of claim 11, wherein dissolution enhancing agent(s) is selected from the group consisting of ascorbic acid, succinic acid, malonic acid, oxalic acid, tartaric acid, fumaric acid, adipic acid, glucono delta-lactone and malic acid.