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(54) Title: CONTROLLED RELEASE PHARMACEUTICAL COMPOSITIONS OF TOLTERODINE AND PROCESSES FOR THEIR PREPARATION

(57) Abstract: The technical field of the present invention pertains to controlled release pharmaceutical composition of tolterodine and processes for the preparation of multiple unit pharmaceutical composition of tolterodine. The controlled release pharmaceutical composition of tolterodine 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.

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CONTROLLED RELEASE PHARMACEUTICAL COMPOSITIONS OF TOLTERODINE AND PROCESSES FOR THEIR PREPARATION

Technical Field of the Invention

The technical field of the present invention pertains to controlled release pharmaceutical composition of tolterodine and processes for the preparation of multiple unit pharmaceutical composition of tolterodine.

Background of the Invention

About 5-10% of the adult population suffers from overactive or unstable urinary bladder, often also referred to as urinary incontinence. The symptoms of an unstable or overactive bladder include urge incontinence, urgency and urinary frequency. The prevalence of overactive bladder, particularly urge incontinence, increases with age. 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. The drug of choice for these conditions for a long time has been oxybutynin.

Recently, however, an improved muscarinic receptor antagonist, tolterodine, (R) N, N-diisopropyl-3- (2-hydroxy-5-methylphenyl)-3-phenylpropanamine, has been marketed for the treatment of urge incontinence and other symptoms of unstable or overactive urinary bladder. Both tolterodine and its major, active metabolite, the 5-hydroxymethyl derivative of tolterodine, which significantly contributes to the therapeutic effect, have considerably fewer side-effects than oxybutynin, especially regarding the tendency to cause dry mouth. While tolterodine is equipotent as oxybutynin in the bladder, its affinity for muscarinic receptors of the salivary gland is eight times lower than that of oxybutynin.

The currently marketed administration form of tolterodine is a film coated tablet containing 1 mg or 2 mg of tolterodine L-tartrate for immediate release in the gastrointestinal tract, the recommended dosage usually being 2 mg twice a day.

Tolterodine tartrate is also marketed by Pharmacia as DETROL LA extended release capsules. The capsules contain either 2 or 4 mg of the active ingredient.

PCT application WO 00/12069 discloses treatment of overactive bladder by the administration of a controlled release formulation that is purported to deliver tolterodine, a tolterodine-related compound, or a pharmacologically acceptable salt thereof such that a substantially constant serum level of the active moiety or moieties is maintained for at least 24 hours.

PCT application WO 00/27364 relates to a formulation containing controlled release beads, and to a method of preparing the beads. These beads include: (i) a core unit of water-soluble or water-insoluble polymer; (ii) a first layer on the core unit of a substantially water-insoluble polymer; (iii) a second layer covering the first layer and containing the active ingredient and (iii) a third layer on the second layer of polymer effective for controlled release of active ingredient. The first layer is adapted to control water penetration into the core.

In light of the above background, it will be appreciated by those versed in the pharmaceutical dispensing art that a need exists for a controlled release pharmaceutical composition that can deliver tolterodine in a controlled, extended dose. At the same time, the composition must be capable of being formulated by employing a simple process that involves fewer layering steps.

Summary of the Invention

In one general aspect there is provided a 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.

Embodiments of the controlled release pharmaceutical composition may include one or more of the following features. For example, the core may include one or more of an inert insoluble core, an inert soluble or swellable core, and a commercially available inert core material. The insoluble inert core may include one or more of dicalcium phosphate and microcrystalline cellulose. The soluble or swellable inert core may be one or more of glucose, mannitol, lactose, xylitol, dextrose, and sucrose. The commercially available inert core material may be one or more of sugar sphere, non-pareil seed, and celphere.

The tolterodine may be one or more of tolterodine base, the (S)-enantiomer, the racemate, the active 5-hydroxymethyl metabolites, a prodrug form, a pharmaceutically acceptable salt thereof, and the tartarate salt thereof.

The hydrophilic polymer may be one or more of polyvinylpyrrolidone, a polyalkylene glycol, polyethylene glycol, gelatin, polyvinyl alcohol, starch and derivatives thereof, cellulose derivatives, hydroxypropyl methylcellulose, hydroxypropyl cellulose, carboxymethyl cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, carboxyethyl cellulose, carboxymethylhydroxyethyl cellulose, acrylic acid polymers, polymethacrylates, or any pharmaceutically acceptable polymer. The ratio of tolterodine to hydrophilic polymer in the first layer may be between about 1:20 to 20:1.

The polymers in the second layer may be one or more of ethyl cellulose, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, polymethacrylates, and mixtures thereof.

The second layer may further include one or more modifiers. The modifiers may be one or more of hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polymers with pH-dependent solubility, such as cellulose acetate phthalate or ammonio-methacrylate copolymer and methacrylic acid copolymer, and mixtures thereof. The second layer may be from about 2 to 50% of the formulation.

Either or both of the first layer and the second layer may include one or more additional pharmaceutical excipients, which may be plasticizers and/or lubricants. The additional pharmaceutical excipients may be one or more of plasticizers and lubricants. The plasticizers may be one or more of propylene glycol, triethylene glycol, oleic acid, ethyleneglycol monoleate, triethyl citrate, triacetin, diethyl phthalate, glyceryl monostearate, dibutyl sebaccate, acetyl triethylcitrate, and castor oil. The lubricants may be one or more of talc, anhydrous colloidal silica, magnesium stearate, glyceryl monostearate, and beeswax.

The coated units may be filled into hard gelatin capsules or compressed into tablets. The coated units may further include a non-functional coating.

The controlled release pharmaceutical composition may show the following in vitro dissolution profile for tolterodine in 900 ml of Phosphate buffer pH 6.8 when tested using USP Apparatus I at 100 rpm:

not more than about 50 percent released in 1 hour;

between about 25 and about 85 percent released in 3 hours; and

not less than about 50 percent released in 7 hours.

In another general aspect there is provided a process for preparing a controlled release pharmaceutical composition of tolterodine. The process includes (a) providing a core; (b) applying a first layer to the core, the first layer comprising tolterodine and one or more hydrophilic polymers; and (c) applying a second layer onto the first layer to form a coated unit, the second layer comprising one or more polymers effective for controlled release of the tolterodine.

Embodiments of the process may include one or more of the following features or those described above. For example, the ratio of tolterodine to hydrophilic polymer in the first layer may be from about 1:20 to 20:1. The core may be coated with tolterodine in a powder form or sprayed as a solution or dispersion. The polymers in the second layer may be one or more of ethyl cellulose, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, polymethacrylates, and mixtures thereof.

The second layer may further include one or more modifiers. The modifiers may be one or more of hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polymers with pH-dependent solubility, such as cellulose acetate phthalate or ammonio-methacrylate copolymer and methacrylic acid copolymer, and mixtures thereof.

The process may further include applying the polymers of the second layer as a solution or dispersion in a solvent. The solvent may further include one or more of water, alcohols, ethyl alcohol, isopropyl alcohol; ketones, acetone, ethylmethylketone; halogenated hydrocarbons, dichloroethane, trichloroethane and mixtures thereof.

The process may further include drying the coated core and/or drying the coated unit. The process may further include filling the coated units into hard gelatin capsules or compressing the coated units into tablets. The process may further include applying a

non-functional coating to the coated units. The second layer may constitute about 2% to about 50% of the formulation. Either or both of the first coating layer and the second coating layer may further include one or more pharmaceutically inert excipients.

The controlled release pharmaceutical composition may show the following in vitro dissolution profile for tolterodine in 900 ml Phosphate buffer pH 6.8 when tested using USP Apparatus I at 100 rpm:

(a) not more than about 50 percent released in 1 hour;

(b) between about 25 and about 85 percent released in 3 hours; and

(c) not less than about 50 percent released in 7 hours.

In another general aspect there is provided a method of treating an overactive bladder with symptoms of one or more of urinary frequency, urgency and urge incontinence. The method includes administering a 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 effective for controlled release of the tolterodine from the first layer.

Embodiments of the method may include any one or more of the features described above.

The pharmaceutical composition may further include at least one active ingredient selected from amongst oxybutynin, α-blockers and 5 α-reductase inhibitors.

The details of various embodiments of the inventions are set forth in the accompanying description below. Other features and advantages of the inventions will be apparent from the description and the claims.

Detailed Description of the Invention

As described in detail herein, the inventors have discovered that controlled release pharmaceutical compositions of tolterodine may be formulated by layering the core directly with the active ingredient dispersed in hydrophilic polymer, without the need for a seal-coat or an extra polymer coat between the core and the active layer.

The term "multiple unit pharmaceutical composition" indicates a pharmaceutical composition that includes one or more individual coated units contained in the formulation in such a form that the individual units will be available from the formulation upon disintegration of the formulation in the stomach. The multiple unit pharmaceutical composition or formulation may be a capsule or a tablet that disintegrates in the stomach to give individual units. The multiple units may be formulated as granules, pellets or beads.

The inert core may be selected from one or more of pharmaceutically inert insoluble or soluble or swellable materials. Alternatively, the inert core may also be a commercially available product. The insoluble inert cores are composed of dicalcium phosphate, microcrystalline cellulose and the like, either alone or in combination. The soluble inert cores are composed of sugar selected from glucose, mannitol, lactose, xylitol, dextrose, sucrose and the like. Commercially available inert cores are selected from sugar sphere, non-pareil seed, celphere and the like. The cores may be of any geometric shape, though spheres are preferred for the ease of uniform coating.

The layer that includes the active ingredient, i.e., the first layer, may contain the active ingredient, e.g., tolterodine, with a polymer. The polymer is usually hydrophilic but may be water-soluble or water-insoluble. Exemplary polymers to be used in the first layer containing the active ingredient are hydrophilic polymers such as polyvinylpyrrolidone; polyalkylene glycol such as polyethylene glycol, gelatin, polyvinyl alcohol, starch and derivatives thereof; cellulose derivatives, such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, carboxymethyl cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, carboxyethylcellulose, carboxy-methyl-hydroxy-ethyl cellulose, acrylic acid polymers, polymethacrylates, or any other pharmaceutically acceptable polymer.

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 such as tartarate. The tolterodine used in the pharmaceutical compositions described herein can be prepared by any known method, such as, for example, using either of the procedures disclosed in U.S. Patent No. 5,382,600 or U.S. Patent No. 5,922,914. Both of these patents are incorporated herein in their entirety by reference.

The ratio of active ingredient to hydrophilic polymer in the first layer may be in the range of 1:20 to 20:1 (w/w).

The core particles may be coated with the first layer by coating with the active ingredient dispersed in the hydrophilic polymers by powder layering technique, i.e., the active ingredient is applied to the core in dry form as powder. Alternatively, the polymer may be sprayed onto the cores as a solution or dispersion in such a way that solvent, preferably water, is evaporated, and the polymer is applied to the cores together with the active ingredient, i.e., forming a homogenous dispersion. The pharmaceutically active ingredient is applied onto the core material preferably by spraying an aqueous/non aqueous solution/suspension in a fluidized bed with a Wurster or top spray technique.

The drug layered cores may be coated with a second layer that is a polymeric layer for modifying and controlling the drug release. Suitable polymers may be selected from water-insoluble polymers or polymers with pH dependent or independent solubility, for example, ethyl cellulose, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, polymethacrylates, or mixtures thereof. Optionally, the controlled release layer may include, in addition to the above polymers, one or more modifiers with different solubility characteristics. These modifiers are used to adjust the permeability, and thereby the release rate, of the controlled release layer.

Exemplary polymers that may be used as a modifier include: hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polymers with pH-dependent solubility, such as cellulose acetate phthalate or ammonio methacrylate copolymer and methacrylic acid copolymer, or mixtures thereof.

Additives also may be included in the controlled release layer, if desired. Suitable additives include sucrose, lactose and pharmaceutical grade surfactants.

The polymers may be applied as a solution or dispersion in a solvent. The solvent may be selected from water, alcohols such as ethyl alcohol or isopropyl alcohol; ketones such as acetone or ethylmethylketone; halogenated hydrocarbons such as dichloroethane and trichloroethane or mixtures thereof.

Any conventional coating equipment may be employed to facilitate coating, including equipment such as centrifugal fluidized bed coating apparatus and pan coating apparatus. The coating may be applied using a conventional coating pan, a spray coater, a

rotating perforated pan, or an automated system. The coated multiple units may be dried in an oven or in a fluidized bed.

The coating may constitute about 2-50% w/w of the formulation. The coating layers may additionally contain pharmaceutically inert excipients such as plasticizers and lubricants.

Suitable plasticizers include propylene glycol, triethylene glycol, oleic acid, ethyleneglycol monoleate, triethyl citrate, triacetin, diethyl phthalate, glyceryl monostearate, dibutyl sebacate, acetyl triethylcitrate , castor oil and the like. Suitable lubricants include talc, anhydrous colloidal silica, magnesium stearate, glyceryl monostearate, beeswax and the like.

Optionally, the multiple units may include a non-functional coating over the second layer.

The coated multiple units are filled into hard gelatin capsules or compressed into tablets that disintegrate in the stomach to make available a multiplicity of individually coated units.

The controlled-release composition shows the following in vitro dissolution profile for tolterodine in 1000 ml Phosphate buffer pH 6.8, when tested using USP Apparatus I at 100 rpm:

(a) not more than 50 percent released in 1 hour.

(b) between 25 and 85 percent released in 3 hours.

(c) not less than 50 percent released in 7 hours.

The following examples illustrate various aspects of the present invention. These examples are for illustration only and should not be construed as limiting the scope of the invention.

EXAMPLE 1

	Ingredients	mg/Capsule
Core	Non pareil beads	140.0
First layer	Tolterodine tartrate	4.0
	Hydroxypropyl methyl cellulose	8.0
Second layer	Ethyl cellulose	9.73
	Hydroxypropyl methyl cellulose	2.43
Total		164.0

Process:

Hydroxypropyl methylcellulose and tolterodine tartrate were dissolved in water and the solution obtained was sprayed onto non-pareil beads and the coating was dried to form drug coated beads. The drug coated beads were further coated with a solution of ethyl cellulose and hydroxypropyl methylcellulose in a mixture of isopropyl alcohol and water (83:17). The resulting coated beads were dried and filled into capsules.

Table 1 shows the dissolution data of tolterodine tartrate 4.0 mg capsules prepared as per composition of Example 1. The dissolution was carried out in 1000 ml of phosphate buffer pH 6.8 using USP Apparatus Type I (basket) at a speed of 100 rpm.

Table 1: Comparative in vitro release of the tolterodine extended release capsules of Example 1 and Detrol LA capsules (4 mg; marketed by Pharmacia)

Time (hrs.)	Cumulative Percent of tolterodine released (%)	
	Capsules of Example 1	Detrol LA capsules
1	12	13
2	35	33
4	62	69
6	76	91
8	83	99
10	90	100

EXAMPLE 2

	Ingredients	**mg/Capsule**
Core	Non pareil beads	140.0
First layer	Tolterodine tartrate	4.0
	Hydroxypropyl methyl cellulose	8.0
Second layer	Ethyl cellulose	15.64
	Hydroxypropyl methyl cellulose	4.36
Total		172.0

Process:

The process followed is similar to that followed in Example 1.

EXAMPLE 3

	Ingredients	**mg/Capsule**
Core	Microcrystalline cellulose	140.0
First layer	Tolterodine tartrate	4.0
	Hydroxypropyl methyl cellulose	6.0
Second layer	Ethyl cellulose	10.34
	Hydroxypropyl methyl cellulose	2.58
Total		197.0

Process:

Hydroxypropyl methylcellulose and tolterodine tartrate were dissolved in water and the solution obtained was sprayed onto microcrystalline cellulose beads and the coating was dried for form drug coated beads. The drug coated beads were further coated with a dispersion of ethyl cellulose and hydroxypropyl methylcellulose in a mixture of isopropyl alcohol and water. The coated beads were dried, lubricated and filled into capsules.

While several particular forms of the invention have been illustrated and described, it will be apparent that various modifications and combinations of the invention detailed in the text can be made without departing from the spirit and scope of the invention. For example, polyvinyl pyrrolidone, carboxymethyl cellulose, hydroxypropyl cellulose can be

used as hydrophilic polymers for the first layer. Accordingly, it is not intended that the invention be limited, except as by the appended claims.

We claim:

1. A controlled release pharmaceutical composition of tolterodine, the pharmaceutical composition comprising one or more coated units, each coated unit comprising:
   a. a core;
   b. a first layer surrounding at least a portion of the core, the first layer comprising tolterodine and one or more hydrophilic polymers; and
   c. a second layer surrounding at least a portion of the first layer and comprising one or more polymers effective for controlled release of the tolterodine from the first layer.

2. The composition according to claim 1 wherein the core comprises one or more of inert insoluble core, inert soluble or swellable core, and commercially available inert core material.

3. The composition according to claim 2 wherein the insoluble inert core comprises one or more of dicalcium phosphate and microcrystalline cellulose.

4. The composition according to claim 2 wherein the soluble or swellable inert core comprises one or more of glucose, mannitol, lactose, xylitol, dextrose, and sucrose.

5. The composition according to claim 2 wherein the commercially available inert core material comprises one or more of sugar sphere, non-pareil seed, and celphere.

6. The composition according to claim 1 wherein the tolterodine comprises one or more of tolterodine base, the (S)-enantiomer, the racemate, the active 5-hydroxymethyl metabolites, a prodrug form, a pharmaceutically acceptable salt thereof, and the tartarate salt thereof.

7. The composition according to claim 1 wherein the hydrophilic polymer comprises one or more of polyvinylpyrrolidone, a polyalkylene glycol, polyethylene glycol, gelatin, polyvinyl alcohol, starch and derivatives thereof, cellulose derivatives, hydroxypropyl methylcellulose, hydroxypropyl cellulose, carboxymethyl cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, carboxyethyl cellulose, carboxymethylhydroxyethyl cellulose, acrylic acid polymers, polymethacrylates, or any pharmaceutically acceptable polymer.

8. The composition according to claim 1 wherein the ratio of tolterodine to hydrophilic polymer in the first layer comprises between about 1:20 to 20:1.

9. The composition according to claim 1 wherein the polymers in the second layer comprise one or more of ethyl cellulose, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, polymethacrylates, and mixtures thereof.

10. The composition according to claim 1 wherein the second layer further comprises one or more modifiers.

11. The composition according to claim 10 wherein the modifiers comprise one or more of hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polymers with pH-dependent solubility, cellulose acetate phthalate, ammonio-methacrylate copolymer, methacrylic acid copolymer, and mixtures thereof.

12. The composition according to claim 1 wherein the second layer comprises from about 2 to 50% of the formulation.

13. The composition according to claim 1 wherein either or both of the first layer and the second layer comprise one or more additional pharmaceutical excipients.

14. The composition according to claim 13 wherein the additional pharmaceutical excipients comprise one or more of plasticizers and lubricants.

15. The composition according to claim 14 wherein the plasticizers comprise one or more of propylene glycol, triethylene glycol, oleic acid, ethyleneglycol monoleate, triethyl citrate, triacetin, diethyl phthalate, glyceryl monostearate, dibutyl sebaccate, acetyl triethylcitrate, and castor oil.

16. The composition according to claim 14 wherein the lubricants comprise one or more of talc, anhydrous colloidal silica, magnesium stearate, glyceryl monostearate, and beeswax.

17. The composition according to claim 1 wherein the coated units are filled into hard gelatin capsules or compressed into tablets.

18. The composition according to claim 1 wherein the coated units further comprise a non-functional coating.

19. The composition according to claim 1 wherein the controlled release pharmaceutical composition shows the following in vitro dissolution profile for tolterodine in 900 ml of Phosphate buffer pH 6.8 when tested using USP Apparatus I at 100 rpm:

not more than about 50 percent released in 1 hour;

between about 25 and about 85 percent released in 3 hours; and

not less than about 50 percent released in 7 hours.

20. A process for preparing a controlled release pharmaceutical composition of tolterodine, the process comprising:

(a) providing a core;

(b) applying a first layer to the core, the first layer comprising tolterodine and one or more hydrophilic polymers; and

(c) applying a second layer onto the first layer to form a coated unit, the second layer comprising one or more polymers effective for controlled release of the tolterodine.

21. The process according to claim 20 wherein the ratio of tolterodine to hydrophilic polymer in the first layer comprises from about 1:20 to 20:1.

22. The process according to claim 20 wherein the core is coated with tolterodine in a powder form or sprayed as a solution or dispersion.

23. The process according to claim 20 wherein the polymers in the second layer comprise one or more of ethyl cellulose, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, polymethacrylates, and mixtures thereof.

24. The process according to claim 20 wherein the second layer further comprises one or more modifiers.

25. The process according to claim 24 wherein the modifiers comprise one or more of hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polymers with pH-dependent solubility, cellulose acetate phthalate, ammonio-methacrylate copolymer, methacrylic acid copolymer, and mixtures thereof.

26. The process according to claim 20 further comprising applying the polymers of the second layer as a solution or dispersion in a solvent.

27. The process according to claim 26 wherein the solvent comprises one or more of water, alcohols, ethyl alcohol, isopropyl alcohol; ketones, acetone, ethylmethylketone; halogenated hydrocarbons, dichloroethane, trichloroethane and mixtures thereof.

28. The process according to claim 20 further comprising drying the coated core.

29. The process according to claim 20 further comprising drying the coated unit.

30. The process according to claim 20 wherein the second layer constitutes about 2% to about 50% of the formulation.

31. The process according to claim 25 wherein either or both of the first coating layer and the second coating layer further comprises one or more pharmaceutically inert excipients.

32. The process according to claim 20 further comprising filling the coated units into hard gelatin capsules or compressing the coated units into tablets.

33. The process according to claim 20 further comprising applying a non-functional coating to the coated units.

34. The process according to claim 20 wherein the controlled release pharmaceutical composition shows the following in vitro dissolution profile for tolterodine in 900 ml Phosphate buffer pH 6.8 when tested using USP Apparatus I at 100 rpm:

(a) not more than about 50 percent released in 1 hour;

(b) between about 25 and about 85 percent released in 3 hours; and

(c) not less than about 50 percent released in 7 hours.

35. A method of treating an overactive bladder with symptoms of one or more of urinary frequency, urgency and urge incontinence, the method comprising administering a controlled-release pharmaceutical compositions of tolterodine, the pharmaceutical composition comprising one or more coated units, each coated unit comprising:

a core;

a first layer surrounding at least a portion of the core, the first layer comprising tolterodine and one or more hydrophilic polymers; and

a second layer surrounding at least a portion of the first layer and comprising one or more polymers effective for controlled release of the tolterodine from the first layer.

INTERNATIONAL SEARCH REPORT

IB2004/001789

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/62 A61K1/137

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/34139 A (STROEMBOM JAN ; HALLEN BENGT (SE); OLSSON BIRGITTA (SE); PHARMACIA AB) 17 May 2001 (2001-05-17) page 5, line 9 - line 13 page 6, line 15 - line 16 page 10 claims 1,17	1-35
Y	WO 00/12069 A (KREILGAARD BO ; HOECK ULLA (DK); KRISTENSEN HELLE (DK); ORUP JACOBSEN) 9 March 2000 (2000-03-09) page 6, line 30 - page 7, line 6 example 1 claim 1	1-35

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 October 2004	21/10/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Sindel, U

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 783 215 A (ARWIDSSON HANS ET AL) 21 July 1998 (1998-07-21) column 3, line 37 - line 46 examples 1,8	1-35
A	OLSSON B ET AL: "MULTIPLE DOSE PHARMACOKINETICS OF A NEW ONCE DAILY EXTENDED RELEASE TOLTERODINE FORMULATION VERSUS IMMEDIATE RELEASE TOLTERODINE" CLINICAL PHARMACOKINETICS, LEA & FEBIGER, PHILADELPHIA, PA, US, vol. 40, no. 3, 2001, pages 227-235, XP001146883 abstract	1-35

INTERNATIONAL SEARCH REPORT

PCT/IB2004/001789

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: -
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 35 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

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