David E. De Lorenzi
Sheila F. McShane
GIBBONS P.C.
One Gateway Center
Newark, New Jersey 07102
Telephone: (973) 596-4500
Facsimile: (973) 596-0545

Dimitrios T. Drivas
Jeffrey J. Oelke
Adam Gahtan
James S. Trainor, Jr.
WHITE & CASE LLP
1155 Avenue of the Americas
New York, New York 10036
Telephone: (212) 819-8200
Facsimile: (212) 354-8113

Attorneys for Plaintiffs Pfizer Inc., Pharmacia & Upjohn Company LLC, and Pfizer Health AB

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

PFIZER INC., PHARMACIA & UPJOHN COMPANY LLC, and PFIZER HEALTH AB, Plaintiffs, v. SANDOZ, INC., Defendant.	Civil Action No.: ____ ***Document electronically filed.*** **COMPLAINT**

Plaintiffs Pfizer Inc., Pharmacia & Upjohn Company LLC, and Pfizer Health AB (collectively, "Pfizer"), by their attorneys, Gibbons P.C., and White & Case LLP, for their Complaint against Defendant Sandoz, Inc., allege:

THE PARTIES

1. Plaintiff Pfizer Inc., is a corporation organized and existing under the laws of the State of Delaware, having a place of business at 235 East 42nd Street, New York, New York.

2. Plaintiff Pharmacia & Upjohn Company LLC is a corporation organized and existing under the laws of the State of Delaware, having a place of business at 7000 Portage Road, Kalamazoo, Michigan. Pfizer Inc., is the ultimate parent of Pharmacia & Upjohn Company LLC.

3. Plaintiff Pfizer Health AB is a company organized and existing under the laws of Sweden, having a place of business at SE-112 87, Stockholm, Sweden. Pfizer Inc., is the ultimate parent of Pfizer Health AB.

4. Upon information and belief, Defendant Sandoz, Inc. ("Sandoz") is a corporation organized and existing under the laws of the State of Colorado, having a principal place of business at 506 Carnegie Center, Suite 400, Princeton, New Jersey.

JURISDICTION AND VENUE

5. This Court has exclusive subject matter jurisdiction over this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

6. This Court has personal jurisdiction over Sandoz by virtue of, inter alia: (1) its presence in New Jersey, (2) its systematic and continuous contacts with New Jersey, including its substantial and ongoing sale of generic drugs in New Jersey; and (3) its prior

consent to personal jurisdiction in this judicial district.

7. Venue is proper in this District pursuant to 28 U.S.C. §§ 1391 and 1400(b).

U.S. Patent No. 6,630,162

8. On October 7, 2003, the United States Patent and Trademark Office issued United States Patent No. 6,630,162 (the "'162 patent"), entitled "Pharmaceutical Formulation and its Use." At the time of its issue, the '162 patent was assigned to Pharmacia AB. Pfizer Health AB currently holds title to the '162 patent. A copy of the '162 patent is attached hereto as Exhibit A.

9. The '162 patent is directed to and claims, inter alia, an oral pharmaceutical formulation for administering *tolterodine* or *tolterodine*-related compounds, as well as a method of treatment comprising administering a therapeutically effective amount of such a formulation.

U.S. Patent No. 6,770,295

10. On August 3, 2004, the United States Patent and Trademark Office issued United States Patent No. 6,770,295 (the "'295 patent"), entitled "Therapeutic Formulation for Administering Tolterodine with Controlled Release." At the time of its issue, the '295 patent was assigned to Pharmacia & Upjohn AB. Pfizer Health AB currently holds title to the '295 patent. A copy of the '295 patent is attached hereto as Exhibit B.

11. The '295 patent is directed to and claims, inter alia, an improved method of treating unstable or overactive bladder, as well as a formulation therefor.

Detrol® LA

12. Pharmacia & Upjohn Company LLC holds an approved New Drug Application (the "Detrol® LA NDA") for *tolterodine tartrate* extended-release capsules, in 2 and

4 mg dosages, which are sold by Pfizer Inc., under the trade name Detrol® LA.

13. Pursuant to 21 U.S.C. § 355(b)(1), and attendant United States Food and Drug Administration ("FDA") regulations, the '162 and '295 patents are listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), with respect to Detrol® LA.

Sandoz's ANDA

14. Sandoz submitted Abbreviated New Drug Application No. 90-332 (the "Sandoz ANDA") to the FDA, pursuant to 21 U.S.C. §§ 355(j), seeking approval to market *tolterodine tartrate* extended-release capsules in a 4 mg dosage form (the "Sandoz Product").

15. The Sandoz ANDA refers to and relies upon the Detrol® LA NDA and contains data that, according to Sandoz, demonstrate the bioequivalence of the Sandoz Product and Detrol® LA.

16. Pfizer received from Sandoz a letter and attached memorandum, dated March 19, 2008 (collectively, the "Sandoz Notification"), stating that Sandoz had included in its ANDA a certification, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), that each of the '162 and '295 patents is invalid, unenforceable, or would not be infringed by the manufacture, use, or sale of the Sandoz Product (the "Paragraph IV Certification").

COUNT FOR INFRINGEMENT OF U.S. PATENT NO. 6,630,162

17. Pfizer hereby realleges and incorporates by reference the allegations of paragraphs 1-16 of this Complaint.

18. Sandoz has infringed the '162 patent, pursuant to 35 U.S.C. § 271(e)(2)(A), by submitting ANDA No. 90-332, by which Sandoz seeks approval from the FDA to engage in the commercial manufacture, use, and/or sale of the Sandoz Product prior to the

expiration of the '162 patent.

19. If Sandoz commercially makes, uses, offers to sell, and/or sells the Sandoz Product within the United States, or imports the Sandoz Product into the United States, or induces or contributes to any such conduct during the term of the '162 patent, it would further infringe the '162 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

20. Pfizer will be irreparably harmed if Sandoz is not enjoined from infringing the '162 patent. Pfizer does not have an adequate remedy at law.

COUNT FOR INFRINGEMENT OF U.S. PATENT NO. 6,770,295

21. Pfizer hereby realleges and incorporates by reference the allegations of paragraphs 1-16 of this Complaint.

22. Sandoz has infringed the '295 patent, pursuant to 35 U.S.C. § 271(e)(2)(A), by submitting ANDA No. 90-332, by which Sandoz seeks approval from the FDA to engage in the commercial manufacture, use, and/or sale of the Sandoz Product prior to the expiration of the '295 patent.

23. If Sandoz commercially makes, uses, offers to sell, and/or sells the Sandoz Product within the United States, or imports the Sandoz Product into the United States, or induces or contributes to any such conduct during the term of the '295 patent, it would further infringe the '295 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

24. Pfizer will be irreparably harmed if Sandoz is not enjoined from infringing the '295 patent. Pfizer does not have an adequate remedy at law.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs Pfizer Inc., Pharmacia & Upjohn Company LLC, and Pfizer Health AB pray for a judgment in their favor and against Defendant Sandoz, Inc., as follows:

A. That Sandoz has infringed U.S. Patent No. 6,630,162;

B. That Sandoz has infringed U.S. Patent No. 6,770,295;

C. That, pursuant to 35 U.S.C. § 271(e)(4)(B), Sandoz, its officers, agents, servants, and employees, and those persons in active concert or participation with any of them, are preliminarily and permanently enjoined from making, using, selling, or offering to sell the Sandoz Product within the United States, or importing the Sandoz Product into the United States prior to the expiration of the '162 and '295 patents;

D. That, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of ANDA No. 90-332 under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)) shall not be earlier than the latest of the expiration dates of the '162 and '295 patents, including any extensions;

E. That Plaintiffs be awarded monetary relief if Sandoz commercially makes, uses, sells, or offers to sell the Sandoz Product within the United States, or imports the Sandoz Product into the United States, prior to the expiration of either of the '162 and '295 patents, including any extensions, and that any such monetary relief be awarded to Plaintiffs with prejudgment interest;

F. That Plaintiffs be awarded reasonable attorneys' fees, costs, and expenses because this is an exceptional case under 35 U.S.C. § 285; and

G. That Plaintiffs be awarded such other relief as the Court deems just and proper.

Dated: June 24, 2010
Newark, NJ

Respectfully submitted,

By: s/ Sheila F. McShane

David E. DeLorenzi
Sheila F. McShane
GIBBONS P.C.
One Gateway Center
Newark, New Jersey 07102
Telephone: (973) 596-4500
Facsimile: (973) 596-0545

Attorneys for Plaintiffs Pfizer Inc., Pharmacia & Upjohn Company LLC, and Pfizer Health AB

OF COUNSEL:

Dimitrios T. Drivas
Jeffrey J. Oelke
Adam Gahtan
James S. Trainor, Jr.
WHITE & CASE LLP
1155 Avenue of the Americas
New York, New York 10036
Telephone: (212) 819-8200
Facsimile: (212) 354-8113

EXHIBIT A

US006630162B1

(12) **United States Patent**
Nilvebrant et al.

(10) **Patent No.: US 6,630,162 B1**
(45) **Date of Patent: *Oct. 7, 2003**

(54) **PHARMACEUTICAL FORMULATION AND ITS USE**

(75) Inventors: **Lisbeth Nilvebrant**, Bromma (SE); **Bengt Hallen**, Sollentuna (SE); **Birgitta Olsson**, Stenhamra (SE); **Jan Strombom**, Vattholm (SE); **Torkek Gren**, Kalamazoo, MI (US); **Anders Ringberg**, Stockholm (SE); **Martin Wikberg**, Kullavik (SE)

(73) Assignee: **Pharmacia AB**, Stockholm (SE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/708,428**

(22) Filed: **Nov. 9, 2000**

Related U.S. Application Data

(63) Continuation-in-part of application No. PCT/SE99/02052, filed on Nov. 11, 1999.
(60) Provisional application No. 60/202,862, filed on May 10, 2000.

(30) **Foreign Application Priority Data**

Mar. 9, 2000 (SE) 0000782

(51) **Int. Cl.**[7] **A61K 9/52**; A61K 9/54; A61K 9/26; A61K 9/16; A61K 9/22

(52) **U.S. Cl.** **424/458**; 424/457; 424/459; 424/461; 424/462; 424/468; 424/469; 424/490; 424/493; 424/494; 424/495

(58) **Field of Search** 424/457, 458, 424/459, 461, 462, 468, 469, 490, 493, 494, 495

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,382,600 A		1/1995	Jonsson et al.
5,559,269 A		9/1996	Johansson et al.

FOREIGN PATENT DOCUMENTS

EP	0061217		9/1982
WO	WO9323025		11/1993
WO	WO9601621		1/1996
WO	WO9612477		5/1996
WO	WO9629992		10/1996
WO	WO 98/03067	*	1/1998
WO	WO9803067		1/1998
WO	WO9811888		3/1998
WO	WO0012069		3/2000
WO	WO0027364		5/2000

OTHER PUBLICATIONS

Nilvebrant et al., *Euro. J. Pharmacology*, vol. 327 (1997) pp. 195–207.
Brynne et al., *Int'l J. Clin. Pharmacology and Therapeutics*, vol. 35, No. 7 (1997) pp. 287–295.
Nilvebrant et al., *Life Sciences*, vol. 60, Nos. 13/14 (1997) pp. 1129–1136.
Stahl et al., *Neurourology and Urodynamics*, vol. 14, (1995) pp. 647–655.

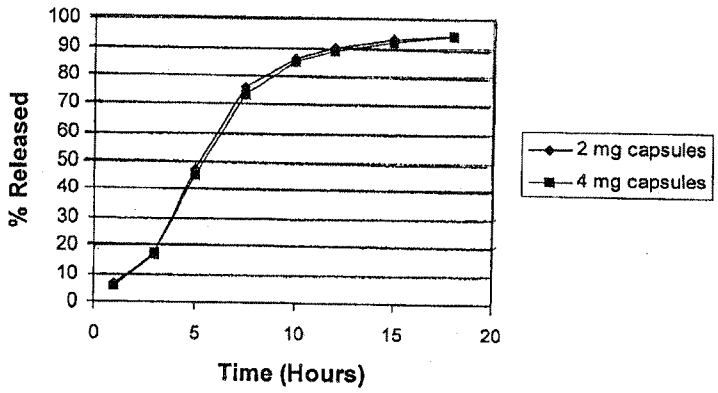
* cited by examiner

Primary Examiner—Thurman K. Page
Assistant Examiner—Todd D Ware
(74) *Attorney, Agent, or Firm*—Craig M. Bell

(57) **ABSTRACT**

The invention relates to a pharmaceutical formulation containing tolterodine or a tolterodine-related compound, or a pharmacologically acceptable salt thereof, as active ingredient, in which the formulation exhibits a controlled in vitro release of the active ingredient in phosphate buffer at pH 6.8 of not less than about 80% after 18 hours, and after oral administration to a patient is capable of maintaining a substantially constant serum level of the active moiety or moieties for 24 hours. The invention also relates to the use of the pharmaceutical formulation for treating overactive bladder and gastrointestinal disorders.

23 Claims, 1 Drawing Sheet



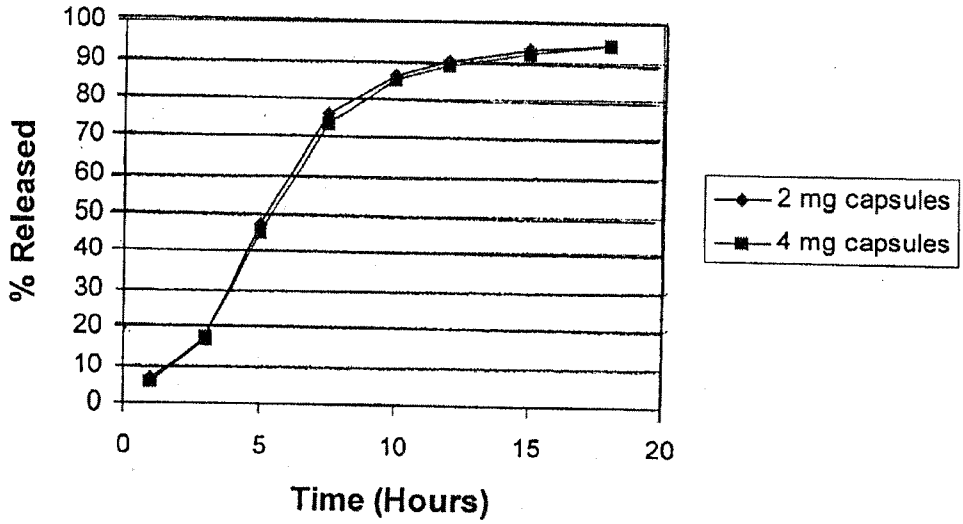

100
90
80
70
60
50
40
30
20
10
0
% Released
0
5
10
15
20
Time (Hours)
2 mg capsules
4 mg capsules

FIG. 1

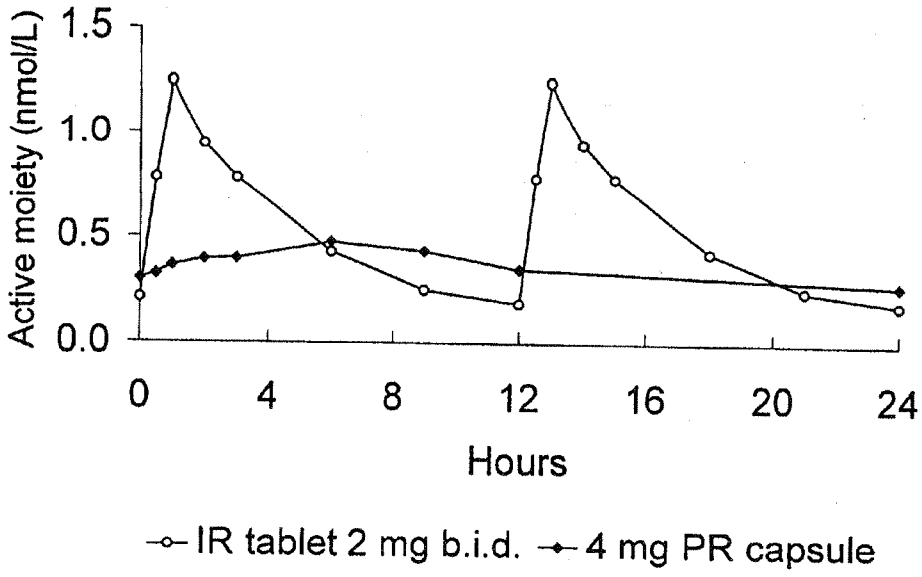

1.5
1.0
0.5
0.0
Active moiety (nmol/L)
0
4
8
12
16
20
24
Hours
IR tablet 2 mg b.i.d.
4 mg PR capsule

FIG. 2

PHARMACEUTICAL FORMULATION AND ITS USE

This application is a continuation-in-part of PCT international application No. PCT/SE99/02052 which has an international filing date of Nov. 11, 1999 and which designated the United States, the entire contents of which are hereby incorporated by reference. This application also claims priority under 35 U.S.C. 119(e) of U.S. Provisional No. 60/202,862, filed on May 10, 2000, the entire contents of which are also hereby incorporated by reference.

The present invention relates to a pharmaceutical formulation for administering tolterodine or a tolterodine-related compound, and to the medical use of such a formulation.

A substantial part (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 comprise urge incontinence, urgency and urinary frequency. The prevalence of overactive bladder, particularly of so-called 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 has for a long time 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 less side-effects than oxybutynin, especially regarding the propensity to cause dry mouth. While tolterodine is equipotent with oxybutynin in the bladder, its affinity for muscarinic receptors of the salivary gland is eight times lower than that of oxybutynin; see, for example, Nilvebrant, L., et al., European Journal of Pharmacology 327 (1997) 195–207. The selective effect of tolterodine in humans is described in Stahl, M. M. S., et al., Neurourology and Urodynamics 14 (1995) 647–655, and Bryne, N., International Journal of Clinical Pharmacology and Therapeutics, Vol. 35, No. 7 (1995) 287–295.

The currently marketed administration form of tolterodine is filmcoated tablets 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. While, as mentioned, the side-effects, such as dry mouth, are much lower than for oxybutynin, they still exist, especially at higher dosages.

Our co-pending international application PCT/SE99/01463 relates to the administration of tolterodine and tolterodine-related compounds through a controlled release formulation and is based on the finding that, contrary to the case of oxybutynin, the substantial elimination of peak serum levels of tolterodine and its active metabolite through controlled release of tolterodine for an extended period of time, such as through a once-daily administration form, while maintaining the desired effect on the bladder, indeed gives a significant reduction of the (already low) side-effects, particularly dry mouth, compared with those obtained for the same total dosage of immediate release tablets over the same period. In other words, eliminating the peak serum levels of the active moiety affects the adverse effects, and particularly dry mouth, more than the desired effect on the detrusor activity, simultaneously as the flattening of the serum concentration does not lead to loss of activity or increased incidence of urinary retention or other safety concerns. Thus, in addition to the convenience advantage of controlled release administration, one may either (i) for a given total dosage of tolterodine, reduce the side-effects, such as dry mouth, or (ii) for a given level of acceptable side-effects, increase the dosage of tolterodine to obtain an increased effect on the bladder, if desired.

Our above-mentioned PCT/SE99/01463 discloses treatment of overactive bladder by the administration of a controlled release formulation that delivers 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.

The present invention is based on the unexpected observation that a substantially constant serum level of the active moiety or moieties for 24 hours may be obtained through oral administration of a controlled release pharmaceutical formulation that releases the major content of active compound in less than about 18 hours, and more particularly that the formulation has an in vitro release of not less than about 80% after 18 hours at the conditions specified below.

In one aspect, the present invention therefore provides a pharmaceutical formulation containing tolterodine or a tolterodine-related compound, or a pharmacologically acceptable salt thereof, as active ingredient, in which the formulation exhibits a controlled in vitro release of the active ingredient in phosphate buffer at pH 6.8 of not less than about 80% after 18 hours, and after oral administration to a patient is capable of maintaining a substantially constant serum level of the active moiety or moieties for 24 hours.

A second aspect of the invention relates to the use of the pharmaceutical formulation for treating a disorder or disease selected from overactive bladder (including i.a. urinary incontinence and nocturia) and gastrointestinal disorders.

A third aspect of the invention relates to the use of tolterodine or a tolterodine-related compound, or a pharmacologically acceptable salt thereof, for the preparation of the pharmaceutical formulation of the above first aspect of the invention.

Preferably, the fraction of tolterodine, tolterodine-related compound or salt thereof that is released is not less than about 80% after 15 hours, especially not less than about 80% after 12 hours.

On the other hand, the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro after 1 hour is preferably not more than about 50%, especially not more than about 30%.

The fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro after three hours is preferably from about 30 to 95%, especially from about 40 to about 85%.

It may be preferred that after 7 hours, the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is not less than about 50%, especially not less than about 80%.

In an exemplary in vitro release profile for the pharmaceutical formulation, the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is less than about 50% after 1 hour, from about 30 to about 95% after 3 hours, and more than about 50% after 7 hours.

The in vitro release measurement conditions referred to above are those for a drug release test that utilizes the United

States Pharmacopea (USP) Apparatus 1 (rotating basket) at 100 rpm with 900 ml of deareated phosphate buffer at pH 6.8 and 37° C., where the phosphate buffer solution is prepared as described on pages 2049–2050 in USP 23. The phosphate buffer nominally contains 0.05 M phosphate.

By the term "active moiety or moities" it is meant, in the case of tolterodine and its related compounds, the sum of free or unbound (i.e. not protein bound) concentrations of (i) tolterodine and active metabolite thereof, when tolterodine (or prodrug form) is administered; or (ii) tolterodine and active metabolite thereof and/or (S)-enantiomer to tolterodine and active metabolite thereof, when the corresponding racemate (or prodrug form) is administered; or (iii) active metabolite, when the (R)-5-hydroxymethyl metabolite of tolterodine (or prodrug form) is administered; or (iv) (S)-enantiomer to tolterodine and active metabolite thereof, when the (S)-enantiomer (or prodrug) is administered; or (v) active (S)-metabolite, when the (S)-5-hydroxymethyl metabolite is administered.

The term "substantially constant" with respect to the serum level of active moiety or moieties means that the serum profile after administration of the controlled release formulation does essentially not exhibit any substantial peak values. This may also be expressed mathematically by reference to the "fluctuation index" (FI) for the serum concentration of (unbound) active moiety (or sum of active moities when relevant), where the fluctuation index FI is calculated as

$$FI=(Cmax-Cmin)/AUC\tau/\tau$$

wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety, AUCτ is the area under the serum concentration profile (concentration vs time curve), and τ is the length of the dosage interval during the time τ. The controlled release formulation according to the present invention readily permits a mean fluctuation index (for n being at least 30) that is not higher than about 2.0, more preferably not higher than about 1.5, particularly not higher than about 1.0, for example not higher than about 0.8.

For tolterodine and its 5-hydroxymethyl metabolite, the 24-hour exposure, expressed as AUC unbound active moiety (tolterodine plus metabolite) is usually in the range of from about 5 to about 150 nM*h, preferably from about 10 to about 120 nM*h, depending on the dosage needed by the particular patient. The indicated limits are based upon calculation of the unbound concentrations of active moiety assuming a fraction unbound of 3.7% for tolterodine and 36% for the 5-hydroxymethyl metabolite (Nilvebrant, L., et al., Life Sciences, Vol. 60, Nos. 13/14 (1997) 1129–1136).

Correspondingly, for tolterodine and its 5-hydroxymethyl metabolite, the average unbound (blood) serum or plasma levels of active moiety (tolerodine plus metabolite) are usually in the range of about 0.2 to about 6.3 nM, preferably in the range of about 0.4 to about 5.0 nM.

The formulation of the present invention is not restricted to any particular type of formulation. Thus, various types of controlled or sustained release type formufations may be used for embodying the present invention, such as, for example, osmotic tablets, gel matrix tablets, coated beads, etc.

A common type of controlled release formulation that may be used for the purposes of the present invention comprises an inert core, such as a sugar sphere, coated with an inner drug-containing layer and an outer membrane layer controlling drug release from the inner layer. A "sealcoat" may be provided between the inert core and the layer containing the active ingredient. When the core is of a water-soluble or water-swellable inert material, the sealcoat is preferably in the form of a relatively thick layer of a water-insoluble polymer. Such a controlled release bead may thus comprise:

(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 on the second layer of polymer effective for controlled release of the active ingredient,

wherein the first layer is adapted to control water penetration into the core.

The term "control water penetration into the core" as used above means that the water influx to the core should be retarded in a controlled manner to such an extent that the drug release profile will be altered in a predictable fashion. Thus, while in many cases it may be preferred that the water penetration into the core is substantially or completely eliminated, a certain, controlled influx of water to the core may be acceptable in other cases.

The above-mentioned first layer of water-insoluble material may also serve to provide mechanical integrity to the core.

Optionally, the above-mentioned third, or controlled release layer is coated with one or more additional layers of water-soluble or insoluble polymer, e.g. a non-thermoplastic soluble polymer to decrease tackiness of the beads for subsequent processing, such as curing and filling into capsules, or a secondary functional coating, such as an enteric coating that delays the onset of drug release. Optionally, such an additional layer may contain drug for immediate release.

Usually, the first layer (ii) above constitutes more than about 2% (w/w) of the final bead composition, preferably more than about 3% (w/w), e.g. from about 3% to about 80% (w/w).

The amount of the second layer (ii) above usually constitutes from about 0.05 to about 60% (w/w), preferably from about 0.1 to about 30% (w/w) of the final bead composition.

The amount of the third layer (iv) above usually constitutes from about 1 to about 50% (w/w), preferably from about 2 to about 25% (w/w) of the final bead composition.

The core unit typically has a size in the range of from about 0.05 to about 2 mm.

The controlled release beads may be provided in a multiple unit formulation, such as a capsule or a tablet.

The cores are preferably of a water-soluble or swellable material, and may be any such material that is conventionally used as cores or any other pharmaceutically acceptable water-soluble or water-swellable material made into beads or pellets. The cores may be spheres of materials such as sucrose/starch (Sugar Spheres NF), sucrose crystals, or extruded and dried spheres typically comprised of excipients such as microcrystalline cellulose and lactose.

The substantially water-insoluble material in the first, or sealcoat layer is generally a "GI insoluble" or "GI partially insoluble" film forming polymer (dispersed or dissolved in a solvent). As examples may be mentioned ethyl cellulose, cellulose acetate, cellulose acetate butyrate, polymethacrylates such as ethyl acrylate/methyl methacrylate copolymer (Eudragit NE-30-D) and ammonio methacrylate copolymer types A and B (Eudragit RL30D and RS30D), and silicone elastomers. Usually, a plasticizer is used together with the

polymer. Exemplary plasticizers include: dibutylsebacate, propylene glycol, triethylcitrate, tributylcitrate, castor oil, acetylated monoglycerides, acetyl triethylcitrate, acetyl butylcitrate, diethyl phthalate, dibutyl phthalate, triacetin, fractionated coconut oil (medium-chain triglycerides).

The second layer containing the active ingredient may be comprised of the active ingredient (drug) with or without a polymer as a binder. The binder, when used, is usually hydrophilic but may be water-soluble or water-insoluble. Exemplary polymers to be used in the second layer containing the active drug are hydrophilic polymers such as polyvinylpyrrolidone (PVP), polyalkylene glycol such as polyethylene glycol, gelatine, polyvinyl alcohol, starch and derivatives thereof, cellulose derivatives, such as hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose, carboxymethyl cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, carboxyethyl cellulose, carboxymethylhydroxyethyl cellulose, acrylic acid polymers, polymethacrylates, or any other pharmaceutically acceptable polymer.

The ratio of drug to hydrophilic polymer in the second layer is usually in the range of from 1:100 to 100:1 (w/w).

Suitable polymers for use in the third layer, or membrane, for controlling the drug release may be selected from water-insoluble polymers or polymers with pH-dependent solubility, such as, for example, ethyl cellulose, hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, polymethacrylates, or mixtures thereof, optionally combined with plasticizers, such as those mentioned above. Optionally, the controlled release layer comprises, in addition to the polymers above, another substance(s) with different solubility characteristics, to adjust the permeability, and thereby the release rate, of the controlled release layer. Exemplary polymers that may be used as a modifier together with, for example, ethyl cellulose include: HPMC, hydroxyethyl cellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, polyethylene glycol, polyvinylpyrrolidone (PVP), polyvinyl alcohol, polymers with pH-dependent solubility, such as cellulose acetate phthalate or ammonio methacrylate copolymer and methacrylic acid copolymer, or mixtures thereof. Additives such as sucrose, lactose and pharmaceutical grade surfactants may also be included in the controlled release layer, if desired.

The above controlled release beads and formulation, respectively may be produced by a method comprising the following steps:

a) providing a core unit of a substantially water-soluble or water-swellable material;

b) applying a first layer of a substantially water-insoluble polymer to said core;

c) applying onto said first layer, a second layer comprising an active ingredient and optionally a polymer binder; and

d) applying onto said second layer, a third polymer layer effective for controlled release of the active ingredient; wherein the amount of material in said first layer is selected to provide a layer thickness that permits control of water penetration into the core.

Optionally, one or more additional polymer layers are applied to the core as has been mentioned above.

The preparation of the multiple unit formulation comprises the additional step of transforming the prepared beads into a pharmaceutical formulation, such as by filling a predetermined amount of the beads into a capsule, or compressing the beads into tablets.

The layering or coating operations are preferably performed by spraying a solution or dispersion of the respective layer materials onto the core, preferably in a fluid bed coating apparatus.

After the final coating step, the beads are optionally "cured", usually in a fluid bed system or in a tray dryer system, by heating to a temperature of about 30–80° C., for 30 to 180 minutes, for example. Suitably, the beads are then cooled below about 35° C. before stopping the process.

As mentioned above, the pharmaceutical formulation according to the present invention may be used for treating, inter alia, urinary disorders including overactive urinary bladder. The overactive bladder condition gives rise to urinary frequency, urgency and/or urge incontinence. Overactive bladder disorders also include nocturia, i.e. awakening at night to urinate. While overactive bladder is often associated with detrusor muscle instability, disorders of bladder function may also be due to neuropathy of the central nervous system (detrusor hyperreflexia) including spinal cord and brain lesions, such as multiple sclerosis and stroke. Overactive bladder symptoms may also result from, for example, male bladder outlet obstruction (usually due to prostatic hypertrophy), interstitial cystitis, local edema and irritation due to focal bladder cancer, radiation cystitis due to radiotherapy to the pelvis, and cystitis. The formulation may also be useful for treating gastrointestinal disorders, including gastrointestinal hyperactivity.

The pharmaceutical formulation according to the present invention has proved to be very suitable for administering the above-mentioned drug tolterodine, the chemical name of which is (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine, and would likewise be suitable for its related compounds, i.e. the major, active metabolite of tolterodine, i.e. (R)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine; the corresponding (S)-enantiomer to tolterodine, i.e. (S)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine; the 5-hydroxymethyl metabolite of the (S)-enantiomer, i.e. (S)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine; as well as the corresponding racemate to tolterodine, i.e. (R,S)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine; and prodrug forms and pharmacologically acceptable salts thereof.

Tolterodine is marketed for the treatment of unstable or overactive urinary bladder with symptoms including urinary incontinence (urge incontinence), urgency and urinary frequency. The 5-hydroxymethyl metabolite of tolterodine mentioned above contributes significantly to the therapeutic effect of tolterodine.

Tolterodine, its corresponding (S)-enantiomer and racemate and the preparation thereof are described in e.g. the above-mentioned U.S. Pat. No. 5,382,600. For a description of the active (R)-5-hydroxymethyl metabolite of tolterodine (as well as the (S)-5-hydroxymethyl metabolite), it may be referred to the above-mentioned U.S. Pat. No. 5,559,269. The (S)-enantiomer, its non-cholinergic spasmolytic activity and use in the treatment of urinary and gastrointestinal disorders are described in WO 98/03067.

The invention will now be described in more detail by the following non-limiting Examples. Reference will be made to the accompanying drawings, wherein:

FIG. **1** is a diagram showing the fraction of tolterodine L-tartrate released in vitro versus time for 2 and 4 mg controlled release capsules according to the Example below; and

FIG. **2** is a diagram showing the variation of serum concentration (nmol/L) of (unbound) active moiety with time (hours) during 24 hours when administering a prede-

termined total dosage of tolterodine (4 mg) through a prolonged release (PR) capsule (4 mg) according to the Example below once daily. The corresponding variation with a prior art immediate release (IR) tablet (2 mg) twice daily is also shown.

EXAMPLE

Preparation of Controlled Release Beads and Capsules

An exemplary bead formulation containing tolterodine L-tartrate as active ingredient has the following structure:

Core:	Starch-containing sugar sphere of about 0.8 mm diameter (commercially available); comprises 73% w/w of the final bead; purpose: coating substrate;
First layer:	Surelease ® "sealcoat" (Surelease ® is an aqueous film-coating dispersion, about 25% solids, consisting primarily of ethylcellulose plasticized with fractionated coconut oil, and manufactured by Colorcon, Inc, USA); comprises about 12% w/w of the final bead; purpose: to provide more consistent core surface; during drug release phase maximize time that drug is saturated inside bead and minimize osmotic effects; control drug release rate together with the third layer;
Second layer:	Tolterodine L-tartrate/hydroxypropylmethylcellulose (HPMC); comprises about 3% w/w of the final bead; ratio of Tolterodine:HPMC is 5:1; purpose: drug supply;
Third layer:	Surelease ®/HPMC; comprises about 12% w/w of the final bead; ratio of Surelease ®:HPMC is 6:1; purpose: drug release rate control;

Beads with a three-layer coating having the above characteristics were prepared as follows:

1200 g of sugar spheres, 20–25 mesh, were charged into a Wurster fluid bed and sequentially coated at a nominal product temperature of 36 to 40° C. with the following three coating liquids:

(1) a Surelease® sealcoating liquid prepared by mixing 788 g of Surelease® with 563 g of purified water;

(2) a drug-containing solution prepared by first dissolving 35.0 g of tolterodine L-tartrate in 2190 g of purified water, and then mixing the solution with 6.6 g of hydroxypropylmethyl cellulose (HPMC) 5 cP; and

(3) a sustained release coating liquid prepared by mixing 29 g of HPMC 5 cP with 375 g of purified water, and then mixing with 695 g of Surelease®.

After tray drying for 3 hours at 70° C., the coated spheres were filled into size #4 or size #3 hard gelatin capsules to obtain 2 mg and 4 mg tolterodine L-tartrate capsules, respectively, of the composition:

	2 mg capsule	4 mg capsule
Tolterodine L-tartrate	2.0 mg	4.0 mg
sugar spheres, 20–25 mesh	68.6 mg	137.2 mg
Surelease ®	21.2 mg	42.4 mg
HPMC 5cP	2.0 mg	4.0 mg

Optionally, a fourth layer may be applied to the bead before drying by Wurster coating.

Fourth layer:	HPMC; comprises about 1% w/w of the final bead; purpose: decrease tackiness of beads for subsequent processing (curing and capsule filling).

In the case of the above described bead, such a fourth layer may be applied with a coating solution prepared by dissolving 16.4 g of HPMC in 234 g of water.

Drug In Vitro Release Study

A drug-release test which utilizes the USP Apparatus 1 (rotating basket) at 100 rpm with 1000 mL of deaerated phosphate buffer prepared at pH 6.8, was used to study the in vitro release at 37° C. of the two three-layered beads-containing 2 and 4 mg capsules prepared above. The buffer was identical to that used for the Buffer Stage testing of Delayed-release dosage forms described in USP 23 General Chapter 724, and nominally contains 0.05 M phosphate and 0.075 M chloride. The results are shown in FIG. 1. As can be seen therein, about 90% of the tolterodine tartrate had been released from both capsules after 12 hours.

Pharmacokinetic Study—Determination of Serum Concentrations of Tolterodine and Main Metabolite

A clinical trial was performed in patients with overactive bladder to determine the pharnacokinetic effects of a (i) a once daily dose of a 4 mg tolterodine controlled release capsule (below referred to as TOD) as described above, and (ii) two doses daily of a tolterodine immediate release tablet (below referred to as TIR), described below. 30 patients were subjected to each of the treatments. The measurements were performed on day seven in each treatment period and included measurements of serum concentrations of tolterodine and its main 5-hydroxymethyl metabolite (below called 5-HM) over time.

Blood samples were drawn immediately before dosing and after 0.5, 1, 2, 3, 6, 9, 12, 24 and 25 hours, and the free (unbound) serum concentrations of tolterodine and its 5-HM metabolite were measured by gas chromatography/mass spectrometry. The unbound concentrations were calculated assuming a fraction unbound of 3.7% for tolterodine and of 36% for 5-HM as obtained from protein binding studies on human 25 serum (Nilvebrant, L., et al., Life Sciences, Vol. 60, Nos. 13/14 (1997) 1129–1136). FIG. **2** shows the obtained variation with time of the sum of the unbound concentrations of tolterodine and 5-HM (which sum is referred to as "active moiety") for, on the one hand, the administration of a 4 mg TOD capsule once daily (PR capsule in FIG. **2**), and, on the other hand, the administration of a 2 mg TIR tablet twice daily (i.e. equivalent 24-hour doses of capsule and tablet). As shown in the Figure, the peaks obtained with the TIR tablet are eliminated with the TOD capsule, the latter thus providing a substantially constant serum concentration of active moiety during the 24 hours illustrated.

The difference in fluctuation of the serum concentrations between TIR tablet and TOD capsule may also be demonstrated by calculation of the "fluctuation index". The fluctuation index, FI, is calculated as FI=(Cmax—Cmin)/AUCτ/τ, where τ is the length of the dosage interval and AUCτ is the area under the serum concentration profile during a dosage interval. Thus, the mean calculated fluctuation index

for the active moiety was 2.29 (95% CI 1.95–2.63) for the TIR tablet (based on n=28), and 0.68 (95% CI 0.59–0.78) for the TOD capsule.

While the invention has been described above with reference to specific embodiments thereof, it is not restricted thereto in any way whatsoever. On the contrary, as will be understood by those skilled in the art, various changes, modifications, substitutions and omissions can be made without departing from the basic concept of the invention as defined in the claims which follow. Thus, for example, other sustained release formulations may be used.

What is claimed is:

1. An oral pharmaceutical formulation containing tolterodine or a tolterodine-related compound, or a pharmaceutically acceptable salt thereof, as active ingredient, wherein said formulation exhibits controlled in vitro release of the active ingredient in phosphate buffer at pH 6.8 of not less than about 80% after 18 hours, and after oral administration to a patient is capable of maintaining a substantially constant serum level of the active moiety or moieties for 24 hours, and wherein the controlled release formulation provides a mean fluctuation index of said serum level of active moiety or moieties that is not higher than about 2.0, said fluctuation index, FI, being defined as FI=(Cmax−Cmin)/AUCτ/τ, wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety or moieties, AUCτ is the area under the serum concentration profile, and τ is the length of the dosage interval.

2. The formulation according to claim 1, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is not less than about 80% after 15 hours.

3. The formulation according to claim 1, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is not less than about 80% after 12 hours.

4. The formulation according to claim 1, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is less than about 50% after 1 hour.

5. The formulation according to claim 4, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is less than about 30% after 1 hour.

6. The formulation according to claim 1, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is from about 30 to about 95% after 3 hours.

7. The formulation according to claim 1, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is from about 40 to about 85% after 3 hours.

8. The formulation according to claim 1, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is more than about 50% after 7 hours.

9. The formulation according to claim 1, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is more than about 80% after 7 hours.

10. The formulation according to claim 1, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is not more than about 50% after 1 hour, from about 30 to about 95% after 3 hours, and not less than about 50% after 7 hours.

11. The formulation according to claim 1, wherein the in vitro release is measured by a drug release test which utilizes the United States Pharmacopea (USP) Apparatus 1 (rotating basket) at 100 rpm with 900 ml of deaerated phosphate buffer at pH 6.8 and 37° C., where the phosphate buffer solution is prepared as described on pages 2049–2050 of USP 23, and nominally contains 0.05 M phosphate.

12. The formulation according to claim 1, which comprises tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine, or a salt thereof.

13. The formulation according to claim 1, which comprises tolterodine, or a salt thereof.

14. The formulation according to claim 1, wherein the 24-hour serum profile, expressed as the AUC of unbound tolterodine and 5-hydroxymethyl metabolite, is from 5 to about 150 nM*h.

15. The formulation according to claim 14, wherein the serum level of unbound tolterodine and 5-hydroxymethyl metabolite is in the range of about 0.2 to about 6.3 nM.

16. A method of treating an overactive bladder, which comprises administering a therapeutically effective amount of a pharmaceutical formulation according to claim 1.

17. A method of treating urinary incontinence, which comprises administering a therapeutically effective amount of a pharmaceutical formulation according to claim 1.

18. A method of treating nocturia, which comprises administering a therapeutically effective amount of a pharmaceutical formulation according to claim 1.

19. A method of treating gastrointestinal disorders, which comprises administering a therapeutically effective amount of a pharmaceutical formulation according to claim 1.

20. A method for orally administering tolterodine or a tolterodine-related compound, or a pharmacologically acceptable salt thereof, to a patient to maintain a substantially constant serum level of the active moiety or moieties for 24 hours, which method comprises administering a pharmaceutical formulation containing tolterodine, a tolterodine-related compound or a salt thereof, which formulation exhibits a controlled in vitro release in phosphate buffer at pH 6.8 of tolterodine, tolterodine-related compound or salt thereof of not less than about 80% after 18 hours.

21. The formulation according to claim 1, wherein the controlled release formulation provides a mean fluctuation index of said serum level of active moiety or moieties that is not higher than about 1.0.

22. The formulation according to claim 15, wherein the 24-hour serum profile, is from about 10 nM*h to about 120 nM*h.

23. The formulation according to claim 16, wherein the serum level of unbound tolterodine and 5-hydroxymethyl metabolite is in the range of about 0.4 to about 5.0 nM.

* * * * *

EXHIBIT B

US006770295B1

(12) **United States Patent**
Kreilgård et al.

(10) **Patent No.: US 6,770,295 B1**
(45) **Date of Patent: Aug. 3, 2004**

(54) **THERAPEUTIC FORMULATION FOR ADMINISTERING TOLTERODINE WITH CONTROLLED RELEASE**

(75) Inventors: **Bo Kreilgård**, Hilleröd (DK); **Lene Orup Jacobsen**, Gentofte (DK); **Ulla Hoeck**, Hilleröd (DK); **Helle Kristensen**, Slangerup (DK); **Torkel Gren**, Uppsala (SE); **Lisbeth Nilvebrant**, Bromma (SE); **Anders Ringberg**, Stockholm (SE); **Martin Wikberg**, Kullavik (SE); **Bengt Hallén**, Sollentuna (SE); **Birgitta Olsson**, Stenhamra (SE); **Jan Strömbom**, Vattholma (SE)

(73) Assignee: **Pharmacia AB**, Stockholm (SE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/582,498**

(22) PCT Filed: **Aug. 26, 1999**

(86) PCT No.: **PCT/SE99/01463**

§ 371 (c)(1),
(2), (4) Date: **Nov. 14, 2000**

(87) PCT Pub. No.: **WO00/12069**

PCT Pub. Date: **Mar. 9, 2000**

(30) **Foreign Application Priority Data**

Aug. 27, 1998 (SE) 9802864
Nov. 11, 1998 (SE) 9803871

(51) **Int. Cl.**[7] **A61K 9/22**; A61K 9/52; A61K 9/70; A61F 13/00

(52) **U.S. Cl.** **424/457**; 424/468; 424/449

(58) **Field of Search** 424/449, 457, 424/468, 458, 459, 461, 462

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,598,123 A * 8/1971 Zaffaroni 128/268
4,008,719 A * 2/1977 Theeuwes et al. 128/260

FOREIGN PATENT DOCUMENTS

WO	WO9323025	11/1993
WO	WO9612477	5/1996
WO	WO9803067	1/1998
WO	WO9811888	3/1998

OTHER PUBLICATIONS

Nilvebrant, L. et al., Euro. J. of Pharmacol., vol. 327 (1997) pp. 195–207.

Nilvebrant, L. et al., Life Sci., vol. 60, Nos. 13/14 (1997) pp. 1129–1136.

Brynne, N. et al., Intl. J. of Clin. Pharmacol. and Thera., vol. 35, No. 7 (1997) pp. 287–295.

Stahl, M.M.S., Neurology and Urodynamics, vol. 14 (1995) pp. 647–655.

Nilsson, C.G. et al., Neurology and Urodynamics, vol. 16 (1997) pp. 533–542.

* cited by examiner

Primary Examiner—James M. Spear
(74) *Attorney, Agent, or Firm*—Craig M. Bell

(57) **ABSTRACT**

The present invention is drawn to a method of treating an unstable or overactive urinary bladder by treating the patient with tolterodine or a tolterodine-related compound, or pharmaceutically acceptable salt thereof, with a controlled release formulation that maintains a substantially constant serum level of the active moiety or moieties for at least 24 hours. The present invention is further drawn to a formulation for the method.

27 Claims, 2 Drawing Sheets

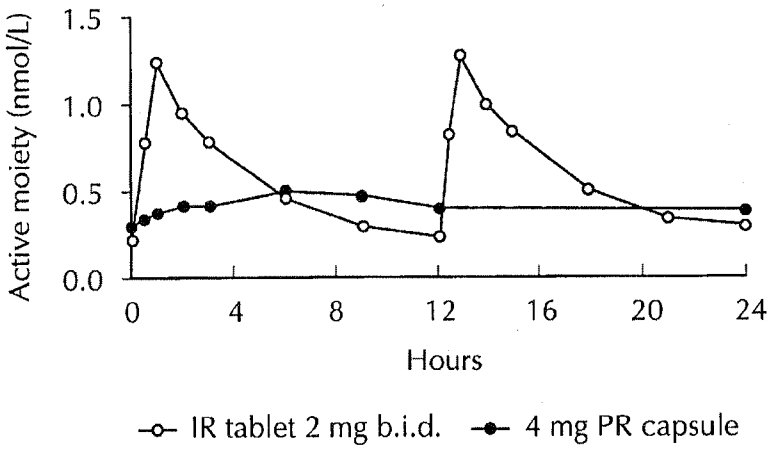


FIG. 1

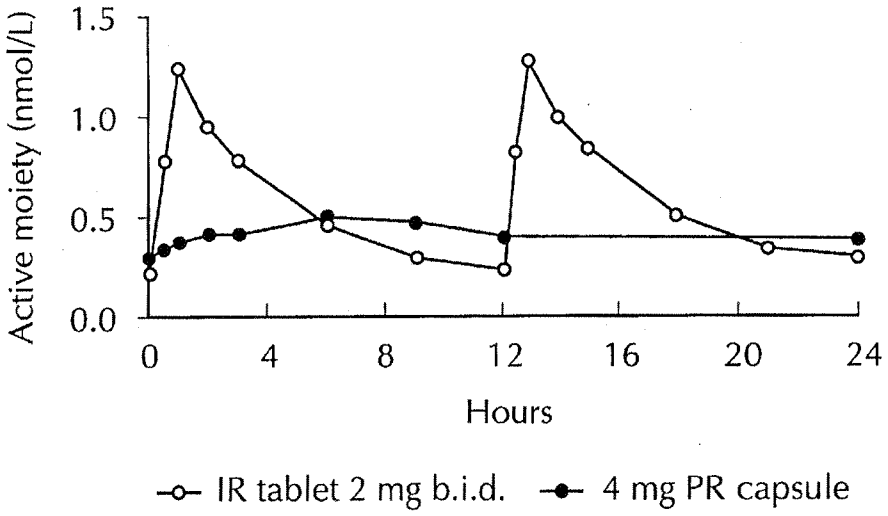

Active moiety (nmol/L)
1.5
1.0
0.5
0.0
0
4
8
12
16
20
24
Hours
IR tablet 2 mg b.i.d.
4 mg PR capsule

FIG. 2

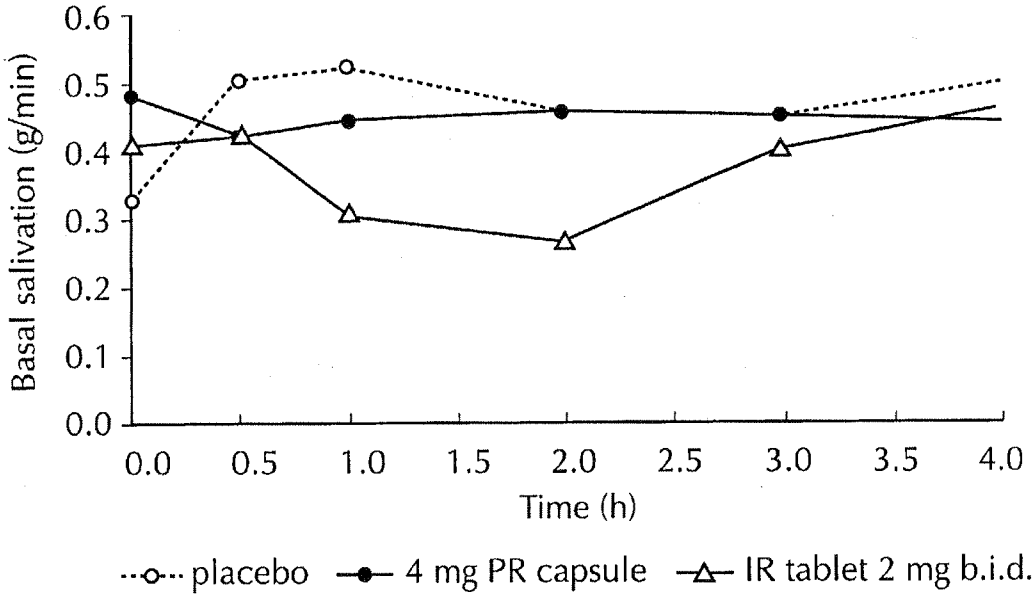
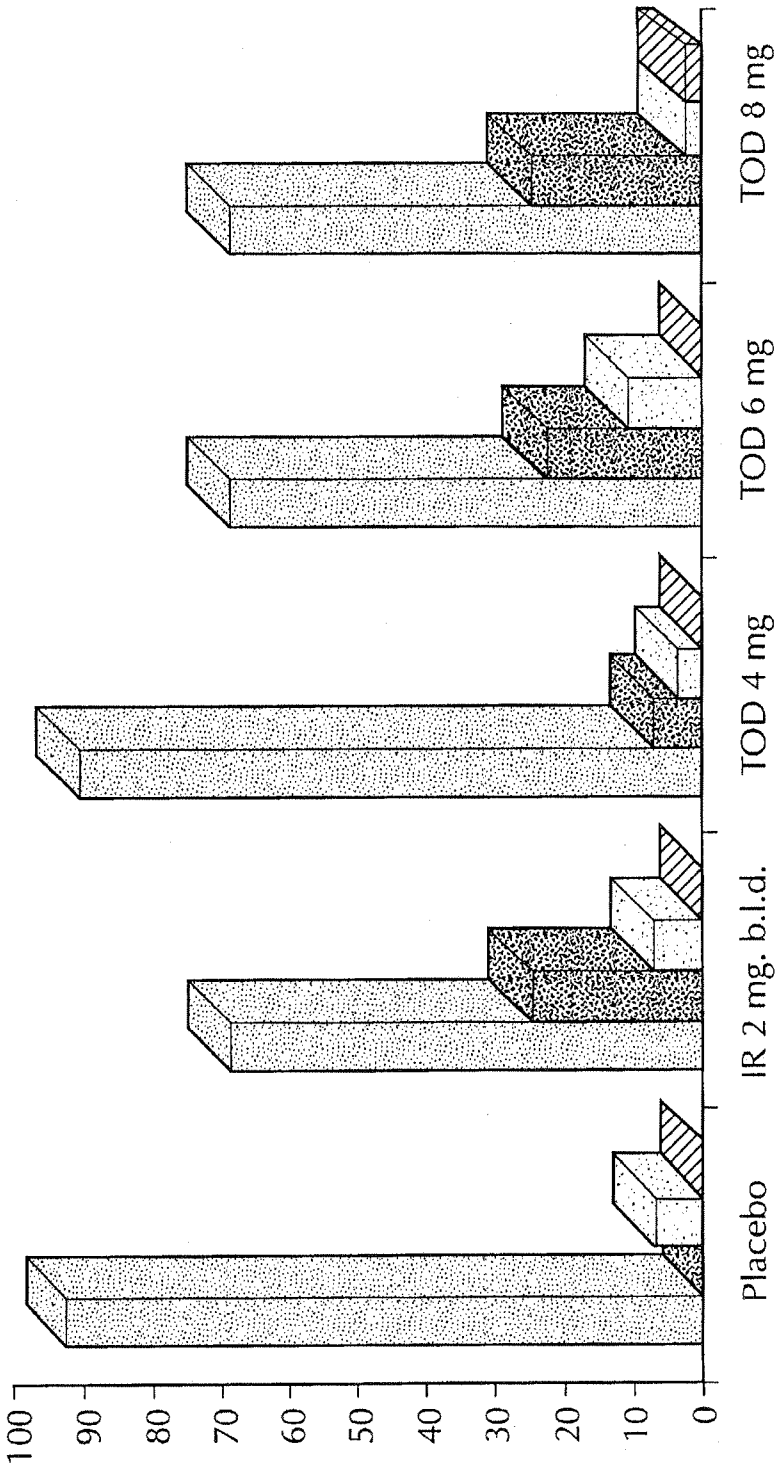

Basal salivation (g/min)
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
Time (h)
placebo
4 mg PR capsule
IR tablet 2 mg b.i.d.

FIG. 3


100
90
80
70
60
50
40
30
20
10
0
Placebo
IR 2 mg. b.l.d.
TOD 4 mg
TOD 6 mg
TOD 8 mg

THERAPEUTIC FORMULATION FOR ADMINISTERING TOLTERODINE WITH CONTROLLED RELEASE

This application is the national phase under 35 U.S.C. §371 of PCT International Application No. PCT/SE99/01463 which has an International filing date of Aug. 26, 1999, which designated the United States of America.

The present invention relates to an improved method of treating unstable or overactive urinary bladder as well as a formulation therefor.

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. The drug of choice has for a long time been oxybutynin.

Oxybutynin, which chemically is the DL-racemic form of 4-diethylamino-2-butynyl-phenylcyclohexylglycolate, is given orally, usually as a tablet or syrup. Oxybutynin, usually administered as the chloride salt, is metabolized to an active metabolite, N-desethyl-oxybutynin. The drug is rapidly absorbed from the gastrointestinal tract following administration and has a duration of from three to six hours. While the effectiveness of oxybutynin has been well documented, its usefulness is limited by classical antimuscarinic side-effects, particularly dry mouth, which often leads to discontinuation of treatment.

WO 96/12477 discloses a controlled release delivery system for oxybutynin, which delivery system is said not only to be of convenience to the patient by reducing the administration to a once daily regimen, but also to reduce adverse side-effects by limiting the initial peak concentrations of oxybutynin and active metabolite in the blood of the patient.

The alleged relief of side-effects by reducing or eliminating peak concentrations through administration of the controlled release delivery system is, however, contradicted by a later published clinical report, Nilsson, C. G., et al., Neurourology and Urodynamics 16 (1997) 533–542, which describes clinical tests performed with the controlled release delivery system disclosed in WO 96/12477 above. In the clinical tests reported, a 10 mg controlled release oxybutynin tablet was compared with the administration of a conventional (immediate release) 5 mg tablet given twice daily to urge incontinent patients. While high peak levels of the drug obviously were eliminated with the controlled release oxybutynin tablet, no difference in side-effects between the controlled release tablet and the conventional tablet was observed. The advantage of the controlled release tablet thus resided merely in enhancing treatment compliance by its once-a-day dosage rather than also reducing side-effects as stated in WO 96/12477.

Recently, 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 less side-effects than oxybutynin, especially regarding the propensity to cause dry mouth. While tolterodine is equipotent with oxybutynin in the bladder, its affinity for muscarinic receptors of the salivary gland is eight times lower than that of oxybutynin; see, for example, Nilvebrant, L., et al., European Journal of Pharmacology 327 (1997) 195–207. The selective effect of tolterodine in humans is described in Stahl, M. M. S., et al., Neurourology and Urodynamics 14 (1995) 647–655, and Bryne, N., International Journal of Clinical Pharmacology and Therapeutics, Vol. 35, No. 7 (1995) 287–295.

The currently marketed administration form of tolterodine is filmcoated tablets 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. While, as mentioned, the side-effects, such as dry mouth, are much lower than for oxybutynin, they still exist, especially at higher dosages.

According to the present invention it has now surprisingly been found that, contrary to the case of oxybutynin, the substantial elimination of peak serum levels of tolterodine and its active metabolite through controlled release of tolterodine for an extended period of time, such as through a once-daily administration form, while maintaining the desired effect on the bladder, indeed gives a significant reduction of the (already low) side-effects, particularly dry mouth, compared with those obtained for the same total dosage of immediate release tablets over the same period. In other words, eliminating the peak serum levels of the active moiety affects the adverse effects, and particularly dry mouth, more than the desired effect on the detrusor activity, simultaneously as the flattening of the serum concentration does not lead to loss of activity or increased incidence of urinary retention or other safety concerns. Thus, in addition to the convenience advantage of controlled release administration, one may either (i) for a given total dosage of tolterodine, reduce the side-effects, such as dry mouth, or (ii) for a given level of acceptable side-effects, increase the dosage of tolterodine to obtain an increased effect on the bladder, if desired.

In one aspect, the present invention therefore provides a method of treating unstable or overactive urinary bladder, which method comprises administering to a (mammal) patient in need of such treatment tolterodine or a tolterodine-related compound, or a pharmaceutically acceptable salt thereof, through a controlled release formulation that administers tolterodine or said tolterodine-related compound, or salt thereof, at a controlled rate for at least 24 hours. It is preferred that the dosage form formulation is capable of maintaining a substantially constant serum level of the active moiety or moieties for said at least 24 hours.

Overactive urinary bladder encompasses detrusor instability, detrusor hyperreflexia, urge incontinence, urgency and urinary frequency.

As mentioned above, the chemical name of tolterodine is (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine. The term "tolterodine-related compound" is meant to encompass the major, active metabolite of tolterodine, i.e. (R)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine; the corresponding (S)-enantiomer to tolterodine, i.e. (S)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine; the 5-hydroxymethyl metabolite of the (S)-enantiomer, i.e. (S)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine; as well as the corresponding racemate to tolterodine, i.e. (R,S)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine; and prodrug forms thereof.

By the term "active moiety or moities" is meant the sum of free or unbound (i.e. not protein bound) concentrations of (i) tolterodine and active metabolite thereof, when tolterodine (or prodrug form) is administered; or (ii) tolterodine and active metabolite thereof and/or (S)-enantiomer to

tolterodine and active metabolite thereof, when the corresponding racemate (or prodrug form) is administered; or (iii) active metabolite, when the (R)-5-hydroxymethyl metabolite of tolterodine (or prodrug form) is administered; or (iv) (S)-enantiomer to tolterodine and active metabolite thereof, when the (S)-enantiomer (or prodrug) is administered; or (v) active (S)-metabolite, when the (S)-5-hydroxymethyl metabolite is administered.

The term "substantially constant" with respect to the serum level of active moiety or moieties means that the release profile of the controlled release formulation should essentially not exhibit any peak values. This may, more sophistically, also be expressed by reference to the "flucuation index" (FI) for the serum concentration of (unbound) active moiety (or sum of active moities when relevant), where the fluctuation index FI is calculated as

$$FI=(Cmax-Cmin)/AUC\tau/\tau$$

wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety, AUCτ is the area under the serum concentration profile (concentration vs time curve) for dosage interval τ, and τ is the length of the dosage interval. Thus, according to the present invention, the controlled release formulation should provide a mean fluctuation index (for n being at least 30) that is usually not higher than about 2.0, more preferably not higher than about 1.5, particularly not higher than about 1.0, for example not higher than about 0.8.

For tolterodine and its 5-hydroxymethyl metabolite, the 24-hour exposure, expressed as AUC unbound active moiety (tolterodine plus metabolite) is usually in the range of from about 5 to about 150 nM*h, preferably from about 10 to about 120 nM*h, depending on the dosage needed by the particular patient. The indicated limits are based upon calculation of the unbound concentrations of active moiety assuming a fraction unbound of 3.7% for tolterodine and 36% for the 5-hydroxymethyl metabolite (Nilvebrant, L., et al., Life Sciences, Vol. 60, Nos. 13/14 (1997) 1129–1136).

Correspondingly, for tolterodine and its 5-hydroxymethyl metabolite, the average (blood) serum or plasma levels are usually in the range of about 0.2 to about 6.3 nM, preferably in the range of about 0.4 to about 5.0 nM.

Tolterodine, its corresponding (S)-enantiomer and racemate and the preparation thereof are described in e.g. WO 89/06644. For a description of the active (R)-5-hydroxymethyl metabolite of tolterodine (as well as the (S)-5-hydroxymethyl metabolite), it may be referred to WO 94/11337. The (S)-enantiomer and its use in the treatment of urinary and gastrointestinal disorders is described in WO 98/03067.

In another aspect, the present invention provides a pharmaceutical formulation containing tolterodine or a tolterodine-related compound, or a pharmaceutically acceptable salt thereof, which formulation when administered to a patient provides controlled release of tolterodine or said tolterodine-related compound, or salt thereof, for at least 24 hours, preferably such that a substantially constant serum level of the active moiety or moieties is maintained for said at least 24 hours.

Still another aspect of the present invention provides the use of tolterodine or a tolterodine-related compound, or a pharmaceutically acceptable salt thereof, for the manufacture of a therapeutical formulation for treating unstable or overactive urinary bladder, which formulation provides a controlled release of tolterodine or said tolterodine-related compound, or salt thereof at a controlled rate for at least 24 hours, preferably such that a substantially constant serum level of the active moiety or moieties is maintained for said at least 24 hours.

The controlled release formulation is preferably an oral delivery system or a transdermal preparation, such as a transdermal patch, but also other controlled release forms may, of course, be contemplated, such as buccal tablets, rectal suppositories, subcutaneous implants, formulations for intramuscular administration.

An exemplary type of oral controlled release formulation, a specific embodiment of which is described in Example 1 below, is a multi-unit formulation comprising controlled-release beads. Each bead comprises (i) a core unit of a water-soluble, water-swellable or water-insoluble inert material (having a size of about 0.05 to 2 about 2 mm), such as e.g. a sucrose sphere; (ii) a first layer on the core of a substantially water-insoluble (often hydrophilic) polymer (this layer may be omitted in the case of an insoluble core, such as e.g. of silicon dioxide), (iii) a second layer of a water-soluble polymer having an active ingredient dissolved or dispersed therein, and (iv) a third polymer layer effective for controlled release of the active ingredient (e.g. a water-insoluble polymer in combination with a water-soluble polymer) In the case of an oral controlled release formulation for once-daily administration, the dosage of tolterodine (or tolterodine related compound) is, for example, 4 mg or 6 mg.

A transdermal patch for tolterodine or tolterodine-related compound is described in our co-pending international application "Transdermally administered tolterodine as anti-muscarinic agent for the treatment of overactive bladder" (based on Swedish patent application no. 9802864-0, filed on Aug. 27, 1998), the full disclosure of which is incorporated by reference herein. Illustrative patch formulations are described in Example 2 below.

With the guidance of the disclosure herein, the skilled person may either adapt controlled release administration forms, such as tablets, capsules, patches etc, known in the art, to obtain the objectives of the present invention, or design modified or new controlled release administration forms.

The invention is illustrated by the following Examples, without, however, limiting the scope of the invention in any way. Percentages are by weight, unless otherwise stated. Reference will be made to the accompnaying drawings, in which:

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a diagram showing the variation of serum concentration (nmol/L) of (unbound) active moiety with time (hours) during 24 hours when administering a predetermined total dosage of tolterodine (4 mg) through (i) an immediate release tablet (2 mg) twice daily as in the prior art, and (ii) a controlled release capsule (4 mg) once daily in accordance with the present invention;

FIG. **2** is a diagram showing the variation of the basal salivation (9/min) with time (hours) during 4 hours after administration of (i) a 4 mg tolterodine controlled release capsule in accordance with the present invention, (ii) a prior art tolterodine immediate release tablet, and (iii) placebo; and

FIG. **3** is is a bar chart diagram showing patients' individual estimates of experienced dry mouth side effect (no dry mouth, mild, moderate, severe) after administration of tolterodine through (i) a conventional 2 mg immediate release tablet, (ii) controlled release capsules of 4, 6 and 8 mg, respectively, according to the present invention, and (iii) placebo.

EXAMPLE 1

TOLTERODINE ORAL CR CAPSULE AND IR TABLET

Preparation of Tolterodine CR Capsules 2 mg and 4 mg

A controlled release (CR) capsule containing non-pareil beads coated by (i) an ethylcellulose layer, (ii) a tolterodine/

HPMC layer, and (iii) a sustained release ethylcellulose/HPMC layer was prepared as follows:

1200 g of (starch-containing) sugar spheres, 20–25 mesh, were charged into a Wurster fluid bed and sequentially coated with the following three coating solutions:

(1) a Surelease® sealcoating solution prepared by mixing 788 g of Sureleasee with 563 g of purified water (Surelease® is an aqueous filmcoating dispersion, about 25% solids, consisting primarily of ethylcellulose plasticized with fractionated coconut oil; manufactured by Colorcon, Inc., West Point, Pa., U.S.A.);

(2) a suspension prepared by first dissolving 35.0 g of tolterodine L-tartrate in 2190 g of purified water, and then mixing the solution with 6.6 g of Hypromellose, 5 cP (hydroxypropylmethyl cellulose (HPMC)); and

(3) a sustained release coating solution prepared by mixing 29 g of Hypromellose, 5 cP, with 375 g of purified water, and then mixing with 695 g of Surelease®.

After drying, the coated spheres were filled into hard gelatin capsule shells (size 3, white/white) to obtain 2 mg and 4 mg capsules, respectively, of the composition (filling mass for 2 mg capsule, 169–207 mg/capsule):

	2 mg capsule	4 mg capsule
Tolterodine L-tartrate	2.0 mg	4.0 mg
sugar spheres, 20–25 mesh	69 mg	137 mg
Surelease ®	21 mg	42 mg
Hypromellose, 5cP	2.0 mg	4.1 mg

Tolterodine L-Tartrate IR Tablets 2 mg

Commercially available tolterodine L-tartate 2 mg tablets for immediate release (IR) (Detrusitol®, Pharmacia & Upjohn AB, Sweden) were used. The tablets had the following composition:

Core	
Tolterodine L-tartrate	2.0 mg
cellulose, microcrystalline	53.4 mg
calcium hydrogen phosphate dihydrate	18.0 mg
sodium starch glycollate	6.0 mg
magnesium stearate	0.4 mg
colloidal anhydrous silica	0.2 mg
Coating	
Methylhydroxypropyl cellulose	1.5 mg
cellulose, microcrystalline	0.3 mg
stearic acid	0.6 mg
titanum dioxide E 171	0.6 mg

PHARMACODYNAMIC AND PHARMACOKINETIC STUDIES

A clinical trial was performed in patients with overactive bladder to determine the pharmacodynamic and pharmacokinetic effects of different daily doses of (i) the above described tolterodine controlled release capsule (below referred to as TOD), compared with (ii) the above described tolterodine immediate release tablet (below referred to as TIR), and (iii) a placebo capsule (containing sugar spheres only). The trial was performed as a double-blind, double dummy, cross-over trial in 60 patients for three one week periods and six treatments (2, 4, 6 and 8 mg TOD once daily, 2 mg TIR twice daily, and placebo). All patients were randomised to three out of six treatments, meaning that 30 patients were subjected to each of the treatments. Pharmacodynamic and pharmacokinetic measurements were performed on day seven in each treatment period. The determinations included measurements of (i) serum concentrations of tolterodine and its main 5-hydroxymethyl metabolite (below called 5-HM) over time, (ii) salivation (dry mouth), and (iii) residual urine volumes.

Serum Concentrations of Tolterodine and Main Metabolite

Blood samples were drawn immediately before dosing and after 0.5, 1, 2, 3, 6, 9, 12, 24 and 25 hours, and the free (unbound) serum concentrations of tolterodine and its 5-HM metabolite were measured by gas chromatography/mass spectrometry. The unbound concentrations were calculated assuming a fraction unbound of 3.7% for tolterodine and of 36% for 5-HM as obtained from protein binding studies on human serum (Nilvebrant, L., et al., Life Sciences, Vol. 60, Nos. 13/14 (1997) 1129–1136). FIG. **1** shows the obtained variation with time of the sum of the unbound concentrations of tolterodine and 5-HM (which sum is referred to as "active moiety") for, on the one hand, the administration of a 4 mg TOD capsule once daily, and, on the other hand, the administration of a 2 mg TIR tablet twice daily (i.e. equivalent 24-hour doses of capsule and tablet). As shown in the Figure, the peaks obtained with the TIR tablet are eliminated with the TOD capsule, the latter thus providing a substantially constant serum concentration of active moiety during the 24 hours illustrated.

The difference in fluctuation of the serum concentrations between TIR tablet and TOD capsule may also be demonstrated by calculation of the "fluctuation index". The fluctuation index, FI, is calculated as $FI=(Cmax-Cmin)/AUC\tau/\tau$, where τ is the length of the dosage interval and $AUC\tau$ is the area under the serum concentration profile during a dosage interval. Thus, the mean calculated fluctuation index for the active moiety was 2.40 (95% CI 1.95–2.63) for the TIR tablet (based on n=28), and 0.68 (95% CI 0.59–0.78) for the TOD capsule.

Salivation (Dry Mouth)

Salivation was measured using dental cotton rolls applied in the mouth for 3×2 minutes. Measurements were performed before breakfast and thereafter after each blood sample on day seven in each treatment period. Based on all measurements after dosing, the mean salivation during 12 hours was calculated. The basal salivation at steady state was measured after treatment with (i) 4 mg TOD capsule, (ii) 2 mg TIR tablet, and (iii) placebo. The results are presented in FIG. **2**. As can be seen in the Figure, the salivation is substantially constant during the period shown for the TOD capsule, whereas a considerable reduction in salivation (i.e. drier mouth) is obtained with the TIR tablet.

While FIG. **2** shows the total salivation as measured, the degree of salivation, or dry mouth, was also determined, based on the patient's estimate of experienced intensity of the phenomenon. The results for 2 mg TIR tablet b.i.d., 4 mg TOD capsule, 6 mg TOD capsule and 8 mg TOD capsule, are presented in bar chart form in FIG. **3**. The four bars for each dosage represent, from left to right in the figure, no dry mouth, mild, moderate, and severe, respectively.

As apparent from FIG. **2**, the dry mouth intensity for the TIR 2 mg b.i.d. tablet is clearly higher than that of the TOD 4 mg capsule, and about twice that dosage, i.e. TOD 8 mg, is required to match the adverse dry mouth effects of the TIR 2 mg b.i.d. tablet.

The results from the salivation determinations thus show that flattening of the concentration peaks of the "active

moiety" (i.e. tolterodine plus 5-HM) leads to a substantial reduction of the undesired dry mouth effect.

Residual Urine Volume

Residual volume is the volume of urine left in the bladder immediately after voiding. Measuring residual volume offers a method of assessing the effect of antimuscarinic treatment on the bladder. In fact, it offers a measure of efficacy (change in residual volume) as well as safety (urinary retention, i.e. inability to pass urine). Efficacy may thus be measured as the mean residual volume per unit of time, and safety as any case where the residual urine exceeds a fixed level. The mean residual volume per micturition was measured by a non-invasive (ultrasonic) method for placebo, TIR tablet 2 mg b.i.d., and for capsules TOD 2 mg, TOD 4 mg, TOD 6 mg, and TOD 8 mg.

The results are presented in Tables 1 and 2 below. Table 1 shows the mean residual volume per micturition, and Table 2 shows the maximum residual volume during 12 hours.

The results presented clearly demonstrate that the TOD capsule dosages are as efficacious as the corresponding TIR b.i.d dosages, and also that the TOD dose may be increased up to 8 mg daily and still be safe with regard to urinary retention.

TABLE 1

Mean Residual Volume per micturition (ml)

	Placebo	TIR 2 mg b.i.d	TOD 2 mg	TOD 4 mg	TOD 6 mg	TOD 8 mg
Estimated mean	29	62	40	59	69	77
95% confidence interval	12 to 46	45 to 79	26 to 55	51 to 66	60 to 78	65 to 89
Estimated difference vs. IR			−22	−4	7	14
			−44 to 1	−23 to 15	−13 to 26	−7 to 36

TABLE 2

Maximum Residual Volume during 12 hours

	Placebo	TIR 2 mg b.i.d	TOD 2 mg	TOD 4 mg	TOD 6 mg	TOD 8 mg
Median value (ml)	46	72	45	55	87	77
min–max	5–267	10–316	0–192	0–349	0–360	0–390

The results from the clinical trial described above demonstrate that a flatter serum concentration of active moiety (tolterodine plus 5-HM) not only does not lead to a loss of efficacy or to untoward side-effects, primarily urinary retention, but, importantly, also provides for a reduced dry mouth effect (unaffected or less reduced salivation).

EXAMPLE 2

TOLTERODINE TRANSDERMAL PATCH FORMULATION

Tolterodine-releasing patches were prepared as follows:

System 1 (Drug-in-Adhesive, Acrylate)

5 g of tolterodine base were dissolved in 11 g of ethanol and added to 20 g of Durotak 387-2287 (National Starch & Chemical, U.S.A.). The drug gel was coated onto a backing membrane (Scotchpak 1012; 3M Corp., U.S.A.) by using a coating equipment (RK Print Coat Instr. Ltd, Type KCC 202 control coater). The wet layer thickness was 400 μm. The laminate was dried for 20 min. at RT and then for 30 min. at 40° C. A polyester release liner (S 2016; Rexam Release) was laminated onto the dried drug gel. The sheet was cut into patches and stored at 2–8° C. until use (packed in Barex pouches). The concentration of tolterodine base in the patches was 2,5 mg/cm^2.

System 2 (Multi-laminate, Acrylate)

5 g of tolterodine base were dissolved in 10 ml of ethanol. A mix of 6,4 g of Eudragit RL 100 (Röhm GmbH Chemische Fabrik, Germany) and 6,4 of ethanol and a mix of 2,6 g of Polyvidone 90 (BASF, Germany) and 10,2 g of ethanol were added to the solution of tolterodine base in ethanol. Finally, 4 g of propylene glycol were added. The drug gel was coated onto a backing membrane (Scotchpak 1109; 3M Corp., U.S.A.) by using the coating equipment above. The wet layer thickness was 400 μm. The laminate was then dried at 40° C. for 2 hours. An adhesive layer consisting of Plastoid E35H was coated onto a polyester film (S 2016; Rexam Release) and dried at 80° C. for 10 min. The two layers were thereafter laminated. The sheet was cut into patches and stored at 2–8° C. until use (packed in Barex pouches). The concentration of tolterodine base in the patches was 2,0 mg/cm^2.

System 3 (Multi-laminate Water-based Acrylate)

1 g of tolterodine base was mixed with Tween 80 (Merck) by heating to 60–70° C. 1,8 g of triethylacetate and 1,3 g of dem. water was added to the mix. The final mix was then added to 25 g of Eudragit RL 30 D (Röhm GmbH Chemische Fabrik, Germany). Finally, 180 mg of 1 N NaOH were added. The drug gel was coated onto a backing membrane (Scotchpak 1109; 3M Corp., U.S.A.) by using the coating equipment. The wet layer thickness was 400 μm. The laminate was dried at 40° C. for 2 hours. An adhesive layer consisting of Plastoid E35H was coated onto a polyester film (S 2016; Rexam Release) and dried at 80° C. for 10 min. The two layers were thereafter laminated. The sheet was cut into patches and stored at 2–8° C. until use (packed in Barex pouches). The concentration of tolterodine base in the patches was 0,5 mg/cm^2.

What is claimed is:

1. A method of treating unstable or overactive urinary bladder, wherein the method comprises administering to a patient in need of such treatment tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine, or a pharmaceutically acceptable salt thereof, in a pharmaceutically effective amount thereof through a controlled release formulation capable of maintaining a substantially constant serum level of the active moiety or moieties for at least 24 hours, wherein the 24-hour serum profile, expressed as the AUC of unbound tolterodine and 5-hydroxymethyl metabolite, is from 5 to about 150 nM*h.

2. The method according to claim **1**, wherein the controlled release formulation provides a mean fluctuation index of said serum level of active moiety or moieties that is not higher than about 2.0, said fluctuation index, FI, being defined as FI=(Cmax−Cmin)/AUCτ/τ, wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety or moieties, AUCτ is the area under the serum concentration profile, and τ is the length of the dosage interval.

3. A method of treating unstable or overactive urinary bladder, wherein the method comprise administering to a patient in need of such treatment tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine, or a pharmaceutically acceptable salt thereof, in a pharmaceutically effective amount thereof through controlled release formulation capable of maintaining a

substantially constant serum level of the active moiety or moieties for at least 24 hours with reduced undesirable side effects and with no reduction in the efficacy of the tolterodine compound, wherein the 24-hour serum profile, expressed as the AUC of unbound tolterodine and 5-hydroxymethyl metabolite, is from 5 to about 150 nM*h.

4. The method according to claim **1**, wherein tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine is administered, and the serum level of unbound tolterodine and 5-hydroxymethyl metabolite is in the range of about 0.2 to about 6.3 nM.

5. The method according to claim **1** wherein the controlled release formulation is a capsule or tablet for oral administration once daily.

6. The method according to claim **1**, wherein the controlled release formulation is a transdermal preparation.

7. The method according to claim **1** wherein tolterodine is administered.

8. The method according to claim **1** wherein urinary incontinence is treated.

9. A pharmaceutical formulation containing tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine, or a pharmaceutically acceptable salt thereof, which formulation when administered to a patient provides controlled release of tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine, or salt thereof, such that a substantially constant serum level of the active moiety or moieties is maintained for at least 24 hours, wherein the 24-hour serum profile, expressed as the AUC of unbound tolterodine and 5-hydroxymethyl metabolite, is from 5 to about 150 nM*h.

10. The formulation of claim **9**, which provides a mean fluctuation index of said serum level of active moiety or moieties that is not higher than about 2.0, said fluctuation index, FI, being defined as $FI=(Cmax-Cmin)/AUC\tau/\tau$, wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety or moieties, $AUC\tau$ is the area under the serum concentration profile, and τ is the length of the dosage interval.

11. A pharmaceutical formulation containing tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine, or a pharmaceutically acceptable salt thereof, which formulation when administered to a patient provides controlled release of said tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine, or pharmaceutically acceptable salt thereof, such that a substantially constant serum level of the active moiety or moieties is maintained for at least 24 hours for efficacious therapy with reduced undesirable side effects, wherein the 24-hour serum profile, expressed as the AUC of unbound tolterodine and 5-hydroxymethyl metabolite, is from 5 to about 150 nM*h.

12. The formulation according to claim **9**, wherein tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine is administered, and the serum level of unbound tolterodine and 5-hydroxymethyl metabolite is in the range of about 0.2 to about 6.3 nM.

13. The formulation according to claim **9**, which is a capsule or tablet for oral administration once daily.

14. The formulation according to claim **1**, which is a transdermal preparation.

15. The formulation according to claim **9**, which provides controlled release of tolterodine.

16. The method of claim **3**, wherein the controlled release formulation is administered orally.

17. The formulation of claim **11**, which is in a form for oral administration.

18. The method according to claim **2**, wherein the controlled release formulation provides a mean fluctuation index of said serum level of active moiety or moieties that is not higher than about 1.0.

19. The method according to claim **3**, wherein the 24-hour serum profile, expressed as the AUC of unbound tolterodine and 5-hydroxymethyl metabolite, is from about 10 nM*h to about 120 nM*h.

20. The method according to claim **4**, wherein the serum level of unbound tolterodine and 5-hydroxymethyl metabolite is in the range of about 0.4 to about 5.0 nM.

21. The method according to claim **6**, wherein the transdermal preparation is a transdermal patch.

22. The formulation of claim **10**, wherein the mean fluctuation index of said serum level of active moiety or moieties that is not higher than about 1.0.

23. The formulation according to claim **11**, wherein the 24-hour serum profile, expressed as the AUC of unbound tolterodine and 5-hydroxymethyl metabolite, is from about 10 nM*h to about 120 nM*h.

24. The formulation according to claim **12**, wherein the serum level of unbound tolterodine and 5-hydroxymethyl metabolite is in the range of about 0.4 to about 5.0 nM.

25. The transdermal preparation of claim **14**, which is a transdermal patch.

26. The method of claim **3**, wherein increased efficacy of the tolterodine compound is obtained with minimal undesirable side effects.

27. The formulation of claim **11**, wherein increased efficacy of the tolterodine compound is obtained with minimal undesirable side effects.

* * * * *