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(54) **Title**: DRY FORMULATION AND PHARMACEUTICAL COMPOSITION COMPRISING FESOTERODINE OR A SALT OR A SOLVATE THEREOF

(57) **Abstract**: The present invention relates to a new pharmaceutical composition of fesoterodine or a salt or a solvate thereof, in particular to a dry formulation. The present invention relates to a new process for the preparation of dry formulation of fesoterodine or a salt or a solvate thereof. The pharmaceutical composition is particularly useful as a medicament, especially for the treatment of urinary incontinence.

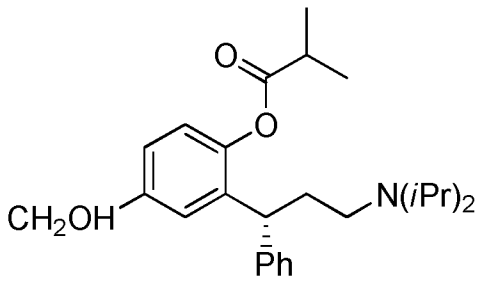
Dry formulation and pharmaceutical composition comprising fesoterodine or a salt or a solvate thereof

Field of the Invention

The present invention relates to a pharmaceutical composition of fesoterodine or a salt or a solvate thereof, in particular to a dry formulation. The present invention relates to a process for the preparation of dry formulation of fesoterodine or a salt or a solvate thereof. The pharmaceutical composition is particularly useful as a medicament, especially for the treatment of urinary incontinence.

Description of Background Art

Fesoterodine ([2-[(1R)-3-(di(propan-2-yl)amino)-1-phenylpropyl]-4-(hydroxymethyl)phenyl] 2-methylpropanoate) is a muscarinic receptor antagonist used for the treatment of overactive bladder including urinary incontinence. Fesoterodine substance was disclosed in WO 98/43942 and WO 99/58478, while salts of fesoterodine were described in EP 1230209.



Fesoterodine is a tolterodine (3-(2-hydroxy–5-methylphenyl)-*N,N*-diisopropyl-3-phenylpropylamine) prodrug that is converted to an active molecule hydroxy metabolite 2-(3-(diisopropylamino)-1-phenylpropyl)-4-(hydroxymethyl)phenol (hydroxytolterodine) in the body. However, fesoterodine substance is prone to conversion to 5-hydroxymethyltolterodine under humid environment and at increased temperature. Said degradation of fesoterodine to 5-hydroxymethyltolterodine in the pharmaceutical formulation is undesirable. Therefore, there is a need to provide a pharmaceutical composition comprising fesoterodine that is stable against fesoterodine degradation over an extended period of time.

So far, two solutions regarding fesoterodine stability in the pharmaceutical composition have been presented. In WO 2007/141298 pharmaceutical excipients such as xylitol, sorbitol,

polydextrose, isomalt and combinations thereof were found to be able to significantly slow down the degradation of fesoterodine under stress conditions. WO 2010/043408 discloses a microencapsuled fesoterodine composition which, distinct from a homogenous mixture of fesoterodine-particle with a matrix, is composed of a particle containing fesoterodine and a shell surrounding the fesoterodine-containing particle. However, the prior art proposed compositions require a certain amount of stabilizers for preventing degradation (cf. WO 2007/141298), or a complex-structured pharmaceutical composition (cf. WO 2010/043408).

Therefore, there is an unmet need for new pharmaceutical composition comprising fesoterodine that are stable against fesoterodine degradation over an extended period of time.

Summary of the invention

The aspects, advantageous features and preferred embodiments of the present invention summarized in the following items, respectively alone or in combination, further contribute to solving the object of the invention:

1. A dry formulation of fesoterodine or a salt or a solvate thereof, comprising said fesoterodine or a salt or a solvate thereof homogeneously admixed with at least one controlled release polymer in said dry formulation, and wherein said dry formulation is free of a stabilizer selected from xylitol, sorbitol, polydextrose, isomalt and dextrose.

2. The dry formulation according to item 1, wherein an optional liquid, when used, was limited during the dry formulation process of preparation at a maximum of 10% liquid relative to the composition subjected to formulation, preferably the dry formulation is obtainable by a process carried out substantially without the presence of water.

3. The dry formulation according to any one of the preceding items, wherein a residual amount of water or moisture in the dry formulation is 4.0 wt.-% or below, preferably is 2.0 wt.-% or below, measured by loss on drying.

4. The dry formulation according to any one of the preceding items, wherein none of excipients or additives added to the formulation are combined with agglomeration liquid, and all the excipients or additives are added in the form of dry material or powders.

5. The dry formulation according to anyone of the preceding items, wherein the content of inactive excipients in the homogeneous admixture with of fesoterodine or a salt or a solvate thereof constitutes a majority, preferably at least 75%, more preferably at least 90% of the total dry formulation.

6. The dry formulation according any of the preceding items, wherein the controlled release polymer is selected from the group consisting of hydroxypropyl methylcellulose, methylcellulose hydroxyethylcellulose, hydroxypropylcellulose, carboxymethylcellulose, ethylcellulose, polyethyleneoxide, carrageenan, agar, alginic acid, pectin and a mixtures thereof, preferably hydroxypropyl methylcellulose.

7. The dry formulation according to any one of the preceding items, including at least one controlled release polymer combined with another polymer of the same polymer type or of different polymer types, the combined polymers differing in their viscosity grades.

8. The dry formulation according to item 7, wherein at least two different hydroxypropyl methylcellulose types differing in viscosity grades are combined.

9. The dry formulation according to anyone of the preceding items, which comprises 15-65 % of said controlled release polymer, relative to the total amount of the dry formulation.

10. The dry formulation according to item 9, comprising about 40-50% of the polymer.

11. The dry formulation according to anyone of the preceding items, further comprising other pharmaceutically acceptable excipients selected from fillers, glidants and lubricants present in said dry formulation.

12. The dry formulation according to any of items 6 to 11, comprising relative to the total amount of the dry formulation:

(i) 0.5-10% fesoterodine or a salt or a solvate thereof, preferably fumarate,

(ii) 5-85% filler selected from a group consisting of microcrystalline cellulose, lactose monohydrate, corn starch, calcium phosphate, calcium hydrogenphosphate, sucrose, mannitol, composed fillers of microcrystalline cellulose and lactose monohydrate, composed fillers of powdered cellulose and lactose monohydrate, composed fillers of corn starch and lactose monohydrate, and combinations thereof,

(iii) 15-65% controlled release polymer, selected from a group consisting of hydroxypropyl methylcellulose, methylcellulose and mixture thereof,
(iv) 0.5-5% % glidant, preferably talc,
(v) 0.5-5% % lubricant, preferably glyceryl behenate.

13. The dry formulation according to any of preceding items further comprising
(i) 2-5% fesoterodine or a salt or a solvate thereof, preferably fumarate,
(ii) 20-75% filler, selected from a group consisting of microcrystalline cellulose, lactose monohydrate, corn starch, calcium phosphate, calcium hydrogenphosphate, sucrose, mannitol, composed fillers of microcrystalline cellulose and lactose monohydrate, composed fillers of powdered cellulose and lactose monohydrate, composed fillers of corn starch and lactose monohydrate, and combinations thereof,
(iii) 20-60% controlled release polymer, selected from a group consisting of hydroxypropyl methylcellulose, methylcellulose and mixture thereof,
(iv) 2-5% glidant, preferably talc,
(v) 2-5% lubricant, preferably glyceryl behenate.

14. The dry formulation according to any of preceding items further comprising
(i) 2-3% fesoterodine or a salt or a solvate thereof, preferably fumarate,
(ii) 40-55% filler, selected from a group consisting of microcrystalline cellulose, lactose monohydrate, corn starch, calcium phosphate, calcium hydrogenphosphate, sucrose, mannitol, composed fillers of microcrystalline cellulose and lactose monohydrate, composed fillers of powdered cellulose and lactose monohydrate, composed fillers of corn starch and lactose monohydrate, and combinations thereof,
(iii) 40-50% controlled release polymer, selected from a group consisting of hydroxypropyl methylcellulose, methylcellulose and mixture thereof,
(iv) 2-3% glidant, preferably talc,
(v) 3-4% lubricant, preferably glyceryl behenate.

15. A pharmaceutical composition, obtained from a dry formulation of fesoterodine or a salt or a solvate thereof according to any one of the preceding items by any one of direct compression or dry granulation followed by compression of obtained dry granulate.

16. The pharmaceutical composition according to item 15, provided in the form of tablets or in the form of powder mixture or granules filled in capsules or in sachets.

17. The pharmaceutical composition according to item 15, wherein said direct compression or dry granulation forms tablet cores, which are respectively coated by a coating.

18. The pharmaceutical composition according to item 17, wherein a coating is provided and comprises an excipient selected from the group consisting of polyvinyl alcohol, hydroxypropyl methylcellulose and hydroxypropyl cellulose.

19. A process for preparing a dry formulation according to any one of items 1 to 14, comprising mixing fesoterodine or a salt or a solvate thereof with at least one of said pharmaceutically acceptable controlled release polymers and optionally further pharmaceutically acceptable excipient(s) under a condition of absence of any liquid or in the presence of maximally 10% liquid.

20. The process according to item 19, comprising:

(i) mixing fesoterodine or a salt or a solvate thereof with
filler selected from a group consisting of microcrystalline cellulose, lactose monohydrate, corn starch, calcium phosphate, calcium hydrogenphosphate, sucrose, mannitol, composed fillers of microcrystalline cellulose and lactose monohydrate, composed fillers of powdered cellulose and lactose monohydrate, composed fillers of corn starch and lactose monohydrate, and combinations thereof,
glidant, preferably talc,
lubricant, preferably glyceryl behenate; and
at least one controlled release polymer selected from a group consisting of hydroxypropyl methylcellulose, methylcellulose and mixture thereof,

(ii) optionally sieving the mixture, or sieving a submixture of fesoterodine or a salt or a solvate thereof with a part of said excipients and subsequently admixing a remainder part of a whole mixture.

21. The process according to item 19 or 20, further comprising direct compression of dry formulation into tablet cores.

22. The process according to item 19 or 20, further subjecting the dry formulation to dry granulation or moisture-activated dry granulation and compressing the obtained dry granulate into tablet cores.

23. The process according to item 22, wherein the dry formulation is subjected to a granulation step comprising

(i) compacting the dry formulation into compacts with roller compactor or tabletting machine by using slugging or tableting tooling,

(ii) milling the obtained compacts into dry granulate.

24. A process for preparing a pharmaceutical composition comprising preparing a dry formulation according to any of the items 19 to 23, wherein the process uses direct compression or dry granulation.

25. The process according to item 24, wherein the mixture is compressed or granulated and tableted into tablet cores, and the cores are coated with coating containing polymer selected from the group consisting of polyvinyl alcohol, hydroxypropyl methylcellulose, hydroxypropyl cellulose.

26. The dry formulation according to any one of items 1 to 14, or the pharmaceutical composition according to any of the items 15 to 18, for use in the method of treatment of urinary incontinence.

27. The dry formulation according to any one of items 1 to 14, or the pharmaceutical composition according to any of the items 15 to 18, for use in the preparation of a medicament for the treatment of urinary incontinence.

28. Any one of the preceding items, wherein the fesoterodine salt is fesoterodine fumarate.

Description of further advantages and preferred embodiments of the invention

The present invention is now described in more detail by preferred embodiments and examples, which are however presented for illustrative purpose only.

The object of the present invention was to provide an improved system with a chemically stable fesoterodine or a salt or a solvate thereof as well as a more robust, economical and acceptable production process thereof.

In one aspect the present invention provides a dry formulation of fesoterodine or a salt or a solvate thereof, comprising fesoterodine or a salt or a solvate thereof homogeneously admixed with at least one controlled release polymer in said dry formulation, and wherein said dry formulation is free of a stabilizer selected from xylitol, sorbitol, polydextrose, isomalt and dextrose.
It was surprisingly found that fesoterodine or a salt or solvate thereof showed an improved stability of fesoterodine, when its dry formulation was prepared in homogeneous admixture with at least one controlled release polymer.

Further surprisingly, the dry formulation according to the present invention disclosed herein shows even improved stability of fesoterodine compared to a comparison product containing stabilizers which were found best in WO 2007/141298. Therefore, when desired that the use of such stabilizers selected from the group consisting of xylitol, sorbitol, polydextrose, isomalt and dextrose can be dispensed with, which in turn means that at least the dry formulation itself and hence tablet cores or granules obtained therefrom can be made free of said specified stabilizers. It is believed that the presence of a homogeneous admixture of pharmaceutically suitable excipient including at least one controlled release polymer, combined with the proviso that a dry formulation in the essential or total absence of liquid is provided, establishes a protective matrix for the labile active compound. Moreover, since the dry formulation provided by the present invention allows to avoid a drying step or a step including heating or a step creating moisture conditions, further potential negative impacts affecting stability of fesoterodine, its salt or solvate can be reduced by the present invention.

The term “dry formulation” used herein means a preparation wherein the active principle fesoterodine or a salt or a solvate thereof and further ingredients for a pharmaceutical dosage form, especially tablets, have been processed while avoiding typical wet conditions, but using essentially dry or completely dry conditions. This is typically made by using limited amounts of liquids during processing of the active principle, for example to a range up to maximally 10 wt.-%, preferably clearly below 10 wt.-%, more preferably lower than 5 wt.-% and particularly lower than 2 wt.% of the whole formulation mass, or preferably totally avoiding liquids otherwise normally used for agglomeration in wet granulation, such as for example water, ethanol or their combination. Accordingly, it is preferred that residual amount of water/moisture in the dry formulation of the present invention is 4.0 wt.-% or below, preferably 2 wt.-% or below of the total dry formulation, respectively measured by loss on drying for 15 minutes at 80°C. As to other non-aqueous auxiliary liquids, which within the aforementioned maximum amount may have optionally been used during processing, notably

low alcohols such as methanol and/or ethanol, it is suitable that these are remained in the dry formulation at a proportion of 1.0 wt.-% or below, preferably 0.5 wt.-% or below and more preferably 0.1 wt.-% or below of the total dry formulation, respectively measurable for example by HPLC.

Stabilization of fesoterodine, its salt or solvate within the dry formulation is particularly efficient when the content of inactive excipients constitutes the major amount, i.e. more than 50%, of the homogeneous admixture in the total dry formulation, preferably at least 75%, particularly at least 90% the total dry formulation. It is believed that addition of such substantial amount of excipients into a common dry granulate to thereby provide a homogeneous admixture significantly contributes to stabilization of the fesoterodine compound even in the absence of a special stabilizer, i.e. distinct from a situation where only a special stabilizer substance (as described in WO2007/141298) is added into a granulation of fesoterodine or its salt or solvate.

In a preferred embodiment the active ingredient of fesoterodine is the salt fesoterodine fumarate.

In a further aspect the present invention provides a dry formulation comprising fesoterodine or a salt or a solvate thereof, wherein the dry formulation is obtainable by a process carried out substantially or even entirely without the presence of liquid.

The term “controlled release polymer”, or its synonymous term “release-rate controlling polymer”, refers to a polymer, on account of which a modified release, a retarded/delayed release, a prolonged release or a pulsatile release of the fesoterodine active ingredient from the dry formulation or the pharmaceutical composition respectively is accomplished, relative to a direct or immediate release (also sometimes called conventional release) defined by unaffected dissolution under a given condition. The terms controlled (i.e. modified, retarded/delayed, prolonged or pulsatile) release as opposed to direct/immediate/conventional release are also generally known and defined e.g. in the Glossary of European Pharmacopoeia 6.0, part 01/2008:1502. Suitable conditions to test controlled release versa direct/immediate/conventional release, for example, can be derived also from European Pharmacopoeia 6.0 (section 2.9.3), such as measured *in vitro* when subjected to dissolution test according to USP, using Apparatus 1 (rotating basket) at 100 rpm with 900 ml of phosphate buffer (50 mM) at pH 6.8 and 37°C.

The controlled release polymer may form a matrix controlling the release of the active ingredient from the dry formulation or pharmaceutical composition, respectively, wherein the matrix may further contain other excipients, the matrix forming a homogeneous admixture

with the active ingredient fesoterodine or a salt or a solvate thereof. Typically the active ingredient fesoterodine or a salt or a solvate thereof is present in particulate form throughout the matrix.

The term "liquid" used herein refers to a material in a liquid state. Typically, the liquid meant is water or lower alcohol such as methanol or ethanol or aqueous mixtures, especially water.

In another aspect, the present invention further provides a pharmaceutical composition that is obtainable from the afore-defined dry formulation by direct compression or dry granulation followed by compression of dry granulate. In this aspect, the applied technique of direct compression or dry granulation followed by compression of dry granulate may form tablet cores. Dry formulation or dry granulate can be filled in capsules or in sachets. Tablet cores can then optionally be respectively coated by a coating.

The term "direct compression" used herein means a preparation wherein dry formulation containing the active principle fesoterodine or a salt or a solvate thereof and further ingredients for a pharmaceutical dosage form have been processed by applying of a sufficient force by the punches of a tablet press on a powder to compact it into a tablet.

The term "dry granulation" used herein means a preparation wherein the dry formulation containing the active principle fesoterodine or a salt or a solvate thereof and further ingredients for a pharmaceutical dosage form have been processed by compacting into compacts with roller compactor or tabletting machine by using slugging tooling or regular tableting tooling and subsequently milling - crushing and sizing these compacts into dry granulate. The term "dry granulation" may also include moisture-activated dry granulation as further described below.

According to the present invention, the dry formulation and correspondingly the pharmaceutical composition contains at least one controlled release polymer. Suitable controlled release polymers include, without being limited thereto, polyvinylpyrrolidone, polymethacrylate, polyvinylacetate, dextranes, starch, cellulose ethers and esters like methylcellulose, methylethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, or carboxymethylcellulose, polyethyleneoxide, carrageenan, agar, alginic acid, pectin or mixtures thereof, wherein where applicable controlled release types of a specified polymer, as opposed to immediate release types, are selected. It is preferably that the controlled release polymer is present in an amount that allows for the formation of a

gel matrix from which the active ingredient can be suitably released in a controlled manner, more preferably by gradual release. According to a further preferred embodiment, the controlled release polymer is hydroxypropyl methylcellulose.

Particularly preferred controlled release polymers are selected from a group consisting of hydroxypropyl methylcellulose (HPMC), methylcellulose and mixture thereof. HPMC is preferably present in an amount that allows for the formation of a gel matrix from which the active ingredient is gradually released.

In a further preferred embodiment the dry formulation and correspondingly the pharmaceutical composition comprises two different types of polymers, at least one of which is a controlled release polymer, which combined polymers can be either of a same or of a different polymer species, and wherein the difference is preferably specified by different viscosity grades (viscosity being suitably determined by the same method). For example and according to a preferred embodiment, one type of controlled release polymer is defined by a nominal viscosity of higher than 50,000 mPas, whereas the other type of controlled release polymer is defined by a nominal viscosity of lower than 50,000 mPas, preferably differing by at least 10,000 mPas.
According to a further preferred embodiment, at least two different hydroxypropyl methylcellulose types defined by at least two different viscosity grades are combined.

Particularly preferred is a combination of HPMC types specified by the brands METHOCEL® K100M having a nominal viscosity of about 100,000 mPas and METHOCEL® K4M having a nominal viscosity of about 4,000 mPas. The weight ratios of METHOCEL® K100M and K4M used in the compositions described herein can be in the range of about 20:1 to about 1:20, and are preferably in the range of about 1:1 to 10:1, and are even more preferably in the range of about 5:1, e.g. from 4:1 to 6:1.

Preferably, the dry formulation or pharmaceutical composition according to anyone of the preceding embodiments comprise 15-65% of the at least one controlled release polymer, relative to the total amount of the dry formulation. In a further preferred embodiment the dry formulation or pharmaceutical composition comprises about 40-50% polymer, relative to the total amount of the dry formulation.

The present invention further provides a set of samples of the dry formulation comprising at least one controlled release polymer.

The present invention further provides a set of samples of the dry formulation, or of the pharmaceutical composition according to the previous aspects, respectively further comprising pharmaceutically acceptable excipients, such as fillers, glidants and lubricants.

The dry formulation or the pharmaceutical composition described herein can further contain fillers and/or binders such as lactose monohydrate, microcrystalline cellulose, powdered cellulose, compressible sugar, starch (e.g., corn starch or potato starch), pregelatinized starch, fructose, sucrose, dextrose, dextranes, other sugars such as sucrose, mannitol, siliconized microcrystalline cellulose, calcium hydrogen phosphate, calcium hydrogen phosphate dihydrate, dicalciumphosphate dihydrate, tricalciumphosphate, calcium lactate and composed fillers of microcrystalline cellulose and lactose monohydrate, composed fillers of powdered cellulose and lactose monohydrate, composed fillers of corn starch and lactose monohydrate, and combinations thereof. The fillers may be present in the form of a single compound or in the form of a mixture of compounds.

Preferably, further excipients include at least one filler selected a group of microcrystalline cellulose, lactose monohydrate, corn starch, calcium phosphate, calcium hydrogenphosphate, sucrose, mannitol, composed fillers of microcrystalline cellulose and lactose monohydrate, composed fillers of powdered cellulose and lactose monohydrate, composed fillers of corn starch and lactose monohydrate. Preferably, a mixture of lactose and microcrystalline cellulose in a ratio of about 1:1 to about 4:1 [w/w] is used as the filler. A particularly preferred further excipient is MICROCELAC® 100, which is a co-processed mixture of lactose monohydrate and microcrystalline cellulose in a ratio of 3:1. Both the filling properties of lactose and the binding capacity of microcrystalline cellulose are synergistically co-processed to one excipient providing improved flow properties and better tabletting performance to the composition.

The dry formulation or the pharmaceutical composition described herein may also comprise binders, such as cellulose derivatives (e.g., methylcellulose and sodium carboxymethylcellulose), gelatin, glucose, lactose, sucrose, polyethylene glycol, polymethacrylates, hydroxypropylcellulose, sugar alcohols, pregelatinized starch and sodium alginate. The binder may be present in the form of a single compound or in the form of a mixture of compounds.

The dry formulation or the pharmaceutical composition described herein may also comprise glidants, such as starches, colloidal silicon dioxide and talc. The term "glidants" as used herein is defined as an agent improving the fluidity of the powder and thus the filling of the

compression chamber of the tablet press. The gliding agent may be present in the pharmaceutical composition in the form of a single compound or in the form of a mixture of compounds. In a preferred embodiment glidant is talc.

The dry formulation or the pharmaceutical composition described herein may also comprise lubricants. The term "lubricant" as used herein is defined as an agent able to decrease adhesion of a powder to punches and friction between particles. The lubricant may be present in the pharmaceutical composition in the form of a single compound or in the form of a mixture of compounds. Various suitable lubricants include but are not limited to stearic acid, talc, hydrogenated vegetable oil (*e.g.* hydrogenated castor oil), sodium lauryl sulfate, glyceryl behenate, polyethylene glycol, magnesium stearate and sodium stearyl fumarate. In a preferred embodiment lubricant is selected from the group consisting of hydrogenated castor oil, polyethylene glycol, glyceryl behenate, magnesium stearate and sodium stearyl fumarate, more preferably lubricant glyceryl behenate, sodium stearyl fumarate, magnesium stearate, calcium stearate or stearic acid. Most preferably the lubricant is glyceryl behenate.

In another embodiment, the dry formulation or the pharmaceutical composition comprises (relative to the total amount of the dry formulation)
about 0.5-10% fesoterodine fumarate,
about 5-85% filler, selected from a group consisting of microcrystalline cellulose, lactose monohydrate, corn starch, calcium phosphate, calcium hydrogenphosphate, sucrose, mannitol, composed fillers of microcrystalline cellulose and lactose monohydrate, composed fillers of powdered cellulose and lactose monohydrate, composed fillers of corn starch and lactose monohydrate, and combinations thereof
about 15-65% controlled release polymer, selected from a group consisting of hydroxypropyl methylcellulose, methylcellulose and mixture thereof,
about 0.5-5% glidant, preferably talc,
about 0.5-5% lubricant, preferably glyceryl behenate.

In a preferred embodiment, the dry formulation or the pharmaceutical composition comprises (relative to the total amount of the dry formulation)
about 2-5% fesoterodine fumarate,
about 20-75% filler, selected from a group consisting of microcrystalline cellulose, lactose monohydrate, corn starch, calcium phosphate, calcium hydrogenphosphate, sucrose, mannitol, composed fillers of microcrystalline cellulose and lactose monohydrate, composed fillers of powdered cellulose and lactose monohydrate, composed fillers of corn starch and lactose monohydrate, and combinations thereof

about 20-60% controlled release polymer, selected from a group consisting of hydroxypropyl methylcellulose, methylcellulose and mixture thereof,
about 2-5% glidant, preferably talc,
about 2-5% lubricant, preferably glyceryl behenate.

In a particularly preferred embodiment, the dry formulation or the pharmaceutical composition comprises (relative to the total amount of the dry formulation)
about 2-3% fesoterodine fumarate,
about 40-55% filler, selected from a group consisting of microcrystalline cellulose, lactose monohydrate, corn starch, calcium phosphate, calcium hydrogenphosphate, sucrose, mannitol, composed fillers of microcrystalline cellulose and lactose monohydrate, composed fillers of powdered cellulose and lactose monohydrate, composed fillers of corn starch and lactose monohydrate, and combinations thereof
about 40-50% controlled release polymer, selected from a group consisting of hydroxypropyl methylcellulose, methylcellulose and mixture thereof,
about 2-3% glidant, preferably talc,
about 3-4% lubricant, preferably glyceryl behenate.

The term “about” generally means within 10%, preferably 5% and more preferably within 1% of a given value or range. Alternatively, the term “about” means within an acceptable standard error of the mean, when considered by one of the ordinary skill in the art.

In a further aspect, the pharmaceutical composition further comprises a coating using a polymer selected from the group consisting of polyvinyl alcohol, hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxyethylcellulose and polymethacrylates.

The term “coating” as used herein refers to a layer which completely covers an object and is applied by film coating. The coating can be selected from the group of ready to form dispersion such as OPADRY. The coating dispersion may comprise hydrophilic film forming polymer (such as for example low viscosity HPMC, HPC, PVA (polyvinylalcohol) and the like), plastificators (*e.g.* PEG), colorants and may optionally include other excipients such as antitacking agents.

Any method for film coating, known in the field of the pharmaceutical technology, may be used.

A pharmaceutical composition according to the present invention is preferably in solid form, including tablets, capsules, caplets, lozenges and sachets. Tablets may be suitably coated (film coated tablets, pills). Capsule formulations may cover both soft and hard capsules. A pharmaceutical composition according to the present invention is preferably in the form of tablet, more preferably coated tablet with appropriate film coating material.

In another aspect, the present invention further provides a process for preparing the pharmaceutical composition comprising fesoterodine or a salt or a solvate thereof.

In a preferred embodiment the process is carried out substantially without the presence of liquid.

The prior art teaches wet granulation as the preferred process for preparation of pharmaceutical composition comprising fesoterodine, as higher degree of degradation of fesoterodine was found by using dry granulation process. Surprisingly, we have observed that using the direct compression or dry granulation process followed by compression of the dry granulate with appropriate excipient gives satisfactory chemical stability of fesoterodine or a salt or a solvate thereof in the resulting pharmaceutical composition, even without special stabilizer as disclosed in WO2007/141298, and at the same time dissolution profiles and variability of final product are acceptable. Moreover, performing energy consuming drying in the production of the tablets can be beneficially omitted in the course of simply using direct compression, or dry granulation followed by compression of the dry granulate. When using dry granulation followed by compression of the dry granulate, the process of the present invention may include only a low number of steps such as, *e.g.* blending, optionally sieving, tableting or briquetting or slugging, and tabletting. Especially when using direct compression, the process of the present invention may include even lower number of steps such as *e.g.* blending, optionally sieving, tabletting, which is in favor of process economy and costs. This together with selecting appropriate excipients and additives as described above makes the whole process of the invention more robust, economical and acceptable.

In one aspect the process according to the present invention comprises mixing fesoterodine or a salt or a solvate thereof with at least one pharmaceutically acceptable excipient, notably with at least one controlled release polymer and optionally other pharmaceutically acceptable excipient(s), and compressing the mixture or subjecting the mixture to dry granulation or moisture-activated dry granulation, followed by compression of dry granulate wherein the mixture can be devoid of any substance selected from xylitol, sorbitol, polydextrose, isomalt and dextrose. The term “moisture-activated dry granulation” (MADG), as described for

example by Christensen et al. in "Drug Development and Industrial Pharmacy" 20(14), pp. 2195-2213 (1994) is based on the addition of limited amount of water to a dry blend of the active compound, binder and filler without the need of a drying step being involved. The use of non-aqueous liquid or aqueous mixtures thereof instead of limited water in an otherwise dry mixing system ("non-aqueous moisture activated dry granulation"; NAMADG) is also possible. Non-aqueous liquids may include alcohols such as ethanol, higher alcohols, oils, liquid glycols such as liquid polyethylene glycols, etc.

In a preferred embodiment the process comprises
mixing fesoterodine or a salt or a solvate thereof with

filler, selected from a group consisting of microcrystalline cellulose, lactose monohydrate, corn starch, calcium phosphate, calcium hydrogenphosphate, sucrose, mannitol, composed fillers of microcrystalline cellulose and lactose monohydrate, composed fillers of powdered cellulose and lactose monohydrate, composed fillers of corn starch and lactose monohydrate, and combinations thereof
glidant, preferably talc,
lubricant, preferably glyceryl behenate and
controlled release polymer selected from a group consisting of hydroxypropyl methylcellulose, methylcellulose and mixture thereof,

optionally sieving the mixture, or sieving a submixture of fesoterodine or a salt or a solvate thereof with a part of said excipients (e.g. at least one filler) and subsequently admixing a remainder part of a whole mixture, preferably the controlled release polymer is admixed after sieving of the previous submixture.

In another aspect, the present invention further provides a process for preparing the pharmaceutical composition from dry formulation further comprising at least one dry granulation step, optionally followed by tabletting, wherein the dry formulation can be devoid of any substance selected from xylitol, sorbitol, polydextrose, isomalt and dextrose.

In yet another aspect, the present invention further provides a process wherein the dry formulation is subjected to a dry granulation step comprising:
compacting the dry formulation into compacts with roller compactor or tabletting machine by using slugging or tableting tooling,
milling the obtained compacts into dry granulate.

The advantages of direct compression and dry granulation over wet granulation include, less manufacturing steps involved, elimination of heat and moisture. The overall process of direct

compression may involve only weighing of the powders, optionally sieving, blending, and finally compression, hence less cost than wet granulation. The overall process of dry granulation followed by the compression of dry granulate may involve only weighing of the powders, briquetting or slugging, optionally sieving, milling and blending, and finally compression, hence also less cost than wet granulation.

In most preferred embodiment the granulation step comprises milling of the compacts obtained by compressing the dry formulation, and compressing the obtained dry granulate.

In another aspect, the present invention further provides a process for preparing the pharmaceutical composition further comprising coating of the compressed mixture with a coating mixture containing polymer selected from the group consisting of polyvinyl alcohol, hydroxypropyl methylcellulose, hydroxypropyl cellulose.

In another aspect, the present invention further provides the dry formulation or the pharmaceutical composition according to the present invention for use in a method of treatment of urinary incontinence.

In the preferred embodiment the pharmaceutical formulation is used in the preparation of a medicament for the treatment of urinary incontinence.

Examples

Comparative example– prepared according to WO2007/141298 (Example G)

Component	Amount per tablet (mg)	Portion	Amount per lab. batch (g)
GRANULATE			
Fesoterodine fumarate	8.000	2.5%	8.000
Xylitol	72.000	22.5%	72.000
Total	80.000	25.0%	80.000
TABLETS			
Granulate	80.000	25.0%	40.000
Lactose monohydrate	58.125	18.2%	29.063
Microcrystalline cellulose	19.375	6.1%	9.688
Hypromellose Methocel K100M	120.000	37.5%	60.000
Hypromellose Methocel K4M	24.000	7.5%	12.000

Gliceryl Behenate	10.000	3.1%	5.000
Talc	8.500	2.7%	4.250
Total	320.000	100.0%	820.000

Fesoterodine fumarate and xylitol were granulated with demineralized water manually in mortar with pestle. Granulate was dried in vacuum chamber drier to LOD 0.5%. Dried granulate was pushed through 0.8 mm screen. Granulate was mixed with lactose and microcrystalline cellulose and passed through screen 0.8 mm. Then Methocel K4M and Methocel K100M were added to the screened mixture and blended in double-cone blender for 5 min. The mixture was then again passed through screen 0.8 mm and blended in double-cone blender for 10 min so that final tabletting blend was obtained. Final blend was compressed into oval biconvex tablets by rotary tabletting machine.

Example 1

Component	Amount per tablet (mg)		Amount per batch (g)
Fesoterodine fumarate	8.000	2.5%	1.600
Microcrystalline cellulose	50.000	15.6%	10.000
Lactose monohydrate	100.000	31.3%	20.000
Hypromellose Methocel K100M	120.000	37.5%	24.000
Hypromellose Methocel K4M	24.000	7.5%	4.800
Gliceryl Behenate	10.000	3.1%	2.000
Talc	8.000	2.5%	1.600
Total	320.000	100.0%	64.000

Fesoterodine fumarate was manually mixed with microcrystalline cellulose and lactose in polyethylene bag for 1 min. Obtained blend was then passed through hand sieve 0.5 mm. Methocel K4M and Methocel K100M were added to screened blend and manually mixed in polyethylene bag for 3 min. Then talc was added to the blend in PE bag, and mixed for 1 min. Then glyceryl behenate was added to the blend in PE bag and mixed for 1 min, so that final tabletting blend was obtained. Final blend was compressed into oval biconvex tablets by eccentric tabletting machine.

Example 2

Component	Amount per tablet (mg)		Amount per lab. batch (g)
Fesoterodine fumarate	8.000	2.5%	60.000
Lactose monohydrate	100.000	31.3%	750.000
Microcrystalline cellulose	50.000	15.6%	375.000
Hypromellose Methocel K100M	120.000	37.5%	900.000
Hypromellose Methocel K4M	24.000	7.5%	180.000
Gliceryl Behenate	10.000	3.1%	75.000
Talc	8.000	2.5%	60.000
Total	320.000	100.0%	2400.000

Fesoterodine fumarate was manually mixed with lactose in polyethylene bag for 1 min to obtain Blend 1. Blend 1 was then passed through 0.5 mm screen on oscillating bar mill. Screened Blend 1 was then transferred to bin blender (double-cone blender) and blended for 2 min. Microcrystalline cellulose, Methocel K4M and Methocel K100M were then added to Blend 1 in bin blender and blended for additional 2 min to obtain Blend 2. Blend 2 was then

passed through 0.5 mm screen on oscillating bar mill and transferred back to double-cone blender and blended for additional 2 min. Then talc was added to the blend in double-cone blender.and mixed for 2 min. Then glyceryl behenate was added to the blend in double-cone g and mixed for 1 min so that final tabletting blend was obtained. Final blend was compressed into oval biconvex tablets by rotary tabletting machine.

Example 3

Component	Amount per tablet (mg)		Amount per lab. batch (g)
Fesoterodine fumarate	8.000	2.5%	60.000
Lactose monohydrate	100.000	31.3%	750.000
Microcrystalline cellulose	50.000	15.6%	375.000
Hypromellose Methocel K100M	120.000	37.5%	900.000
Hypromellose Methocel K4M	24.000	7.5%	180.000
Gliceryl Behenate	10.000	3.1%	75.000
Talc	8.000	2.5%	60.000
Total	320.000	100.0%	2400.000

Fesoterodine fumarate was manually mixed with lactose in polyethylene bag for 1 min to obtain Blend 1. Blend 1 was then passed through 0.5 mm screen on oscillating bar mill. Screened Blend 1 was then transferred to bin blender (double-cone blender) and blended for 2 min. Microcrystalline cellulose, Methocel K4M and Methocel K100M were then added to Blend 1 in bin blender and blended for additional 2 min to obtain Blend 2. Blend 2 was then passed through 0.5 mm screen on oscillating bar mill and transferred back to double-cone blender and blended for additional 2 min. Then talc was added to the blend in double-cone blender, and mixed for 2 min. Then glyceryl behenate was added to the blend in double-cone g and mixed for 1 min, so that final tabletting blend was obtained. Final blend was compressed into oval biconvex tablets by rotary tabletting machine.
Obtained tablets were milled by impact hammer mill with blades and screen 1.0 mm.
Obtained dry granulate was compressed into oval biconvex tablets by rotary tabletting machine.

Example 4

Component	Amount per tablet (mg)		Amount per lab. batch (g)
Tablet cores Example 3	320.000	95.5%	800.000
Opadry II	15.000	4.5%	*75.000

Demineralized water	60.000		*300.000
Total	335.000	100.0%	837.500

*The coating dispersion was prepared in double amount, due to possible losses and the coating end was determined by weighing of coated tablets.

Tablet cores prepared as disclosed in Example 3 were film coated in perforated pan coater by spraying the coating dispersion onto tablet cores. The coating dispersion was prepared by dispersing of Opadry II in demineralized water.

Example 5

Component	Amount per tablet (mg)		Amount per lab. batch (g)
Tablet cores Example 3	320.000	95.5%	800.000
Hypromellose Pharmacoat 606	8.775	2.6%	*43.875
Hydroxypropyl cellulose	0.975	0.3%	*4.875
Polyethylene glycol	1.500	0.4%	*7.500
Titanium dioxide	2.400	0.7%	*12.000
Blue Pigment Indigotin	0.600	0.2%	*3.000
Talc	0.750	0.2%	*3.750
Demineralized water	135.000		*675.000
Total	335.000	100.0%	837.500

* The coating dispersion was prepared in double amount, due to possible losses and the coating end was determined by weighing of coated tablets.

Tablet cores prepared as disclosed in Example 3 were film coated in perforated pan coater by spraying the coating dispersion onto tablet cores. The coating dispersion was prepared by dispersing of Hypromellose, Hydroxypropyl cellulose, Polyethylene glycol, titanium dioxide, pigment and talc in demineralized water.

Stress stability tests:

A stress stability test was designed to show intrinsic stability of test formulations in comparison to a reference formulation, known from prior art. The test samples (tablets) were exposed to elevated temperature (60℃) and a controlled relative humidity (21%). The appropriate relative humidity was achieved by means of a saturated solution of potassium fluoride, stored in an impermeable cabined inside a thermostatically controlled chamber, set

at 60°C. Tablets were exposed to this stress condition for two weeks with no primary packaging (open dish). After two weeks, samples were analyzed for content of 5-HMT by means of high performance liquid chromatograph (HPLC).

HPLC method was run on an Alliance HPLC instrument (Waters) using BEH Shield RP18 column (50 x 2.1 mm 1.7 um particles). The mobile phase consisted of 0.05% phosphoric acid (A) and acetonitrile (B). The mobile phase was pumped at 0.5 ml/min with a gradient, beginning at 10% mobile phase B, increasing to 90% mobile phase B in 4 minutes, followed by column re-equilibration for two minutes. Chromatograms were followed at 220 nm and typical retention times of fesoterodine fumarate and 5-HMT were 2.5 and 1.5 min, respectively. Evaluation is done by the Area% method

Stability evaluation:

A formulation is preferred, if the amount of 5-HMT, formed after exposure to the indicated stress conditions, is below or equal to that of the comparative example.

	% 5-HMT (hydrolysis product)	Total degradation products
Example 1	2.0	4.5
Example 2	2.4	5.0
Example 3	2.4	5.0
Example 4	2.2	5.1
Example 5	2.4	5.3
Comparative example	4.0	10.8

Claims

1. A dry formulation of fesoterodine or a salt or a solvate thereof, comprising said fesoterodine or a salt or a solvate thereof homogeneously admixed with at least one controlled release polymer in said dry formulation, and wherein said dry formulation is free of a stabilizer selected from xylitol, sorbitol, polydextrose, isomalt and dextrose.

2. The dry formulation according to claim 1, wherein an optional liquid, when used, was limited during the dry formulation preparation process at a maximum of 10% liquid relative to the composition subjected to dry formulation.

3. The dry formulation according to claim 1 or 2, wherein the at least one controlled release polymer is selected from the group consisting of hydroxypropyl methylcellulose, methylcellulose hydroxyethylcellulose, hydroxypropylcellulose, carboxymethylcellulose, ethylcellulose, polyethyleneoxide, carrageenan, agar, alginic acid, pectin and a mixtures thereof, preferably hydroxypropyl methylcellulose.

4. The dry formulation according to any one of the preceding claims, including at least one controlled release polymer combined with another polymer of the same polymer type or of different polymer types, the combined polymers differing in their viscosity grades.

5. The dry formulation according to any one of the preceding claims, wherein the at least one controlled release polymer is a combination of at least two different viscosity grades of hydroxypropyl methylcellulose.

6. The dry formulation according to anyone of the preceding claims, further comprising pharmaceutically acceptable excipients selected from fillers, glidants and lubricants present in said dry formulation.

7. The dry formulation according to any one of the proceeding claims, comprising relative to the total amount of the dry formulation:
   (i) 0.5-10% fesoterodine fumarate,
   (ii) 5-85% filler selected from a group consisting of microcrystalline cellulose, lactose monohydrate, corn starch, calcium phosphate, calcium hydrogenphosphate, sucrose, mannitol, composed fillers of microcrystalline cellulose and lactose monohydrate, composed fillers of

powdered cellulose and lactose monohydrate, composed fillers of corn starch and lactose monohydrate, and combinations thereof

(iii) 15-65% controlled release polymer, selected from a group consisting of hydroxypropyl methylcellulose, methylcellulose and mixture thereof,

(iv) 0.5-5% % glidant, preferably talc,

(v) 0.5-5% % lubricant, preferably glyceryl behenate.

8. A pharmaceutical composition, obtained from a dry formulation of fesoterodine or a salt or a solvate thereof according to any one of the preceding claims by direct compression or dry granulation followed by compression of dry granulate.

9. The pharmaceutical composition according to claim 8, wherein said direct compression or dry granulation followed by compression of dry granulate forms tablet cores, which are respectively coated by a coating.

10. The pharmaceutical composition according to claim 9, wherein a coating comprises a polymer excipient selected from the group consisting of polyvinyl alcohol, hydroxypropyl methylcellulose and hydroxypropyl cellulose.

11. A process for preparing a dry formulation according to any one of claims 1 to 7, comprising mixing fesoterodine or a salt or a solvate thereof with said at least one controlled release polymer and optionally further pharmaceutically acceptable excipient(s) under a condition of absence of any liquid or in the presence of maximally 10% liquid.

12. The process according to claim 11, comprising:

(i) mixing fesoterodine or a salt or a solvate thereof with
filler selected from a group consisting of microcrystalline cellulose, lactose monohydrate, corn starch, calcium phosphate, calcium hydrogenphosphate, sucrose, mannitol, composed fillers of microcrystalline cellulose and lactose monohydrate, composed fillers of powdered cellulose and lactose monohydrate, composed fillers of corn starch and lactose monohydrate, and combinations thereof,
lubricants, preferably glyceryl behenate; and
at least one controlled release polymer selected from a group consisting of hydroxypropyl methylcellulose, methylcellulose and mixture thereof, and

(ii) optionally sieving the mixture, or sieving a submixture of fesoterodine or a salt or a solvate thereof with a part of said excipients and subsequently admixing a remainder part of a whole mixture.

13. The process according to claim 11 or 12, further comprising direct compression of dry formulation into tablet cores.

14. The process according to claim 11 or 12, further subjecting the dry formulation to dry granulation or moisture-activated dry granulation and compressing the obtained dry granulate into tablet cores.

15. The process according to claim 14, wherein the dry formulation is subjected to a dry granulation step comprising:
(i) compacting the dry formulation into compacts with roller compactor or tabletting machine by using slugging or tableting tooling,
(ii) milling the obtained compacts into dry granulate.

16. The process according to any of claims 11 to 15 to prepare a pharmaceutical composition, wherein the mixture is compressed or dry granulated and tabletted into tablet cores, and the cores are coated with coating, preferably the coating contains a polymer selected from the group consisting of polyvinyl alcohol, hydroxypropyl methylcellulose, hydroxypropyl cellulose.

17. The dry formulation according to any one of claims 1 to 7, or the pharmaceutical composition according to any of the claims 8 to 10 for use as a medicament, preferably for use in a treatment of urinary incontinence.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/056397

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K9/28 A61K31/222
ADD.

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)
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 practicable, search terms used)
EPO-Internal, WPI Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/043408 A2 (RATIOPHARM GMBH [DE]; RIMKUS KATRIN [DE]; MUSKULUS FRANK [DE]; BRUECK) 22 April 2010 (2010-04-22) page 2, line 12 - page 19, line 10 examples 2-5	1-17
X	WO 2007/072169 A2 (PFIZER PROD INC [US]; MASTRELL CARL ERIK JOHAN [US]; SUESSERMAN MICHAE) 28 June 2007 (2007-06-28) example 3	1-17
X	WO 2010/010464 A2 (ACTAVIS GROUP PTC EHF [IS]; NEELA PRAVEEN KUMAR [IN]; CHARUGUNDLA KISH) 28 January 2010 (2010-01-28) claims 1-88 examples 7-10	1-17

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

[X] See patent family annex.

* Special categories of cited documents :

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

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"O" document referring to an oral disclosure, use, exhibition or other means

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"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
16 May 2012	04/06/2012

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/056397

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2009/044278 A1 (ACTAVIS GROUP PTC EHF [IS]; CHARUGUNDLA KISHORE [IN]; CHANDRAMOHAN UDH) 9 April 2009 (2009-04-09) page 4, line 19 - page 8, line 10 -----	1-17

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2012/056397

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