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(54) Title: EXTENDED RELEASE PHARMACEUTICAL COMPOSITION CONTAINING FESOTERODINE AND PROCESS FOR THE PREPARATION THEREOF

(57) Abstract: The present invention relates to an extended release pharmaceutical composition for oral administration comprising a therapeutically effective quantity of fesoterodine or a pharmaceutically acceptable salt, metabolite or derivative thereof, as an active ingredient, an effective quantity of ion exchange resin as a stabilizer in order to prevent the degradation and improve the physicochemical stability of the active ingredient in the finished dosage form and at least one pharmaceutically acceptable excipient as a rate controlling agent to modify/control the release of the active ingredient in the finished dosage form.



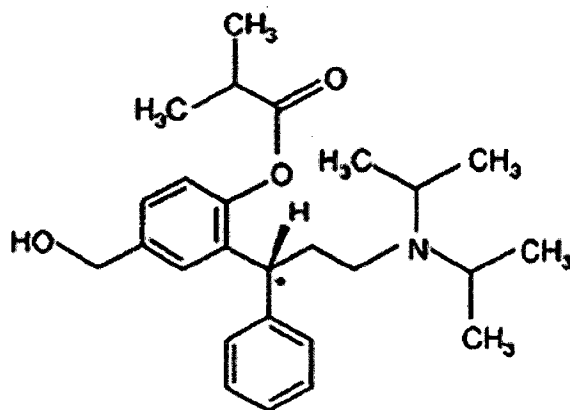
EXTENDED RELEASE PHARMACEUTICAL COMPOSITION CONTAINING FESOTERODINE AND PROCESS FOR THE PREPARATION THEREOF

5 TECHNICAL FIELD OF THE INVENTION

The present invention relates to an improved extended release dosage form, and in particular to a pharmaceutical composition for oral administration comprising a therapeutically effective quantity of fesoterodine or a pharmaceutically acceptable salt, metabolite, or derivative thereof, as an active ingredient, and an effective quantity of ion exchange resin in order to prevent the degradation of said active ingredient, and a process for the preparation thereof.

BACKGROUND OF THE INVENTION

Fesoterodine is a muscarinic receptor antagonist used for the treatment of overactive bladder syndrome including urinary incontinence. Fesoterodine's chemical name is [2-[(1R)-3-(Di(propan-2-yl)amino)-1-phenylpropyl]-4-(hydroxymethyl)phenyl]2-methylpropanoate) and its chemical structure is presented by the following Formula I.



Formula I

Fesoterodine is rapidly hydrolyzed in vivo into its active metabolite 5-hydroxy methyl tolterodine, which binds and inhibits muscarinic receptors on the bladder detrusor muscle, thereby preventing bladder contractions or spasms caused by acetylcholine. This results in the relaxation of bladder smooth muscle and greater bladder capacity, in addition to a reduction in involuntary muscle contractions and involuntary loss of urine.

Said conversion of fesoterodine into 5-hydroxymethyltolterodine under humid environment and at increased temperature is undesirable in the pharmaceutical formulation. Therefore, there is a need to provide a pharmaceutical composition comprising fesoterodine that is stable against fesoterodine degradation over an extended period of time.

Furthermore, the dissolution profile of extended release pharmaceutical compositions containing fesoterodine or a pharmaceutical acceptable salt, derivative and metabolite thereof can also be influenced by the selection of the excipients, as the drug release rate is dependent from the gastrointestinal pH-value and/or ionic strength. It is favorable for an extended release formulation to possess drug release rates, independent or less dependent from the ionic strength and/or pH of the environment through out the whole gastrointestinal tract in order to achieve better treatment to a patient.

Various methods are already known for the industrial preparation of extended release oral dosage forms comprising Fesoterodine or a pharmaceutical acceptable salt, derivative and metabolite thereof as an active ingredient due to its useful therapeutical properties. However, the prior art has encountered substantial difficulties in the production of a stable extended release and bioavailable fesoterodine composition of a desirable dissolution profile and a cost effective manufacturing process.

EP-B-2029134 discloses a pharmaceutical granulate comprising fesoterodine or a pharmaceutically acceptable salt or solvate thereof and a pharmaceutically acceptable stabilizer against hydrolysis, such as sorbitol, xylitol, polydextrose, isomalt, dextrose or combinations thereof. Further, said fesoterodine and stabilizer granulate is embedded in a gel matrix formed by a water swellable sustained release agent such as hydroxypropyl methylcellulose. According to said document, fesoterodine is more stable in a composition comprising sugar alcohols and in the presence of water e.g. by wet granulation. Dry granulation or direct compression resulted in higher amounts of undesirable degradation products.

EP-A-2508175 discloses a microencapsulated fesoterodine composition which is composed of a particle containing fesoterodine and a shell surrounding the fesoterodine-containing particle, wherein the shell comprises a hydrophobic polymer as rate-controlling agent, such as acrylate-based polymers, acrylates or methylacrylates and a pore-forming agent, such as water soluble polymer or water soluble salt. According to said document, in order to prevent degradation of fesoterodine, the proposed composition requires a complex-structured pharmaceutical composition.

Although each of the above patents represents an attempt to achieve a desirable release rate for once a day administration and to overcome the stability problems of the active ingredient associated with pharmaceuticals compositions comprising fesoterodine, there still exists a need for improving fesoterodine's stability of such pharmaceutical compositions in a less complicated production approach.

SUMMARY OF THE INVENTION

It is, therefore, an object of the present invention to provide an improved sustained release solid dosage composition for oral administration containing fesoterodine or pharmaceutical acceptable salt, derivative and metabolite thereof as an active ingredient, which overcomes the deficiencies of the prior art.

It is another object of the present invention to provide a stable sustained release solid pharmaceutical composition for oral administration containing fesoterodine or pharmaceutical acceptable salt, derivative and metabolite thereof as an active ingredient, which is bioavailable

and effective with sufficient self-life, good pharmacotechnical properties, enhancing patient compliance and reducing possible side effects.

Moreover, it is another object of the present invention to provide a suitable process for the preparation of an extended release pharmaceutical composition for oral administration comprising a therapeutically effective quantity of fesoterodine or a pharmaceutically acceptable salt, derivative or metabolite thereof as an active ingredient, which is cost effective and reproducible.

In accordance with the above objects of the present invention, an extended release pharmaceutical composition for oral administration is provided comprising a therapeutically effective quantity of fesoterodine or a pharmaceutically acceptable salt, metabolite or derivative thereof, as an active ingredient and an effective quantity of ion exchange resin as a stabilizer in order to prevent the degradation and improve the physicochemical stability of the active ingredient in the finished dosage form.

According to another embodiment of the present invention, a process for the preparation of an extended release pharmaceutical composition for oral administration comprising a therapeutically effective quantity of fesoterodine or a pharmaceutically acceptable salt, metabolite or derivative thereof as an active ingredient, and an effective quantity of ion exchange resin as a stabilizer in order to prevent the degradation of said active ingredient is provided, wherein said process comprises following steps:

a) Complexation: Dissolving the total quantity of fesoterodine or a pharmaceutically acceptable salt, metabolite or derivative thereof into an appropriate solvent and forming a homogenous mixture by adding the total quantity of an ion exchange resin and mixing for appropriate time until the complexation reaction is completed, and subsequently separating the solid fraction (resinate) from prepared slurry by discarding the filtrate;

b) Drying the wetted resinate mass from step a);

c) Sizing the dried resinate obtained from step b) by passing through a sieve;

d) Adding to the sieved resinate from step c) the total quantity of a rate controlling agent and at least one optional additional excipient such as binder, diluent, lubricant and/or glidant and mixing for appropriate time.

e) Compressing the final blend from step d) into a desired tablet form in a rotary compression machine using appropriate punches.

Further preferred embodiments of the present invention are defined in dependent claims 2 to 9, 11 and 12.

Other objects and advantages of the present invention will become apparent to those skilled in the art in view of the following detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows dissolution profiles of fesoterodine containing pharmaceutical composition according to the present invention (composition 1)

DETAILED DESCRIPTION OF THE INVENTION

For the purposes of the present invention, a pharmaceutical composition comprising fesoterodine or salts, metabolites or derivatives thereof is considered to be “stable” if said ingredient
5 degrades less or more slowly than it does on its own and/or in known pharmaceutical compositions during storage.

An excipient is considered to be “incompatible” with fesoterodine or salts, metabolites or derivatives thereof if it promotes the degradation of said active ingredient, that is to say, if said active ingredient degrades more or faster in the presence of said excipient when compared with
10 the degradation of said active ingredient on its own. The terms “incompatibility”, “compatible” and “compatibility” are defined accordingly.

The active ingredient contained in a dosage form is “bioavailable”, if when administered in a dosage form is released from the dosage form, absorbed and reaches, at least the same, concentration levels in plasma as any of the marketed products containing the same quantity of
15 the same active ingredient and intended for the same use.

Although the pharmaceutical composition may be in various forms, the preferred solid forms are tablets, capsules and caplets.

One of the main disadvantages of fesoterodine or salts, metabolites or derivatives thereof is the fact that, it is very labile and consequently many limitations concerning the choice of excipients
20 are raised.

It has been surprisingly found that the object of the present invention is achieved by employing an ion exchange resin such as Sodium Polystyrene Sulfonate, in order to prevent the degradation and improve the physicochemical stability of the active ingredient in the finished dosage form.

Ion exchange resins are insoluble polymers that contain acidic or basic functional groups and
25 have the ability to exchange counter-ions within aqueous solutions surrounding them. The efficacy of ion exchange resins mainly depends upon their physical properties such as degree of cross-linking, porosity, acid base strength, stability, purity and particle size. The most common resins used in pharmaceutical formulations are cross-linked polystyrene and polymethacrylate polymers.

The use of ion exchange resins into drug delivery systems have been encouraged because of the their physico-chemical stability, inert nature, uniform size, spherical shape assisting coating and equilibrium driven reproducible drug release in ionic environment. The physical and chemical properties of the ion exchange resins will release the drug more uniformly than that of simple matrix formulations.

Complexes between ion exchange resins and drugs are known as resinates, which have been used in pharmaceutical formulations for several decades. Resinates are usually prepared by mixing the resin with a drug solution and allowing sufficient time for loading. The resin/fluid slurry is then filtered and the filtrate washed. The resinate is then dried. The dried resinate will be free of flowing powder with physical properties similar to the original resin, which can be
40 formulated into tablets, capsules, lozenges etc.

The weight ratio of fesoterodine to ion exchange resin in the solid composition according to the present invention may be selected from 1 : 05 to 1 : 80, preferably from 1 : 1.5 to 1 : 6, more preferably from 1 : 1.5 to 1 : 5, and most preferably from 1 : 2 to 1 : 4. The hydrophilic polymer with carboxylic acid groups to be used in accordance with the present invention has carboxylic acid groups in the Na⁺ form. Ion exchange resin polymers according to the present invention may be selected from polyacrylate a copolymer of methacrylic acid and an acrylic or methacrylic ester, a copolymer of methacrylic acid and divinylbenzene or a sulfonated copolymer of styrene and divinylbenzene. The preferred copolymer to be used in accordance with the present invention is also known as Sodium Polystyrene Sulfonate, which is a strong acid cation exchange resin. Said resin is the sodium salt of a sulfonated copolymerization between styrene and divinylbenzene. Said resins are commercially available under the trademark AmberliteTM IRP69.

The pharmaceutical compositions of the present invention may also contain one or more additional formulation ingredients selected from a wide variety of excipients. According to the desired properties of the composition, any number of ingredients may be selected, alone or in combination, based upon their known uses in preparation of solid dosage form compositions (tablet/capsule compositions).

Such ingredients include, but are not limited to, diluents, binders, rate controlling agents, compression aids, glidants, lubricants, water scavengers, colorants, coating agents and preservatives.

The optional excipients must be compatible with fesoterodine or salt, metabolite or derivative thereof so that it does not interfere with it in the composition.

Moreover, any excipient may optionally be added to the above composition, provided that they are compatible with the active ingredient of the composition, in order to overcome problems associated with unfavorable pharmacotechnical characteristics of these substances, and in order to increase the stability of the drug and the self-life of the pharmaceutical product, and provide a product exhibiting excellent bioavailability.

The composition of the present invention may include further additives (alone or in a combination) such as absorbents, acids, adjuvants, anticaking agents, glidants, antitacking agents, antifoamers, anticoagulants, antimicrobials, antiseptics, diluents, binders, chelating agents, sequestrants, coating agents, colorants, dyes, pigments, complexing agents, softeners, crystal growth regulators, denaturants, desiccants, dehydrating agents, dispersants, solubilizers, emollients, emulsifiers, fillers, flavor masking agents, gelling agents, humectants, lubricants, moisturizers, bufferants, pH control agents, plasticizers, retarding agents, stabilizers, suspending agents, thickening agents, surfactants, opacifiers, coloring agents, preservatives, antigellants, rheology control agents, tonicifiers etc.

Diluents may be selected from calcium carbonate, calcium phosphate dibasic, calcium phosphate tribasic, calcium sulfate, microcrystalline cellulose, microcrystalline silicified cellulose, powdered cellulose, dextrates, dextrose, fructose, lactitol, lactose anhydrous, lactose monohydrate, lactose dihydrate, lactose trihydrate, mannitol, sorbitol, starch, pregelatinized starch, sucrose, talc, xylitol, maltose, isomalt, maltodextrin, maltitol and the like. Diluents may be in the range of 10-90 weight % of the total weight of the composition.

Binders may be selected from acacia, alginic acid, carbomer, carboxymethylcellulose calcium, carbomethylcellulose sodium, microcrystalline cellulose, powdered cellulose, ethyl cellulose, gelatin liquid glucose, guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, maltodextrin, methylcellulose, polydextrose, polyethylene oxide, sodium alginate, starch paste, pregelatinized starch, sucrose, tragacanth, low-substituted hydroxypropyl cellulose, glucose, sorbitol. Binders may be in the range of 1-40 weight % of the total weight of the composition.

Rate controlling agents may be selected from one or more polymers/copolymers of cellulose or its derivatives such as hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxyethyl methyl cellulose, methylcellulose, carboxymethylcellulose and its salts; polyacrylates, methylacrylates, polyethylene oxides, polyethylene glycols, gums, chitosan, starch derivatives, polyurethanes, galactomannans, polysaccharides, polyalcohols, acrylic acid or its derivatives, ethyl cellulose, glycerol palmitostearate, beeswax, glycowax, carnaubawax, hydrogenated vegetable oil, glycerol monostearate, stearylalcohol, glyceryl behenate, polyanhydrides, methylacrylates, polyamides, polycarbonates, polyalkylene, polyalkylene glycols, polyalkylene oxides, polyalkylene terephthalates, polyvinyl alcohols, polyvinyl ethers, polyvinyl halides, polyvinylpyrrolidone, polyglycolides, polysiloxanes, polyurethanes, polystyrene, polymers of acrylic and methacrylic esters, polylactides, poly(butyric acid), poly(valeric acid), poly(lactide-co-glycolides), polyanhydrides, polyorthoesters, poly(fumaric acid), poly(maleic acid), cellulose acetate, cellulose propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxymethylcellulose, cellulose triacetate, cellulose sulfate sodium salt, poly(methylmethacrylate), poly(ethylmethacrylate), poly(butylmethacrylate), poly(isobutylmethacrylate), poly(hexylmethacrylate), poly(isodecylmethacrylate), poly(lauryl-methacrylate), poly(phenylmethacrylate), poly(methylacrylate), poly(isopropyl-methacrylate) and the like. Rate controlling agents may be in the range of 1-95 weight % of the total weight of the composition.

Glidants may be selected from calcium silicate, powdered cellulose, starch, talc, colloidal silicon dioxide and the like. Glidants may be in the range of 0.01-2 weight % of the total weight of the composition.

Lubricants may be selected from magnesium stearate, stearic acid, sodium stearyl fumarate, magnesium lauryl sulphate, talc, polyethylene glycol, glyceryl behenate and the like. Lubricants may be in the range of 0.01-2 weight % of the total weight of the composition.

All percentages stated herein are weight percentages based on total composition weight, unless otherwise stated.

Another embodiment of the present invention is the use of a complexation process for the preparation of solid dosage forms for oral administration containing fesoterodine or salt, metabolite or derivative thereof. The steps in complexation technique may be as follows:

a) Dissolving the total quantity of fesoterodine or a pharmaceutically acceptable salt, metabolite or derivative thereof, in aqueous or non-aqueous solvent and suspending/mixing the total quantity of an ion exchange resin in the resulting solution;

b) Mixing the resulting slurry for appropriate time until the complexation reaction is completed. Temperature modification and/or pH adjustment may be needed in order to optimize the complexation reaction.

- c) Separating the solid fraction (resinate) from prepared slurry and discard the filtrate.
- d) Drying the resinate until suitable LOD (Loss on Drying).
- e) Sizing the dried resinate from previous step
- 5 f). Adding to the sieved resinate from step e) the total quantity of a rate controlling agent and at least one optional additional excipient such as binder, diluent and/or glidant and mixing for appropriate time.
- g) Lubricating the blend from step f) with suitable lubricants for appropriate time.
- 10 h) Compressing the final blend of step g) into a desired tablet form in a rotary compression machine using appropriate punches.
- i) Optionally, film coating the prepared tablets.

The complexation process of the present invention may optionally be prepared by mixing the ion exchange resin with the total quantity of Fesoterodine fumarate, and then adding them in the suitable solvent.

- 15 The extended release pharmaceutical composition of the present invention comprising Fesoterodine fumarate as an active ingredient has been compared to extended release reference product Toviaz™ consisting of fesoterodine fumarate with the following excipients xylitol, Lactose monohydrate, Microcrystalline cellulose, Hypromellose, Glycerol dibehenate, Talc, and as film-coating comprising Poly(vinyl alcohol), Titanium dioxide, Macrogol, Talc, Soya lecithin
- 20 and indigo carmine aluminium lake.

The pharmaceutical compositions according to the present invention are characterized by excellent pharmacotechnical properties, such as homogeneity, flowability and compressibility. Thanks to these properties, the solid dosage forms prepared by the process according to the present invention exhibit excellent technical characteristics including dissolution rate, hardness,

25 and stability.

Table 1: Dissolution profile of Composition 1

	% Dissolved at pH 6.8
Time (hrs)	Composition 1
1	6.4
2	11.2
4	20.1
6	29.7
8	39.2
12	54.7
16	68.5
20	80.8

One of the most critical pharmacotechnical tests is the Dissolution test as it is strongly correlated with the bioavailability of the product. For the dissolution method a Paddle Apparatus was used at rotation speed 75rpm, in aqueous dissolution medium with pH 6.8.

- 5 As it is shown in Table 1, composition 1 according to the present invention shows an extended release of Fesoterodine as depicted in Fig. 1.

One of the main objects of the present invention was to prepare a product with acceptable stability. For this reason 3 batches of composition 1 were exposed to normal and accelerated stability studies according to the current ICH guidelines.

- 10 The results showed that the stability of the present invention was good. Particularly diol and total impurities for Composition 1 (when stored in open vials at accelerated conditions, 40°C/75%RH) were 1.88% and 3.29% respectively, compared to reference product wherein diol impurity was 3.57% and total impurities were 6.50%.

- 15 The selection of appropriate materials (excipients, reagents etc.) should be done carefully in order to avoid any incompatibility problems or non-compliance with European Pharmacopoeia and FDA guidelines for inactive ingredients.

The tablets may be film coated with functional or non-functional coating.

The following examples illustrate preferred embodiments in accordance with the present invention without limiting the scope or spirit of the invention:

20 EXAMPLES

Example 1: Composition 1 of Fesoterodine fumarate and Amberlite™ IRP69 (weight ratio: Fesoterodine fumarate : Amberlite™, 1:2)

TABLE 2: Fesoterodine composition 1

s. no	Ingredients	mg/tab
1	Fesoterodine Fumarate	8.0
2	Amberlite™ IRP69	16.0
3	HPMC K100M	120.0
4	HPMC K15M	24.0
5	MicroceLac™ 100	130.3
6	Colloidal Silicon Dioxide	3.2
7	Talc	8.5
8	Glyceryl Behenate	10.0
9	Opadry™ 200F	16.0

A preferred Fesoterodine composition 1 according to the present invention is illustrated in Table 2.

5 Tablets of fesoterodine composition 1 of the present invention were prepared according to the following manufacturing process:

The total quantity of fesoterodine fumarate was dissolved in water. In said solution Amberlite™ IRP69 as ion exchange resin was suspended and mixed for ~ 7 hour until the complexation reaction is completed. Subsequently, the formed resinate was separated by filtration. The wetted resinate mass was then dried, passed through a sieve to achieve the desired granule size and further mixed with the HPMC K100M and HPMC K15M (used as rate controlling agents), Microcelac™ (as diluent/binder), and Colloidal Silicon Dioxide and Talc (as glidants) until a uniform blend is obtained. Subsequently, the obtained blend is mixed with Glyceryl Behenate (as lubricant).

15 The final blend was then compressed into the desired tablets in a rotary compression machine using appropriate punches. The prepared tablets were coated using Opadry™ 200F in a suitable pan coater.

Another object of the present invention was to prepare a pharmaceutical composition that is stable for a long period of storage time. Therefore, tablets of Composition 1 in open vials were exposed to normal ($25^{\circ}\text{C}\pm 2^{\circ}\text{C}/60\%\pm 5\% \text{ RH}$) and accelerated ($40^{\circ}\text{C}\pm 2^{\circ}\text{C}/75\%\pm 5\% \text{ RH}$) stability studies according to the current ICH guidelines.

The stability results of Composition 1 at accelerated conditions, $40^{\circ}\text{C}/75\% \text{ RH}$ in comparison to the reference product, Toviaz® are shown in TABLE 3 below.

TABLE 3: Comparative stability results of Composition 1 and reference product Toviaz®

	% diol impurity	% total impurity
Composition 1	1.88	3.57
Toviaz®	3.29	6.50

25 The results showed that the stability of the composition 1 of the present invention was improved compared to Toviaz®. Particularly, diol and total impurities of Composition 1 were 1.88% and 3.29%, respectively compared to reference product wherein diol impurity was 3.57% and total impurities was 6.50%.

30 In addition, as shown in Fig. 1, Fesoterodine Composition 1 showed extended release of the active ingredient for a time period more than 20h.

Consequently, a novel improved extended release composition of fesoterodine fumarate has been achieved comprising a complex formed with an ion exchange resin, namely Sodium Polystyrene Sulfonate (Amberlite™ IRP69). The use of Sodium Polystyrene Sulfonate (Amberlite™ IRP69) is able to improve the physicochemical stability of the active ingredient in the finished dosage form by protecting said active ingredient from degradation, and maintaining an extended release profile of said active ingredient.

The stability of the product as well as the simple and economic manufacturing process indicates the advantages of the present invention relative to the commonly used method and excipients for the formulation of fesoterodine.

- 5 While the present invention has been described with respect to the particular embodiments, it will be apparent to those skilled in the art that various changes and modifications may be made in the invention without departing from the spirit and scope thereof, as defined in the appended claims.

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CLAIMS

1. An extended release pharmaceutical composition for oral administration comprising a therapeutically effective quantity of fesoterodine or a pharmaceutically acceptable salt, metabolite, or derivative thereof, as an active ingredient and an effective quantity of ion exchange resin as a stabilizer in order to prevent the degradation and improve the physicochemical stability of the active ingredient in the finished dosage form.
2. The pharmaceutical composition according to claim 1, wherein said active ingredient is fesoterodine fumarate.
3. The pharmaceutical composition according to claim 2, wherein the ratio of fesoterodine fumarate to ion exchange resin is from 1:0.5 to 1:80.
4. The pharmaceutical composition according to claim 2, wherein said ion exchange resin is crosslinked polymer of divinylbenzene methacrylate or its pharmaceutically acceptable salt(s), such as Sodium Polystyrene Sulfonate.
5. The pharmaceutical composition according to claim 4, wherein it further comprises at least one pharmaceutically acceptable excipient as rate controlling agent, such as HPMC, to modify/control the release of the active ingredient in the finished dosage form.
6. The pharmaceutical composition according to any preceding claim, wherein the amount of fesoterodine in said composition is in the range of 1-50 weight % of the total weight of the composition.
7. The pharmaceutical composition according to any preceding claim, wherein the amount of ion exchange resin in the composition is at least 1 weight % of the total weight of the composition.
8. The pharmaceutical composition according to any preceding claim, wherein said pharmaceutical composition further comprises pharmaceutically acceptable additives selected from a group comprising of absorbents, acids, adjuvants, anticaking agents, glidants, antitacking agents, antifoamers, anticoagulants, antimicrobials, antiseptics, diluents, binders, chelating agents, sequestrants, coating agents, colorants, dyes, pigments, complexing agents, softeners, crystal growth regulators, denaturants, desiccants, dehydrating agents, dispersants, solubilizers, emollients, emulsifiers, fillers, flavor masking agents, gelling agents, humectants, lubricants, moisturizers, bufferants, pH control agents, plasticizers, retarding agents, stabilizers, suspending agents, sweeteners, , thickening agents, surfactants, opacifiers, coloring agents, preservatives, antigellants, rheology control agents, tonicifiers and their combinations thereof.
9. The pharmaceutical composition according to claim 5, wherein said composition further comprises Microcellac as diluent, Colloidal Silicon Dioxide and talc as glidants and Glyceryl Behenate as lubricant.
10. A process for the preparation of an extended release pharmaceutical composition for oral administration comprising a therapeutically effective quantity of fesoterodine or a pharmaceutically acceptable salt, metabolite, or derivative thereof, as an active ingredient, and an effective quantity of ion exchange resin in order to prevent the degradation and improve the physicochemical stability of the active ingredient in the finished dosage form, wherein said process comprises following steps:

-2-

- 5 a) Complexation: Dissolving the total quantity of fesoterodine or a pharmaceutically acceptable salt, metabolite or derivative thereof into an appropriate solvent and forming a homogenous mixture by adding the total quantity of an ion exchange resin and mixing for appropriate time until the complexation reaction is completed, and subsequently separating the solid fraction (resinate) from prepared slurry by discarding the filtrate;
- b) Drying the wetted resinate mass from step a);
- c) Sizing the dried resinate obtained from step b) by passing through a sieve;
- 10 d) Adding to the sieved resinate from step c) the total quantity of a rate controlling agent and at least one optional additional excipient such as binder, diluent, lubricant and/or glidant and mixing for appropriate time.
- e) Compressing the final blend from step d) into a desired tablet form in a rotary compression machine using appropriate punches.
- 15 11. The process for the preparation of a pharmaceutical composition according to claim 10, wherein the ratio of fesoterodine fumarate to ion exchange resin is from 1:0.5 to 1:80.
12. The process for the preparation of a pharmaceutical composition according to claim 10, wherein said ion exchange resin is crosslinked polymer of divinylbenzene methacrylate or its pharmaceutically acceptable salt(s), such as Sodium Polystyrene Sulfonate.

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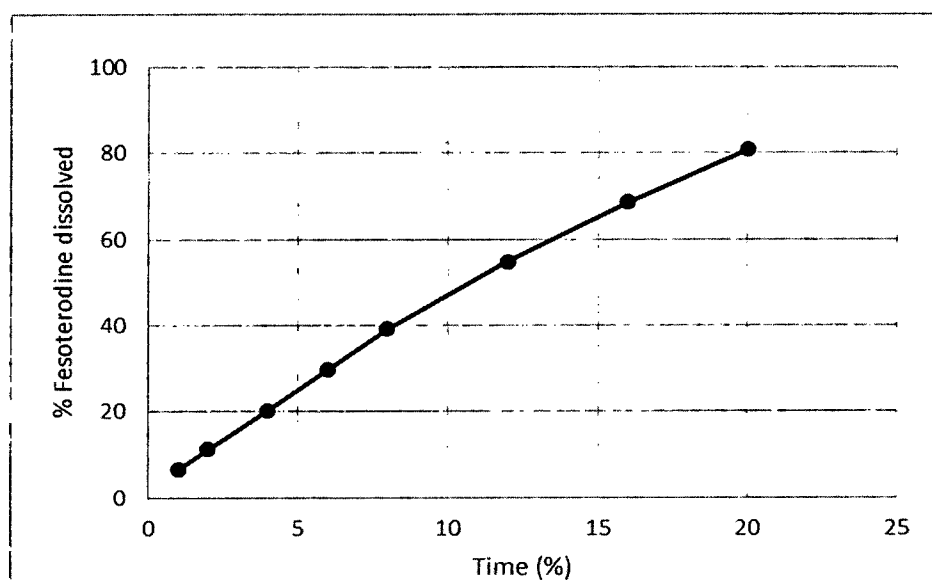


Fig. 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/000829

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 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, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2016/001937 A2 (RUBICON RES PRIVATE LTD [IN]) 7 January 2016 (2016-01-07)	1-12
Y	the whole document claims 1,4,6,20; example 1 -----	2,11
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Further documents are listed in the continuation of Box C.



See patent family annex.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2017/000829

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