(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 November 2019 (21.11.2019)

WIPO | PCT

(10) International Publication Number
WO 2019/221684 A2

(51) International Patent Classification:
Not classified

(21) International Application Number:
PCT/TR2018/050859

(22) International Filing Date:
21 December 2018 (21.12.2018)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2017/21437 25 December 2017 (25.12.2017) TR
2018/19312 13 December 2018 (13.12.2018) TR

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

(54) Title: THE BILAYER TABLET FORMULATION OF FESOTERODINE

(57) Abstract: The present invention relates to a bilayer tablet formulation comprising fesoterodine or a pharmaceutically acceptable salt thereof.

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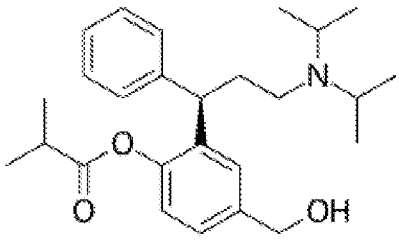
THE BILAYER TABLET FORMULATION OF FESOTERODINE

Field of the Invention

The present invention relates to a bilayer tablet formulation comprising fesoterodine or a pharmaceutically acceptable salt thereof.

Background of the Invention

The chemical name of fesoterodine is (2-[(1R)-3-[bis(1-methylethyl) amino]-1-phenylpropyl]-4-hydroxymethylphenyl isobutyrate or alternatively R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester). Its empirical formula is $C_{30}H_{41}NO_7$, corresponding to a molecular weight of 527.66 having the following structural Formula I:



Formula I

The drug fesoterodine fumarate is the active ingredient in a product being sold as TOVIAZ® tablets to treat urinary incontinence and frequency problems. Inactive ingredients are glyceryl behenate, hypromellose, lactose monohydrate, soya lecithin, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and xylitol.

Fesoterodine is known in the art for its potency in treating urinary incontinence. However, fesoterodine may exhibit substantial degradation under stress conditions. It is believed that hydrolyzation and oxidation are among the major mechanisms resulting in degradation.

Synthesis pathways for fesoterodine is described EP 1 077 912 B1. Salts of fesoterodine is described in EP 1 230 209 B1.

WO 2010/043408 discloses a microencapsuled fesoterodine composition in which distinct from a homogenous mixture of fesoterodine particle with a matrix, is composed of a particle containing fesoterodine and a shell surrounding fesoterodine containing particle. However, in the case, stability of compositions is provided a complex-structured pharmaceutical composition. The process described in prior art are complex, time consuming and costs are high. Also, no specific auxiliary substances that should contribute to stabilization of fesoterodine are used.

There is thus still a need for a composition having desired dissolution profile comprising fesoterodine which are stable against fesoterodine degradation over an extended period of time.

In the present invention, the formulation provides a desired dissolution profile and a desired stability and an excellent pharmacotechnical properties such as flowability, compressibility and homogeneity. Also, the formulation has been developed by using standard techniques which is simple and cost-effective.

Detailed Description of the Invention

The main object of the present invention is to provide a formulation which is characterized by a desired dissolution profile and excellent pharmacotechnical properties, such as flowability, compressibility and homogeneity by using bilayer form of the tablet.

Another object of the present invention is to provide pharmaceutical formulations of fesoterodine which are more stable against degradation over storage period and also provide the desired modified release of the drug.

The term "fesoterodine" as used throughout the specification refers to not only fesoterodine, but also its other pharmaceutically acceptable salts, pharmaceutically acceptable solvates, pharmaceutically acceptable hydrates, pharmaceutically acceptable enantiomers, pharmaceutically acceptable derivatives, pharmaceutically acceptable polymorphs or pharmaceutically acceptable prodrugs thereof.

The term “stability” as used herein includes both chemical stability, physical and polymorphic stability.

The term “modified release phase” refers to any pharmaceutical formulation that maintain constant levels of a drug in the patient's bloodstream by releasing the drug over an extended period of time. Modified release is formulated to release the active ingredient gradually and predictably over a 12-hour to 24-hour period. Modified release formulations are also referred to controlled release, sustained release, delayed release, extended release or repeat action systems or mixtures thereof.

According to an embodiment of the present invention, the modified release formulation is preferred. Modified release formulations comprise controlled release, sustained release, delayed release, extended release, repeat action system or mixtures thereof.

In the present invention, a bilayer tablet is used. Because, the dissolution profile of the active substance is very important when preparing modified release formulations. It is necessary to release the active substance at the right amount and at the right time. Thus, it is important to provide the efficiency of the formulation by providing a tablet formulation which helps to the desired dissolve. It has surprisingly been found that improved dissolution profile can be obtained when a bilayer tablet is used.

According to an embodiment of the present invention, the bilayer tablet formulation comprises;

-a first layer comprising fesoterodine or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient and

- a second layer comprising at least one pharmaceutically acceptable excipient.

According to an embodiment of the present invention, the amount of fesoterodine is between 0.5% and 35.0% w/w of the composition, preferably it is between 0.5% and 20.0% w/w of the composition, more preferably it is between 0.5% and 10.0% w/w of the composition.

According to an embodiment of the present invention, the weight ratio of the second layer to the first layer is between 0.1 and 4.0, preferably between 0.6 and 2.0. This ratio is important in order to provide a desired dissolution profile in the present bilayer tablet.

According to an embodiment of the present invention, the bilayer tablet further comprises at least one sugar as stabilizer.

Suitable sugars are selected from the group sucrose, fructose, maltitol, mannitol, lactitol or mixtures thereof.

According to an embodiment of the present invention, the bilayer tablet further comprises at least two sugars as stabilizers, and optionally granulated.

According to an embodiment of the present invention, the amounts of stabilizers is between 0.5% and 30.0% w/w of the bilayer tablet, preferably it is between 0.5% and 15.0% w/w of the bilayer tablet.

According to an embodiment of the present invention, the ratio of fesoterodine to stabilizers is in the range of between 1:60 and 60:1 by weight, preferably between 1:20 and 20:1 by weight, preferably between 1:15 and 15:1 by weight, more preferably between 1:10 and 10:1 by weight of the bilayer tablet.

According to an embodiment of the present invention, the bilayer tablet comprises fructose-sucrose mixture as stabilizer.

Fructose is more soluble than other sugars and hard to crystallize because it is more hygroscopic and holds onto water stronger than the others. This means that fructose can be used to extend the shelf life of the bilayer tablet more than other sugars. But, fructose has some side-effects when is not used in reasonable amounts. Thereof, fructose-sucrose mixture is used. Surprisingly, it has been found that using both fructose and sucrose as the stabilizer provides improved stability and better dissolution rate to the bilayer tablet formulation and prevented degradation of fesoterodine.

According to one embodiment in the present invention, the fructose-sucrose has also binder properties. In addition, it further enhances excellent pharmacotechnical properties (flowability, compressibility and homogeneity).

In one embodiment of this present invention, the amount of the fructose-sucrose mixture is between 3.0% and 30.0% by weight of the composition, preferably it is between 9.0% and 20.0% by weight.

In one embodiment of this present invention, the weight ratio of fructose to sucrose is in the range of between 1:200 and 200:1 by weight, preferably between 1:50 and 50:1 by

weight, preferably between 40:1 and 1:40 by weight, more preferably between 35:1 and 1:35 by weight of the total bilayer tablet. These ratios are important in order to provide stability in the present bilayer tablet formulation.

The pharmaceutically acceptable excipient which is used in the formulation and process for preparation of the formulation of the present invention must be compatible with fesoterodine.

According to another embodiment of this invention, the bilayer tablet formulation further comprises at least one pharmaceutically acceptable excipient which is selected from the group comprising rate controlling polymers, diluents, lubricants, coating agents or the mixtures thereof.

According to a preferred embodiment of this present invention, the bilayer tablet formulation is formulated as modified release formulation using rate controlling polymers.

According to this embodiment, suitable rate controlling polymers are selected from the group comprising hydroxypropylmethyl cellulose, carbomer, xanthan gum, polyethylene oxides, glyceryl dibehenate, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxyethyl methyl cellulose, methylcellulose, carboxymethylcellulose and its salts, polyacrylates, methylacrylates, polyethylene glycols, starch derivatives, galactomannans, polysaccharides, polyalcohols, acrylic acid or its derivatives, glycerol monostearate, polyanhydrides, methylacrylates, polyamides, polycarbonates, polyalkylene, polyalkylene glycols, polyalkylene oxides, polyvinyl alcohols, polyvinyl ethers, polyvinylpyrrolidone, polymers of acrylic and methacrylic esters, polylactides, polyorthoesters, poly(fumaric acid) or mixtures thereof.

Particularly, the preferred rate controlling polymers are selected from a group comprising hydroxypropylmethyl cellulose, carbomer, xanthan gum, polyethylene oxides, glyceryl dibehenate or mixture thereof. The selected controlled release polymers are preferably present in an amount that allows for the formation of a gel matrix from which the active ingredient is gradually released.

In one embodiment of this present invention, the rate controlling polymers are hydroxypropylmethyl cellulose or polyethylene oxides or glyceryl dibehenate or mixtures thereof.

The amount of the rate controlling polymers in the pharmaceutical composition are between 10.0% and 65.0% w/w of the bilayer tablet formulation, preferably between 20.0% and 55.0% w/w of the bilayer tablet formulation. The rate controlling polymers is present in the first layer or the second layer or both.

According to another embodiment of this invention, the ratio of the rate controlling polymers in the first layer to the rate controlling polymers in the second layer is in the range of between 0.1 and 2.0 by weight. This ratio provides desired dissolution profile.

In one embodiment of this present invention, the ratio of fesoterodine to hydroxypropylmethyl cellulose is in the range of between 10:1 and 1:10 by weight, preferably this ratio is in the range of between 8:1 and 1:8 by weight of the total bilayer tablet. While this ratio helps to protect improved stability in the present formulation, at the same time provide a desired modified release of the drug.

The amount of the hydroxypropylmethyl cellulose is between 12.0% and 60.0% w/w of the total bilayer tablet.

Suitable diluents are selected from the group lactose monohydrate, microcrystalline cellulose, calcium carbonate, calcium phosphate dibasic, calcium phosphate tribasic, calcium sulfate, microcrystalline silicified cellulose, powdered cellulose, dextrates, dextrose, fructose, lactitol. lactose anhydrous, lactose dihydrate or mixtures thereof. The amounts of diluents are between 10.0% and 45.0% w/w of the composition, preferably the amounts of diluents are between 15.0% and 35.0% w/w of the composition.

Suitable lubricants are selected from the group from talc, colloidal silicon dioxide, calcium silicate, powdered cellulose, starch, or mixtures thereof. Lubricants are between 0.06% and 6.0% w/w of the formulation.

In another embodiment of this present invention, the compositions comprise a film coating. The film coating on the tablet protects it from moisture and further contributes to the ease with which it can be swallowed. Preferably, a moisture barrier film coating is used in order to minimize the degradation of fesoterodine due to moisture.

Suitable coating agents are selected from the group comprising polyvinyl alcohol (PVA), talc, polymethacrylates, hydroxypropyl methylcellulose, sodium lauryl sulfate, glyceryl monocaprylocaprate, lactose monohydrate, hydroxypropyl cellulose, polyethylene glycol (PEG), polyvinyl alcohol-polyethylene glycol copolymers, ethylcellulose dispersions, polyvinylprolidone, polyvinylprolidone-vinyl acetate copolymer (PVP-VA), all kinds of Opadry®, pigments, dyes, titanium dioxide, macrogol, coloring agent or mixtures thereof.

Suitable coloring agents are selected from the group comprising ferric oxide, titanium dioxide, Food, Drug & Cosmetic (FD&C) dyes (such as; FD&C blue, FD&C green, FD&C red, FD&C yellow, FD&C lakes), poncau, indigo Drug & Cosmetic (D&C) blue, indigotine FD&C blue, carmoisine indigotine (indigo Carmine); iron oxides (such as; iron oxide red, yellow, black), quinoline yellow, flaming red, carmine, carmoisine, sunset yellow or mixtures thereof.

According to one embodiment of the invention, the bilayer tablet comprises;

a. first layer comprising fesoterodine, fructose, sucrose, lactose monohydrate, glyceryl dibehenate, microcrystalline cellulose, talc, hydroxypropyl methylcellulose
b. second layer comprising microcrystalline cellulose, talc, colloidal silicon dioxide, hydroxypropyl methylcellulose.

In one embodiment of the invention, the bilayer tablet formulation comprises;

First layer;

0.5% - 35.0% by weight of fesoterodine
2.5% - 20.0% by weight of fructose
0.1% - 10.0% by weight of sucrose
2.0% - 13.0% by weight of lactose monohydrate
0.5% - 3.0% by weight of glyceryl dibehenate
5.0% - 12.0% by weight of microcrystalline cellulose
0.02% - 2.0% by weight of talc
10.0% - 25.0% by weight of hydroxypropyl methylcellulose

Second layer;

3.0% - 20.0% by weight of microcrystalline cellulose
10.0% - 37.0% by weight of hydroxypropyl methylcellulose

0.02% - 2.0% by weight of talc

0.02% - 2.0% by weight of colloidal silicon dioxide

Coating;

2.0% - 8.0% by weight of coating agents of the composition.

Another embodiment of the present invention is to provide a process for preparing the bilayer tablet formulation comprises the following steps:

- For the first layer;

a) mixing fesoterodine, fructose and sucrose

b) granulating the mixture with water then, sieving

c) drying the mixture at 40°C until the humidity is less than 0.5%, then sieving the mixture

d)adding lactose monohydrate, glyceryl dibehenate, microcrystalline cellulose, hydroxypropyl methylcellulose and then mixing

e) then, adding talc and mixing and the first layer is obtained.

- For the second layer;

f) mixing microcrystalline cellulose, colloidal silicon dioxide, hydroxypropyl methylcellulose

g) then, adding talc and mixing and the second layer is obtained

- then, pressing to form bilayer tablets

- coating tablets with coating agent

The bilayer tablet formulation of the present invention may be prepared by direct compression, wet or dry granulation, hot melt granulation, hot melt extrusion, fluidized bed granulation, extrusion/spheronization, slugging, spray drying or solvent evaporation.

Preferably, the bilayer tablet formulation is prepared wet granulation which is simple and cost-effective method. Also, this process helps to provide stability and dissolution profile of the bilayer tablet.

It has been found that using wet granulation process, wherein granulating fesoterodine and the fructose-sucrose mixture as stabilizer with the addition of excipients for wet

granulation showed an improved stability of fesoterodine in the granulate and in the bilayer tablet formulation.

Also, it has been found that when the bilayer tablet formulation is prepared using water-based granulation, resulting bilayer tablets possess improved stability.

The given below examples describes the bilayer tablet formulation comprising fesoterodine.

Example 1: Bilayer tablet formulation comprising fesoterodine

Agents	Amount (% by weight of the total)
First layer	
Fesoterodine	0.5% to 7.0%
Fructose	5.0% to 15.0%
Sucrose	0.1% to 5.0%
Lactose monohydrate	5.0% to 11.0%
Glyceryl dibehenate	0.5% to 3.0%
Microcrystalline cellulose	5.0% to 10.0%
Talc	0.1% to 1.5%
Hydroxypropyl methylcellulose	15.0% to 22.0%
Second layer	
Microcrystalline cellulose	7.0% to 17.0%
Hydroxypropyl methylcellulose	17.0% to 35.0%
Talc	0.1% to 1.5%
Colloidal silicon dioxide	0.1% to 1.5%
Coating	
Coating agents	2.5% to 7.0%
Total	**100**

Example 2: Bilayer tablet formulation comprising fesoterodine

Agents	Amount (% by weight of the total)
First layer	
Fesoterodine	1.2%
Fructose	10.8%
Sucrose	0.3%
Lactose monohydrate	9.1%
Glyceryl dibehenate	1.5%
Microcrystalline cellulose	6.5%
Talc	0.6%
Hydroxypropyl methylcellulose	19.2%
Second layer	
Microcrystalline cellulose	14.3%
Hydroxypropyl methylcellulose	30.8%
Talc	0.7%
Colloidal silicon dioxide	0.4%
Coating	
Coating agents	4.6%
Total	**100**

Process for example 1 and 2:

The process for preparation of the bilayer tablet comprises the following steps:

- For the first layer;

a) mixing fesoterodine, fructose and sucrose

b) granulating the mixture with water then, sieving

c) drying the mixture at 40°C until the humidity is less than 0.5%, then sieving the mixture

d)adding lactose monohydrate, glyceryl dibehenate, microcrystalline cellulose, hydroxypropyl methylcellulose and then mixing

e) then, adding talc and mixing and the first layer is obtained.

- For the second layer;

f) mixing microcrystalline cellulose, colloidal silicon dioxide, hydroxypropyl methylcellulose

g) then, adding talc and mixing and the second layer is obtained

- then, pressing to form bilayer tablets
- coating tablets with coating agents

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CLAIMS

1. A bilayer tablet formulation comprising;

-a first layer comprising fesoterodine or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient and

- a second layer comprising at least one pharmaceutically acceptable excipient.

2. The bilayer tablet formulation according to claim 1, wherein the amount of fesoterodine is between 0.5% and 35.0% w/w of the total bilayer tablet.

3. The bilayer tablet formulation according to claim 2, wherein the amount of fesoterodine is between 0.5% and 20.0% w/w of the total bilayer tablet.

4. The bilayer tablet formulation according to claim 3, wherein the amount of fesoterodine is between 0.5% and 10.0% w/w of the total bilayer tablet.

5. The bilayer tablet formulation according to claim 1, wherein the weight ratio of the second layer to the first layer is between 0.1 and 4.0.

6. The bilayer tablet formulation according to claim 5, wherein the weight ratio of the second layer to the first layer is between 0.6 and 2.0.

7. The bilayer tablet formulation according to claim 1, further comprising at least one sugar as stabilizer.

8. The bilayer tablet formulation according to claim 7, wherein the sugars are selected from sucrose, fructose, maltitol, mannitol, lactitol or mixtures thereof.

9. The bilayer tablet formulation according to claim 8, wherein the weight ratio of fesoterodine to stabilizers is in the range of between 1:20 and 20:1 by weight, preferably between 1:15 and 15:1 by weight of the total bilayer tablet.

10. The bilayer tablet formulation according to claim 9, wherein the weight ratio of fesoterodine to stabilizers is in the range of between 1:10 and 10:1 by weight of the bilayer tablet.

11. The bilayer tablet formulation according to claim 8, wherein the sugars are the fructose-sucrose mixture.

12. The bilayer tablet formulation according to claim 11, wherein the amount of fructose-sucrose mixture is between 3.0% and 30.0% w/w of the total bilayer tablet.

13. The bilayer tablet formulation according to claim 11, wherein the weight ratio of fructose to sucrose is in the range of between 1:50 and 50:1 by weight, preferably between 40:1 and 1:40 by weight of the total bilayer tablet.

14. The bilayer tablet formulation according to claim 1, further comprising at least one pharmaceutically acceptable excipient which is selected from the group comprising rate controlling polymers, diluents, lubricants, coating agents or mixtures thereof.

15. The bilayer tablet formulation according to claim 14, wherein the rate controlling polymers are selected from the group comprising hydroxypropylmethyl cellulose, carbomer, xanthan gum, polyethylene oxides, glyceryl dibehenate, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxyethyl methyl cellulose, methylcellulose, carboxymethylcellulose and its salts, polyacrylates, methylacrylates, polyethylene glycols, starch, galactomannans, polysaccharides, polyalcohols, acrylic acid, glycerol monostearate, polyanhydrides, methylacrylates, polyamides, polycarbonates, polyalkylene, polyalkylene glycols, polyalkylene oxides, polyvinyl alcohols, polyvinyl ethers, polyvinylpyrrolidone, polymers of acrylic and methacrylic esters, polylactides, polyorthoesters, poly(fumaric acid) or mixtures thereof.

16. The bilayer tablet formulation according to claim 15, wherein the rate controlling polymers are selected from a group comprising of hydroxypropylmethyl cellulose, carbomer, xanthan gum, polyethylene oxides, glyceryl dibehenate or mixture thereof.

17. The bilayer tablet formulation according to claim 16, wherein the rate controlling polymers are hydroxypropylmethyl cellulose or polyethylene oxides or glyceryl dibehenate or mixtures thereof.

18. The bilayer tablet formulation according to claim 17, wherein the amount of the rate controlling polymers in the pharmaceutical composition is between 10.0% and 65.0% w/w, preferably between 20.0% and 55.0% w/w of the total bilayer tablet.

19. The bilayer tablet formulation according to claim 18, wherein the rate controlling polymers is present in the first layer or in the second layer or both.

20. The bilayer tablet formulation according to claim 18, wherein the weight ratio of the rate controlling polymers in the first layer to the rate controlling polymers in the second layer is in the range of between 0.1 and 2.0 by weight.

21. The bilayer tablet formulation according to any preceding claims, wherein the bilayer tablet comprising;

- first layer comprising fesoterodine, fructose, sucrose, lactose monohydrate, glyceryl dibehenate, microcrystalline cellulose, talc, hydroxypropyl methylcellulose
- second layer comprising microcrystalline cellulose, talc, colloidal silicon dioxide, hydroxypropyl methylcellulose.

22. The bilayer tablet formulation according to any preceding claims, the formulation comprising;

First layer;

0.5% - 35.0% by weight of fesoterodine

2.5% - 20.0% by weight of fructose

0.1% - 10.0% by weight of sucrose

2.0% - 13.0% by weight of lactose monohydrate

0.5% - 3.0% by weight of glyceryl dibehenate

5.0% - 12.0% by weight of microcrystalline cellulose

0.02% - 2.0% by weight of talc

10.0% - 25.0% by weight of hydroxypropyl methylcellulose

Second layer;

3.0% - 20.0% by weight of microcrystalline cellulose

10.0% - 37.0% by weight of hydroxypropyl methylcellulose

0.02% - 2.0% by weight of talc

0.02% - 2.0% by weight of colloidal silicon dioxide

Coating;

2.0% - 8.0% by weight of coating agents of the composition.

23. Process for preparing the bilayer tablet formulation according to claim 22, the formulation comprising the following steps;

- for the first layer;
  a) mixing fesoterodine, fructose and sucrose
  b) granulating the mixture with water then, sieving
  c) drying the mixture at 40°C until the humidity is less than 0.5%, then sieving the mixture
  d) adding lactose monohydrate, glyceryl dibehenate, microcrystalline cellulose, hydroxypropyl methylcellulose and then mixing
  e) then, adding talc and mixing and the first layer is obtained.

- for the second layer;
  f) mixing microcrystalline cellulose, colloidal silicon dioxide, hydroxypropyl methylcellulose
  g) then, adding talc and mixing and the second layer is obtained

- then, pressing to form bilayer tablets
- coating tablets with coating agent