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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
02 July 2020 (02.07.2020)

WIPO | PCT

(10) International Publication Number
WO 2020/139237 A2

(51) International Patent Classification:
A61K 9/16 (2006.01) *A61K 31/401* (2006.01)
A61K 9/20 (2006.01) *A61K 31/397* (2006.01)

(21) International Application Number:
PCT/TR2019/051006

(22) International Filing Date:
28 November 2019 (28.11.2019)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2018/20324 25 December 2018 (25.12.2018) 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))*
— *in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE*

(54) Title: A BILAYER TABLET FORMULATION OF ATORVASTATIN CALCIUM AND EZETIMIBE

(57) Abstract: The present invention relates to a pharmaceutical bilayer tablet formulation comprising atorvastatin calcium and ezetimibe. Further, the present invention provides a process that eliminates disadvantages of active agents.

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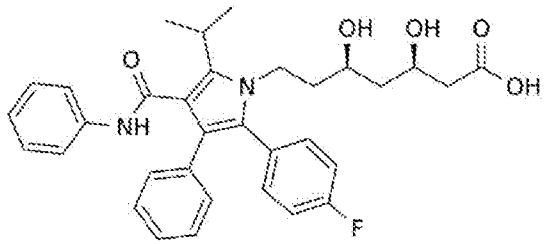
A BILAYER TABLET FORMULATION OF ATORVASTATIN CALCIUM AND EZETIMIBE

Field of Invention

The present invention relates to a pharmaceutical bilayer tablet formulation comprising atorvastatin calcium and ezetimibe. Further, the present invention provides a process that eliminates disadvantages of active agents.

Background of Invention

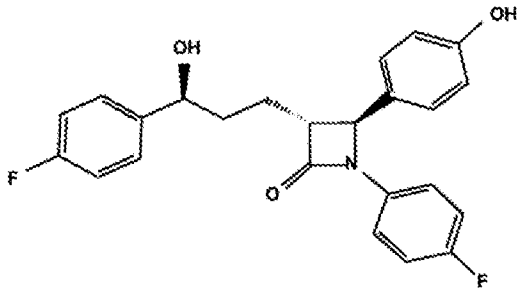
The chemical name of atorvastatin is (3R,5R)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-propan-2-ylpyrrol-1-yl]-3,5-dihydroxyheptanoic acid and has a chemical structure which is shown in Formula I.



Formula I

Atorvastatin belongs to the statin lipid regulating drugs, it is a HMG-CoA reductase inhibitors. Atorvastatin is reductase competitively in the body, reducing the synthesis of cholesterol, but also low-density lipoprotein (LDL) receptor synthesis the main site of action in the liver, resulting in blood cholesterol and low-density lipoprotein cholesterol levels, a moderate decrease in serum triglyceride levels, and elevated blood levels of high-density lipoprotein (HDL).

Ezetimibe is in a class of compounds known as lipid-lowering compounds that selectively inhibits the intestinal absorption of cholesterol and related phytosterols. Its chemical name is as(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4hydroxyphenyl) azetidin-2-one and has a chemical structure which is shown in Formula II.



Formula II

Ezetimibe reduces blood cholesterol by inhibiting the absorption of cholesterol by the small intestine. Its mechanism of action differs from those of other classes of cholesterol-reducing compounds, such as HMG-CoA reductase inhibitors. It doesn't inhibit cholesterol synthesis in the liver or increase bile acid excretion but inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. Such mechanism is complementary to that of HMG-CoA reductase inhibitors.

When atorvastatin combined with ezetimibe, it is effective than atorvastatin alone, so that the plasma levels of LDL-C was significantly reduced, the difference was statistically significant, and atorvastatin and ezetimibe combined with the use of a double dose atorvastatin compared the efficacy of lowering LDL-C similar difference was statistically significant. Thus, atorvastatin combined with ezetimibe and atorvastatin alone compared, can reduce LDL-C to obtain additional benefits, can make more high-risk or very high risk of coronary heart disease (CHD) patients with blood lipid standards. Statins likely to cause liver function, myopathy and gastrointestinal (GI) and the like.

Chinese patent CN103340852 A discloses a pharmaceutical composition comprising ezetimibe and atorvastatin, characterized in that the two active ingredients are present in separate solid dosage forms in a single solid dosage form. The preparation method of the two-layer sheet is used to improve the stability of the active ingredient.

The patent application WO2013166114 (A1) discloses a combination comprising atorvastatin calcium, ezetimibe and a process for the preparation of the combination.

In the prior art, there are other pharmaceutical dosage forms comprising atorvastatin calcium and ezetimibe, but it is needed to develop a formulation which has a desired dissolution profile and long-term stability for use and a simple process.

The ezetimibe substance is low water-soluble, low permeable, incompatible with most of the excipients usually used in formulation, presents stability problems, and is not inherently

compressible. Therefore, there is a need to provide a stable composition with an acceptable dissolution profile. This also affects its bioavailability negatively.

Finally, in this invention, formulation overcomes the above problems challenges and enables a fixed combination formulation that has simultaneously:

a) a better dissolution profile to individual active ingredients,

b) a stable formulation despite the incompatibilities of two component molecules - atorvastatin calcium and ezetimibe

c) eliminates especially the low solubility problem of ezetimibe and the stability problem of atorvastatin calcium to enhance the good dissolution profile and good shelf-life of the final pharmaceutical product.

Detailed Description of The Invention

The main object of the present invention is to provide a bilayer tablet comprising atorvastatin calcium and ezetimibe to provide high stability and solubility.

Another object of the present invention is to provide desired level of dissolution rate and compressibility which overcomes the above described problems in prior art and have additive advantages over them.

A further object of the present invention is to provide a process that eliminates the above-mentioned disadvantages of ezetimibe.

It has been surprisingly found according to the invention that formulations of ezetimibe can be provided in a more robust and economical way and can display a good balance of properties including chemical and physical stability and compressibility and particularly acceptable to good dissolution profiles.

In this invention, at least one binder is used in the second layer of the bilayer tablet which comprises ezetimibe, so this overcomes the problems of stability problems and solubility problems of ezetimibe. The total amount of binder in the second layer is 1.1% to 10.0% by weight of the bilayer tablet.

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

a. a first layer comprising atorvastatin calcium and
b. a second layer comprising ezetimibe

wherein the tablet comprising at least one binder in each layer.

According to one embodiment of the invention, the amount of atorvastatin calcium in the tablet is 0.5% to 10.0% by weight and the amount of ezetimibe in the tablet is 0.5% to 8.0% by weight.

According to one embodiment of the invention, the total amount of binder in the first layer is 1.1% to 10.0% by weight and the total amount of binder in the second layer is 1.1% to 10.0% by weight.

According to one embodiment of the invention, the total amount of binder in the first layer is 1.1% to 7.0% by weight, the total amount of binder in the second layer is 3.0% to 9.0% by weight.

Suitable binders are selected from the group comprising polyethylene glycol, hydroxypropyl methyl cellulose, hydroxypropylcellulose, sugars, alginates, polyvinylpyrrolidone, carbomers, carboxymethylcellulose sodium, cellulose acetate phthalate, copovidone, starch, pregelatinized starch, dextrose, ethylcellulose, glyceryl behenate, hydroxyethyl cellulose, hydroxypropyl starch, magnesium aluminum silicate, maltodextrin, methylcellulose, poloxamer, polydextrose, polyethylene oxide, polymethacrylates, cetostearyl alcohol, polyoxyethylene-alkyl ethers or mixtures thereof.

In the prior art, used excipients especially binders do not help to reduce the disadvantages of active substances. For example; disadvantages of ezetimibe are low water-soluble, low permeable, incompatible with most of the excipients usually used in formulation, presents stability problems, and is not inherently compressible.

According to this embodiment of the invention, preferably the binders are selected from the group comprising polyethylene glycol, polyvinylpyrrolidone, hydroxypropyl methyl cellulose, hydroxypropylcellulose or mixtures thereof.

According to this embodiment of the invention, the first layer comprises a binder which is hydroxypropylcellulose.

According to this embodiment of the invention, the second layer comprises two binders. The binders are polyethylene glycol and hydroxypropyl methyl cellulose.

According to this embodiment of the invention, binder, especially polyethylene glycol (PEG) is very effective excipient in the preparation of the tablet. It has been surprisingly found that the object of the present invention is achieved when polyethylene glycol is used in a certain

ratio in the second layer. The amountof the polyethylene glycol in the second layer is between 1.0% and 6.0% by weight. Said amount provides desired dissolution profile and stability of the bilayer tablet.

In general terms, excipients provided in a formulation may positively or negatively influence the physicochemical and pharmacokinetic properties, i.e. the solubility, absorption, bioavailability of an active agent. For this reason, the excipients which accompany an active agent have to be selected in a careful and conscious manner while a formulation is developed. The formulations should have no physicochemical incompatibility between the active ingredients and the excipients.

The pharmaceutical bilayer tablet further comprises pharmaceutically acceptable excipients which are selected from the group comprising fillers, surface active agents, disintegrants, lubricants, glidants, stabilizers or mixtures thereof.

Suitable fillers are selected from the group comprising microcrystalline cellulose, lactose monohydrate, starch, sucrose, glucose, dextrose, maltodextrin, natural and synthetic gums (e.g. acacia tree), gelatin, pregelatinized starch, polyvinylpyrrolidone, cellulose derivatives or mixtures thereof, preferably fillers are microcrystalline cellulose and lactose monohydrate. They maintain the stability of the active ingredients during shelf-life.

According to this embodiment of the invention, the amount of the fillers in the first layer is between 40.0% and 75.0% by weight.

According to this embodiment of the invention, the amount of the fillers in the second layer is between 55.0% and 80.0% by weight.

Suitable surface active agents are selected from the group comprising sodium lauryl sulphate, polysorbate, polyoxyethylene glycol esters, sulphate or mixtures thereof. Preferably the agent in the second layer is sodium lauryl sulphate which avoids crystallization of ezetimibe, and thus the dissolution of ezetimibe is not affected adversely. Preferably the agent in the first layer is polysorbate.

Suitable disintegrants are selected from the group comprising croscarmellose sodium, sodium starch glycolate, alginic acid, crospovidone, sodium alginate, starch (e.g., corn, potato) or mixtures thereof, preferably disintegrant is crosscarmellose sodium.

Suitable lubricants are selected from the group comprising sodium stearyl fumarate, magnesium stearate, polyethylene glycol, stearic acid or mixtures thereof. Preferably lubricants of this invention are sodium stearyl fumarate and magnesium stearate.

Suitable glidants are selected from the group comprising silica colloidal anhydrous, talc, aluminium silicate or mixtures thereof. Preferably the glidant of this invention is silica colloidal anhydrous.

Suitable stabilizers are selected from the group comprising calcium carbonate, calcium hydroxide, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulphate, calcium acetate, calcium gluconate, calcium glycerol phosphate, magnesium carbonate, magnesium hydroxide, magnesium sulphate, magnesium acetate, magnesium silicate, magnesium aluminate or mixtures thereof. Preferably the stabilizer is calcium carbonate. It is used only in the first layer and the amount of the calcium carbonate in the first layer is between 17.0% and 26.0% by weight of the bilayer tablet.

Finally, each individual layer compressed into a tablet. The composition is more stable when the tablet is coated with film coating.

The pharmaceutical bilayer tablet composition comprises film coating to protect the composition against the moisture and light to maintain the stability. Suitable coating agents are selected from the group comprising hydroxypropylmethylcellulose, polyethylene glycol (PEG), talc, lecithin, titanium dioxide, polyvinyl alcohol (PVA), polyvinyl alcohol-polyethylene glycol copolymers, polyvinylprolidone, polyvinylprolidone-vinyl acetate copolymer (PVP-VA), pigments, dyes, iron oxide or mixtures thereof. The amount of the film coating in the bilayer tablet is 0.5%-5.0% by weight.

Another aspect of the present invention is the manufacturing process of the pharmaceutical tablet compositions of atorvastatin calcium and ezetimibe. The pharmaceutical tablet compositions of atorvastatin calcium and ezetimibe of the present invention can be prepared in a fast, efficient and commercially cost low manufacturing process.

The tablets may be prepared by a granulation process. A characteristic of the methods is given below based on wet granulation and spray granulation used for the production of the formulations of the invention. Suitable granulation solutions are selected from a group comprising pure water, ethyl alcohol, glycerin, sorbitol, polyethylene glycol, propylene glycol, isopropyl alcohol, or mixtures thereof, preferably granulation solution is pure water or ethyl alcohol.

Granulation process comprises wet, dry or spray granulation. In the present invention, at least one granulation process is used for the bilayer tablet.

Another embodiment of the present invention is to provide a process for preparing the pharmaceutical bilayer tablet composition comprising the following steps:

1st layer:

a) mixing atorvastatin calcium, microcrystalline cellulose, calcium carbonate, lactose monohydrate, a part of croscarmellose sodium,
b) granulating hydroxypropylcellulose, polysorbate with pure water,
c) sieving the wet granules,
d) drying the granules and sieving the mixture
e) adding the remaining part of croscarmellose sodium, silica colloidal anhydrous to step (d) mixture and mixing them
f) adding magnesium stearate to step (e) mixture and mixing them.

2nd layer:

a) mixing microcrystalline cellulose, hydroxypropylmethylcellulose, lactose monohydrate, a part of croscarmellose sodium,
b) heating polyethylene glycol about 65°C and dissolving with ethanol till obtained a clear solution
c) adding ezetimibe and obtained a clear solution
d) granulation using this solution with spray method
e) preparing second granulation solution comprising pure water and sodium lauryl sulfate
f) granulation using the second solution with the spray method
g) wet grinding granules,
h) drying the wet granules and dry grinding the dry granules,
i) adding the remaining part of croscarmellose sodium and silica colloidal anhydrous and mixing them
j) adding sodium stearyl fumarate and mixing them.

- After, compressing these two mixtures for each layer into bilayer tablets,
- Coating these tablets with a film coating comprising coating agents.

Example 1: Bilayer tablet

First Layer	**(%) amount (w/w)**
Atorvastatin calcium	4.0- 15.0
Microcrystalline cellulose Ph101	25.0- 44.0
Calcium carbonate	17.0-26.0
Lactose monohydrate	15.0-31.0
Croscarmellose sodium	3.0-13.0
Hydroxypropylcellulose (LF)	1.1-10.0
Polysorbate 80	0.1-3.0
Magnesium stearate	0.1-5.0
Silica colloidal anhydrous	0.1-5.0
Total (First layer)	**100**
Second Layer	**(%) amount (w/w)**
Ezetimibe	3.0-10.0
Microcrystalline cellulose	27.0-40.0
Lactose monohydrate	28.0-40.0
Croscarmellose sodium	5.0-15.0
Polyethylene glycol	1.0-6.0
Hydroxypropylmethylcellulose E5 LV	0.1-4.0
Sodium lauryl sulfate	1.0-6.0
Sodium stearyl fumarate	0.1-5.0
Silica colloidal anhydrous	0.05-5.0
Total (Second Layer)	**100**

Example 2: Bilayer tablet

First Layer	**(%) amount (w/w)**
Atorvastatin calcium	10.85
Microcrystalline cellulose Ph101	38.0
Calcium carbonate	22.0
Lactose monohydrate	20.0
Croscarmellose sodium	6.0
Hydroxypropylcellulose (LF)	2.0
Polysorbate 80	0.40
Magnesium stearate	0.50
Silica colloidal anhydrous	0.25
Total (First layer)	**100**
Second Layer	**(%) amount (w/w)**
Ezetimibe	5.0
Microcrystalline cellulose	35.0
Lactose monohydrate	35.0
Croscarmellose sodium	12.0
Polyethylene glycol	3.0
Hydroxypropylmethylcellulose E5 LV	3.0
Sodium lauryl sulfate	5.0
Sodium stearyl fumarate	1.5
Silica colloidal anhydrous	0.50
Total (Second Layer)	**100**

CLAIMS

1. A pharmaceutical bilayer tablet comprising;
   a. a first layer comprising atorvastatin calcium and
   b. a second layer comprising ezetimibe

   wherein the tablet comprising at least one binder in each layer.

2. The pharmaceutical bilayer tablet according to claim 1, wherein the total amount of binder in the first layer is 1.1% to 10.0% by weight and the total amount of binder in the second layer is 1.1% to 10.0% by weight of the bilayer tablet.

3. The pharmaceutical bilayer tablet according to claim 2, wherein the total amount of binder in the first layer is 1.1% to 7.0% by weight and the total amount of binder in the second layer is 3.0% to 9.0% by weight of the bilayer tablet.

4. The pharmaceutical bilayer tablet according to claim 3, wherein the binders are selected from the group comprising polyethylene glycol, hydroxypropyl methyl cellulose, hydroxypropylcellulose, sugars, alginates, polyvinylpyrrolidone, carbomers, carboxymethylcellulose sodium, cellulose acetate phthalate, copovidone, starch, pregelatinized starch, dextrose, ethylcellulose, glyceryl behenate, hydroxyethyl cellulose, hydroxypropyl starch, magnesium aluminum silicate, maltodextrin, methylcellulose, poloxamer, polydextrose, polyethylene oxide, polymethacrylates, cetostearyl alcohol, polyoxyethylene-alkyl ethers or mixtures thereof.

5. The pharmaceutical bilayer tablet according to claim 4, wherein the binders are selected from the group comprising polyethylene glycol, polyvinylpyrrolidone, hydroxypropyl methyl cellulose, hydroxypropylcellulose or mixtures thereof.

6. The pharmaceutical bilayer tablet according to claim 5, wherein the second layer comprising two binders.

7. The pharmaceutical bilayer tablet according to claim 6, wherein the second layer comprising polyethylene glycol and hydroxypropyl methyl cellulose.

8. The pharmaceutical bilayer tablet according to claim 7, wherein the amount of the polyethylene glycol in the second layer is between 1.0% and 6.0% by weight of the bilayer tablet.

9. The pharmaceutical bilayer tablet according to claim 1, further comprising pharmaceutically acceptable excipients selected from the group comprising fillers, surface active agents, disintegrants, lubricants, glidants, stabilizers or mixtures thereof.

10. The pharmaceutical bilayer tablet according to claim 9, wherein the fillers are selected from the group comprising microcrystalline cellulose, lactose monohydrate, starch, sucrose, glucose, dextrose, maltodextrin, natural and synthetic gums, gelatin, pregelatinized starch, polyvinylpyrrolidone, cellulose derivatives or mixtures thereof, preferably the fillers are microcrystalline cellulose and lactose monohydrate.

11. The pharmaceutical bilayer tablet according to claim 10, wherein the amount of the fillers in the first layer is 40.0%-75.0% and the amount of the fillers in the second layer is 55.0%-80.0% by weight of the bilayer tablet.

12. The pharmaceutical bilayer tablet according to claim 9, wherein the stabilizers are selected from the group comprising calcium carbonate, calcium hydroxide, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulphate, calcium acetate, calcium gluconate, calcium glycerol phosphate, magnesium carbonate, magnesium hydroxide, magnesium sulphate, magnesium acetate, magnesium silicate, magnesium aluminate or mixtures thereof.

13. The pharmaceutical bilayer tablet according to claim 12, wherein the stabilizer is calcium carbonate whose total amount in the first layer is 17.0%- 26.0% by weight of the bilayer tablet.

14. The pharmaceutical bilayer tablet according to any preceding claim, wherein the bilayer tablet is coated with film-coating.

15. The pharmaceutical bilayer tablet according to claim 14, wherein the amount of the film coating is 0.5%-5.0% by weight of the bilayer tablet.

16. The pharmaceutical bilayer tablet according to any preceding claims comprising;

a) A First Layer comprising

4.0 - 15.0% by weight of atorvastatin calcium

25.0 - 44.0% by weight of microcrystalline cellulose
17.0 - 26.0% by weight of calcium carbonate
15.0 - 31.0% by weight of lactose monohydrate
3.0 - 13.0% by weight of croscarmellose sodium
1.1 - 10.0% by weight of hydroxypropylcellulose
0.1 - 3.0% by weight of polysorbate
0.1 - 5.0% by weight of magnesium stearate
0.1 - 5.0% by weight of silica colloidal anhydrous of the first layer.

b) A Second Layer comprising

3.0 - 10.0% by weight of ezetimibe
27.0 - 40.0% by weight of microcrystalline cellulose
28.0 - 40.0% by weight of lactose monohydrate
5.0 - 15.0% by weight of croscarmellose sodium
1.0 - 6.0% by weight of polyethylene glycol
0.1 - 4.0% by weight of hydroxypropylmethylcellulose
1.0 - 6.0% by weight of sodium lauryl sulfate
0.1 - 5.0% by weight of sodium stearyl fumarate
0.05 - 5.0% by weight of silica colloidal anhydrous of the second layer.

17. The pharmaceutical bilayer tablet according to claim 16, wherein the pharmaceutical bilayer tablet is prepared by granulation process in which the granulation solutions are selected from a group comprising pure water, ethyl alcohol, glycerin, sorbitol, polyethylene glycol, propylene glycol, isopropyl alcohol or mixtures thereof.

18. A process for preparing the pharmaceutical bilayer tablet according to claim 16 or 17, comprising the following steps:

<u>1st layer:</u>

a) mixing atorvastatin calcium, microcrystalline cellulose, calcium carbonate, lactose monohydrate and a part of croscarmellose sodium,
b) granulating hydroxypropylcellulose, polysorbate with pure water,
c) sieving the wet granules,
d) drying the granules and sieving the mixture
e) adding the remaining part of croscarmellose sodium, silica colloidal anhydrous to step (d) mixture and mixing them

f) adding magnesium stearate to step (e) mixture and mixing them.

2nd layer:

a) mixing microcrystalline cellulose, hydroxypropylmethylcellulose, lactose monohydrate and a part of croscarmellose sodium,
b) heating polyethylene glycol at 65°C and dissolving it with ethanol till obtained a clear solution
c) adding ezetimibe to obtain a clear solution
d) granulating using this solution with spraying method
e) preparing second granulation solution comprising pure water and sodium lauryl sulfate
f) granulation using the second solution with the spraying method
g) wet grinding the granules,
h) drying the wet granules and dry grinding the dry granules,
i) adding the remaining part of croscarmellose sodium and silica colloidal anhydrous and mixing them
j) adding sodium stearyl fumarate and mixing them.

- Pressing these two mixtures for each layer into bilayer tablets,
- Then, coating these tablets with a film coating comprising coating agents.