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(54) Title: STABLE PHARMACEUTICAL COMPOSITIONS CONTAINING ROSUVASTATIN CALCIUM

(57) Abstract: Present invention relates to stable pharmaceutical compositions of rosuvastatin calcium which comprise at least 60% lactose, processes for preparation this composition, and use of the prepared composition for treatment.

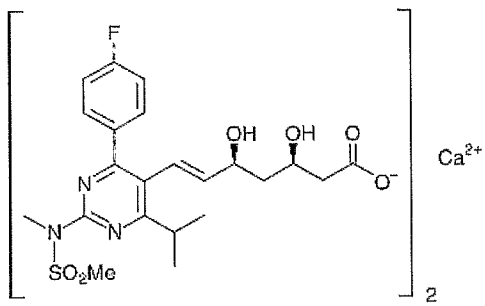
STABLE PHARMACEUTICAL COMPOSITIONS CONTAINING ROSUVASTATIN CALCIUM

Technical Field

The present invention relates to pharmaceutical compositions comprising rosuvastatin calcium as active agent and at least 60% of lactose as stabilizing agent.

Background of the Invention

Rosuvastatin calcium which is also known as (E)-7-[4-(4-fluorophenyl)-6- isopropyl -2-[methyl (methylsulphonyl) amino]pyrimidyn-5-yl]-(3R,5S)-3,5-Dihydroxyhept-6-enoic acid] calcium salt was first described in EP0521471. The compound is defined as an inhibitor of 3-hydroxy-3-methylglutaryl CoA reductase (HMG CoA reductase) and indicated for treatment of hyperlipidproteinemia, aterosclerosis and hypercholesterolemia.



Formula 1

An important problem about rosuvastatin calcium is conversion of this compound into lactone through "intramolecular esterification" reaction that takes place between the carboxylic acid in this compound and the hydroxyl groups that are present on the β and δ carbons. The reaction takes place in acidic medium and basic agents reverse the reaction. This phenomenon decreases the stability of the compound and as a result lowers the shelf-life of the product.

The patent numbered EP0547000 relates to a stable formulation comprising 7-substituted-3,5-dihydroxy-6-heptanoic acid derivatives. The patent discloses use of a basic agent such as carbonates to prepare pharmaceutical compositions whose aqueous solution has a pH of 8, in order to solve the abovementioned problem and to prevent this unwanted reaction that takes place at low pH values. The aim of the method is to prevent lactone formation and as a result prevent degradation of the active agent.

Patents numbered WO 01/54668 and WO 01/54669 are the formulation patents of the product that is sold with the tradename "Crestor". The patent document disclosed that adjusting the pH is not enough and to solved the abovementioned problem by using tribasic phosphate salts wherein the cation is multivalent (e.g. tribasic calcium phosphate, tribasic magnesium phosphate, tribasic aluminum phosphate) to stabilize pharmaceutical compositions comprising rosuvastatin calcium. The products with the trade name "crestor" contains tribasic calcium phosphate as stabilizing agent.

The patent application numbered WO 2008/035128 discloses use of magnesium hydroxide and/or calcium acetate as stabilizing agents for preperation of formulations comprising amorphous rosuvastatin calcium.

As seen in the examples related to prior art, the methods for solving the stability problem of pharmaceutical compositions comprising rosuvastatin calcium are generally directed to use of basic agents. However, a general problem about use of basic agents is the fact that pharmaceutical compositions comprising these agents effect the mucus membrane of stomach and damage the digestive system upon long-term use for treatment of chronic diseases, such as for treatment of chronic heart diseases.

When state of the art is considered it is apparent that stable rosuvastatin calcium formulations that has lower side effects, low-cost and can be easily formulated should be developed in order to prepare stable pharmaceutical compositions of rosuvastatin calcium.

To sum up, present invention relates to stable pharmaceutical compositions of rosuvastatin calcium which comprise at least 60% lactose, processes for preparation this composition, and use of the prepared composition for treatment.

Detailed Description of the Invention

Subject of the present invention is rosuvastatin formulations which can remain stable for longer periods. In an unexpected way, formulations comprising at least 60% of lactose with respect to the total weight of the composition are found to be more stable when compared to the known formulations.

Unlike the current state of the art, it was seen that upon use of at least 60% of lactose, using high amounts of alkali agents that might damage the gastric mucosa is eliminated. This leads to reduction in the side effects related to digestive system.

Present invention is differentiated from the prior art solutions that are based on forming basic medium because stability is achieved by using high amount of lactose instead of using high amounts of basic agents. The use of basic agents is minimized this way and side effects originating from using these agents are therefore eliminated.

Lactose which is used as a stabilizing agent in the formulations has a lower price than its alternatives in the market and this condition decreases the cost of the final medication. Hence, it is another object of the invention to increase the accessibility of the drug by patients by reducing the total costs of the drug.

Accordingly, first aspect of the invention is a pharmaceutical composition comprising rosuvastatin calcium and at least 60% of lactose.

The second aspect of the inveention is use of at least 60% of lactose to stabilize and to increase the shelf life of rosuvastatin calcium.

Pharmaceutical compositon of the present invention is preferably formulated as an oral tablet dosage form. Accordingly, another aspect of the present invention is pharmaceutical compositions comprising rosuvastatin calcium and at least 60 % lactose and additionally a diluent, at least one disintegrant, at least one lubricant and other pharmaceutically acceptable excipients.

Rosuvastatin calcium that is used as an active agent is used in a stable form, preferably in amorphous form.

Diluent can be selected from a group consisting of dibasic sodium phosphate, starch, cellulose derivatives, mannitol, sorbitol, sucrose, lactitol. Preferably dibasic calcium phosphate, more preferably dibasic calcium phosphate monohydrate is used.

Disintegrant can be selected from a group consisting of croscarmellose sodium, crospovidone, polyvinylpyrrolidone, sodium starch glycolate, maize starch, microcrystalline cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose. Disintegrant is preferably crospovidone or microcrystalline cellulose or a mixture thereof.

Lubricant can be chosen from a group consisting of magnesium stearate, stearic acid, palmitic acid, calcium stearate, talc, carnuba wax, hydrogenated vegetable oil, mineral oil, polyethylene glycols, sodium stearyl fumarate. Preferably magnesium stearate is used.

In addition to the ones mentioned above, additional excipients such as antioxidants, protecting agents, glidants, silica flow agents can be used, however the excipients that can be used should not be limited with this.

Other diluents, fillers, binders, disintegrants, lubricants and additional excipients are described in *Handbook of Pharmaceutical Excipients*, 4th Edition, American Pharmaceutical Association.

Rosuvastatin calcium can be present in the composition in an amount of 1-50%, preferably in an amount of 1-35%, more preferably in an amount of 2-18% with respect to the total weight of the tablet composition.

Lactose that is used as a stabilizing agent is typically present in the composition in an amount of 60-90 %, preferably in an amount of 65-85% and more preferably in an amount of 70-85 % with respect to the total weight of the tablet composition.

Typically, diluent is present in an amount of 1-15 %, preferably in an amount of 1-10% and more preferably in an amount of 1-3% with respect to the total weight of the composition.

Typically one or more disintegrant is present in an amount of 1-15% with respect to the total weight of the composition.

Typically one or more lubricant can be present in an amount of 1-5% with respect to the total weight of the composition.

Pharmaceutical composition of the present invention can be prepared by using the techniques and processes known in the state of the art such as dry blending of the components. For example; rosuvastatin calcium and at least 60% by weight lactose, are mixed togather with a diluent, one or more disintegrants and other excipients. Prior to mixing the components or the composition itself is sieved thorugh a sieve which has mesh size of 20-40. Lubricant is added to the mixture and the composition is mixed until a homogenous mixture is obtained. After the mixing process the composition is compressed to obtain tablet.

Afterwards, the tablets obtained are coated with water based film coating solution by using sprey coating method. The coating can contain, for example polyethylene glycol, ferric oxide, polyvinyl alcohol, lecithin and talc. As mentioned in the examples the coating agent can be chosen from commercially available agents. The coating agent comprises 1-10% preferably 2-4 % of the total weight of the tablet.

Another aspect of the invention is related to a process for prepration of stable pharmaceutical composition comprising rosuvastatin calcium and at least 60% lactosee by weight. Said process comprises addition of at least 60% of lactose into pharmaceutical composition.

Example:

CORE	
Contents	**Amount (mg/tablet)**
Rosuvastatin Calcium	5,0 mg
Microcrystalline Cellulose	1,1 mg
Lactose D.C.	57,1 mg
Dibasic calcium phosphate	2,9 mg
Crospovidon	4,3 mg
Magnesium stearate	1,1 mg
COATING	
Content	**Amount (mg/tablet)**
Opadry II 85G34078 Pink	2,2 mg
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Rosuvastatin calcium, microcrystalline cellulose, lactose D.C. , dibasic calcium phosphate and crospovidon are mixed for 10 minutes. The mixture is then passed through 25 mesh sieve and then magnesium stearate is added to the sieved mixture and mixed for 5 more minutes. The homegenous mixture obtained at the end of this process is compressed to obtain tablets. The tablets may optionally be coated with conventional methods. The increase in weight of the tablet is in an amount of 1-5%, preferably 2-4% as a result of the coating process

CLAIMS

1. A pharmaceutical composition comprising rosuvastatin calcium, characterized in that said composition comprises at least 60% of lactose as stabilizing agent.

2. A pharmaceutical composition comprising rosuvastatin calcium according to claim 1, wherein lactose is used in an amount of 60-90%, preferably 65-85%, more preferably 70-85% with respect to the total weight of the tablet.

3. A pharmaceutical composition comprising rosuvastatin calcium according to claim 1, wherein said composition comprises a diluent, at least one lubricant, at least one disintegrant and additionally other pharmaceutically acceptable excipients.

4. A pharmaceutical composition for oral administration according to claim 1 wherein said composition comprises rosuvastatin calcium as active agent, at least one lubricant, at least one disintegrant, a diluent, at least 60% by weight lactose and in addition to these other pharmaceutically acceptable excipients.

5. The pharmaceutical composition according to any of the preceeding claims wherein rosuvastatin calcium that is used as an active agent is preferably in amorphous form.

6. A pharmaceutical composition comprising rosuvastatin calcium according to claim 5, wherein active agent in this composition constitutes 1-50%, preferably 1-35% and more preferably 2-18 % of the total tablet weight.

7. A pharmaceutical composition according to any of the preceeding claims wherein said composition comprises; a) at least one disintegrant in an amount of 1-15%, b) a diluent in an amount of 1-15%, preferably 1-10% and more preferably 1-3%, c) at least one lubricant in an amount of 1-5% of the total tablet weight.

8. A pharmaceutical composition according to any one of the preceeding claims wherein disintegrant is chosen from a group comprising croscarmelose sodium, crospovidone, polyvinylpyrrolidone, microcrystalline cellulose and hydroxypropyl methyl cellulose.

9. A pharmaceutical composition according to claim 8, wherein the disintegrant is crospovidon or microcrystalline cellulose or a mixture thereof.

10. A pharmaceutical composition according to any of the preceeding claims wherein the diluent is selected from a group comprising starch, cellulose derivatives, dibasic calcium phosphate and sucrose.

11. A pharmaceutical composition according to claim 10, wherein the preferred diluent is dibasic calcium phosphate.

12. A pharmaceutical composition according to claim 11, wherein dibasic calcium phosphate that is used as diluent is in monohydrate form.

13. A pharmaceutical composition according to any of the preceeding claims wherein the lubricant is selected from a group comprising magnesium stearate, stearic acid, palmitic acid and calcium stearate.

14. A pharmaceutical composition according to claim 13, wherein lubricant is magnesium stearate.

15. A process for the preparation of a pharmaceutical composition according to any of the preceeding claims wherein said process comprises compression of the mixture of rosuvastatin calcium, at least 60% of lactose, diluent, disintegrant, lubricant and other pharmaceutically acceptable excipients to form tablets.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
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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 practical, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 2008/075320 A2 (RANBAXY LAB LTD [IN]; MADAN SUMIT [IN]; RAVINDER SINGH [IN]; TYAGI PUN) 26 June 2008 (2008-06-26) page 19	1-15
X	WO 2008/062476 A2 (GLENMARK PHARMACEUTICAL LTD [IN]; MAHAJAN ABHAY [IN]; MEHTA KAMAL [IN]) 29 May 2008 (2008-05-29) the whole document page 1 - lines 26-27 claims 14-16	1-15
X	WO 2009/010787 A2 (GENERICS UK LTD [GB]; STANLEY TIMOTHY [GB]; DELGADO ISABEL [ES]; LLORE) 22 January 2009 (2009-01-22) claims 5,6 page 4, line 16 - page 5, line 9	1-15

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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
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Nyeki, Agnes

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International application No
PCT/TR2010/000103

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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