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(71) Applicant *(for all designated States except US)*: **MATRIX LABORATORIES LIMITED** [IN/IN]; 1-1-151/1, 4th Floor, Sai Ram Towers, Alexander Road, Secunderabad 500 003, Andhra Pradesh (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **RAO, P. V. Srinivas** [IN/IN]; c/o Matrix Laboratories Limited, Plot No. 34A, Anrich Industrial Estate, Bollaram, Jinnaram Mandal 502 325, Medak Dist., Andhra Pradesh (IN). **CHAUHAN, Yogendra, Kumar** [IN/IN]; c/o Matrix Laboratories Limited, Plot No. 34A, Anrich Industrial Estate, Bollaram, Jinnaram Mandal 502 325, Medak Dist., Andhra Pradesh (IN). **SRIVASTAVA, Tushar, Kumar** [IN/IN]; c/o Matrix Laboratories Limited, Plot No. 34A, Anrich Industrial Estate, Bollaram, Jinnaram Mandal 502 325, Medak Dist., Andhra Pradesh (IN). **RAY, Purna, Chandra** [IN/IN]; c/o Matrix Laboratories Limited, Plot No. 34A, Anrich Industrial Estate, Bollaram, Jinnaram Mandal 502 325, Medak Dist., Andhra Pradesh (IN). **TYAGI, Om, Dutt** [IN/IN]; c/o Matrix Laboratories Limited, Plot No. 34A, Anrich Industrial Estate, Bollaram, Jinnaram Mandal 502 325, Medak Dist., Andhra Pradesh (IN).

(74) Agents: **BABU, M.R. Ramesh** et al.; M/s Lex Orbis (Intellectual Property Practice), 709/710, Tolstoy House, 15-17 Tolstoy Marg, 110 001 New Delhi (IN).

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(54) Title: PROCESS FOR PRODUCING AMORPHOUS ATORVASTATIN CALCIUM

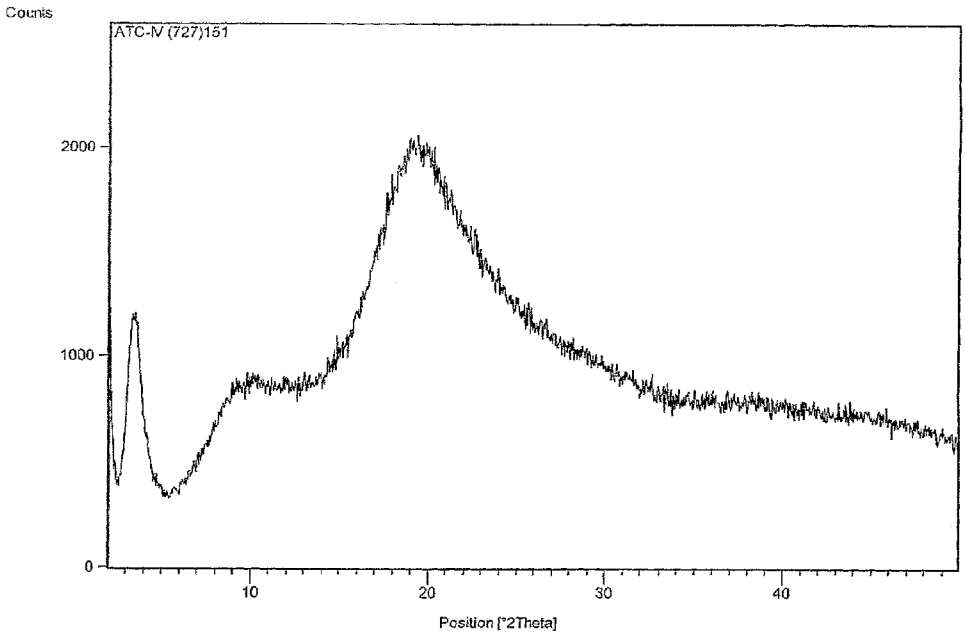


Figure 1

(57) Abstract: Disclosed herein is an improved process for producing amorphous atorvastatin calcium and a method of packaging thereof.

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PROCESS FOR PRODUCING AMORPHOUS ATORVASTATIN CALCIUM

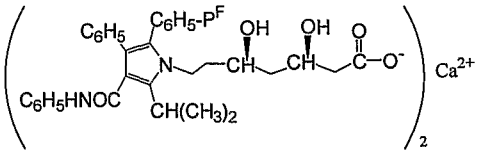
Field of the Invention

This invention, in general relates to a synthetic HMG-CoA reductase inhibitor. More particularly, the present invention provides an improved process for producing amorphous form of atorvastatin calcium and a method of packaging thereof.

Background of the Invention

[R(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenyl amino)carbonyl]-1H-pyrrole-1-heptanoic acid, commonly known as atorvastatin is known to be therapeutically useful compound. Atorvastatin calcium, a synthetic HMG-CoA reductase inhibitor, is used for the treatment of hyperlipidemia and hypercholesterolemia, both of which are risk factors for arteriosclerosis and coronary heart disease. open dihydroxy carboxylic acid, lactone and various salt forms of atorvastatin have been synthesized for use in the treatment of aforementioned diseases.

Atorvastatin in its calcium salt form, *i.e.* [R(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1) having formula I is more preferable for developing formulations and has been recommended as a drug.



Formula I

US Patent No. 4,681,893 discloses certain trans-6-[2-(3- or 4-carboxamido substituted- pyrrol-1-yl)alkyl]-4-hydroxy-pyran-2-ones, which includes trans(+)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-lH-pyrrole-3-carboxamide.

US Patent No. 5,273,995 discloses that R-enantiomer of the ring-opened acid form of trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-lH-pyrrole-3-carboxamide exhibits inhibition of the biosynthesis of cholesterol.

US Patent Nos. 5,003,080; 5,097,045; 5,103,024; 5,124,482; 5,149,837; 5,155,251; 5,216,174; 5,245,047; 5,248,793; 5,280,126; 5,342,952 and 5,397,792 disclose various processes and key intermediates for producing atorvastatin and its polymorphic forms.

The atorvastatin calcium produced by the prior art processes does not produce amorphous form consistently instead provides a mixture of crystalline and amorphous forms. The mixtures are unsuitable for filtration and drying. As a result, the prior art process are not suitable for large-scale production of the amorphous form of atorvastatin.

The amorphous forms of pharmaceutical substances exhibit different dissolution characteristics and bioavailability patterns compared to the crystalline forms (Konno T., Chem. Phar. Bull. 1990, 38, 2003-2007). Amorphous form of the atorvastatin calcium is more soluble than the crystalline forms, thereby resulting in increased bioavailability. The bioavailability is one of the key parameters in determining the form of the substance to be used in a pharmaceutical formulation.

It has been observed that the amorphous atorvastatin calcium is an unstable substance, which is susceptible to moisture and picks up moisture easily when exposed to atmosphere. Moreover, the reaction of atorvastatin with atmospheric oxygen leads to the formation of the sulfoxide impurity. The susceptibility of the amorphous atorvastatin calcium leads to deviation of the drug product from regulatory purity requirements even prior to the product reaching the patient.

In light of the foregoing discussion, there still exists a need to develop processes which enable the preparation of atorvastatin in an amorphous form without simultaneous formation of crystalline forms, or which will enable the conversion of the crystalline forms into the amorphous form. In addition the process should provide consistent purity of the amorphous atorvastatin calcium and prevents the pick up of moisture with minimal formation of oxidized impurities.

Accordingly, the present invention provides an improved process for producing amorphous atorvastatin calcium, which obviates the drawback associated in the prior arts.

Summary of the Invention

It is an aspect of the present invention to provide an improved process for producing amorphous atorvastatin calcium.

It is another aspect of the present invention to provide a novel method for packaging amorphous atorvastatin calcium, wherein the method increases the shelf life by reducing moisture uptake and oxidation.

In accordance with one preferred embodiment of the present invention, there is provided an improved process for producing amorphous atorvastatin calcium comprises of dissolving crystalline Form M of atorvastatin calcium in ester solvent, treating with anti solvent and isolating amorphous atorvastatin calcium.

In accordance with another embodiment of present invention, there is provided a method for packaging amorphous atorvastatin calcium comprises of placing atorvastatin calcium in low density polyethylene ("LDPE") sealed container under an inert atmosphere, placing the sealed container, a desiccant and an oxygen adsorbent in a second sealed container, placing the second sealed container in a triple laminated bag and sealing and enclosing the triple laminated bag in a closed high density polyethylene ("HDPE") container.

Brief Description of the Drawings

Further objects of the present invention together with additional features contributing thereto and advantages accruing there from will be apparent from the following description of preferred embodiments of the invention which are shown in the accompanying drawing figures, wherein:

Figure 1 illustrates the powder XRD pattern of amorphous atorvastatin calcium.

Detailed Description of the Invention

While this specification concludes with claims particularly pointing out and distinctly claiming that, which is regarded as the invention, it is anticipated that the invention can be more readily understood through reading the following detailed description of the invention and study of the included examples.

The present invention describes an improved process for producing the amorphous atorvastatin calcium. According to the present invention the process for producing the amorphous atorvastatin calcium comprises dissolving crystalline Form M of atorvastatin calcium in an ester solvent, treating with an anti solvent and isolating the resultant amorphous atorvastatin calcium.

According to one embodiment of the present invention, the ester solvent employed in the process is ethyl acetate. The atorvastatin calcium Form M is dissolved in the ester solvent at elevated temperature preferably 40-60 °C.

The anti solvent used in the process is hydrocarbon selected from the group consisting of hexane, pentane, heptane, cyclohexane or mixture thereof, preferably pentane.

According to the present invention, the anti solvent is added at a temperature 5-25 °C and subsequently isolating pure amorphous atorvastatin calcium.

According to the present invention atorvastatin calcium Form M can be prepared by treating atorvastatin hemi-calcium amorphous form or form-I or mixture of any polymorphic forms with alcohol, preferably methanol at room temperature to reflux temperature preferably at temperature of 15 to 35^0C for a period of 2 hrs to 30 hrs preferably for about 4hrs to 18 hrs. After the precipitation of form M, it can be isolated as per the conventional methods.

According to an embodiment of the present invention the amorphous atorvastatin calcium prepared by the process of the invention is packaged in a way to reduce the uptake of moisture and formation of oxidized products, thereby increasing the shelf life of the product. According to the present invention the method for packaging amorphous atorvastatin calcium comprises of placing the amorphous atorvastatin calcium in low density polyethylene ("LDPE") sealed container under an inert atmosphere, placing the sealed container, a desiccant and an oxygen adsorbent in a second sealed container, placing the second sealed container in a triple laminated bag and sealing and enclosing the triple laminated bag in a closed high density polyethylene ("HDPE") container.

According to the present invention, the oxygen adsorbent employed in the package includes any material that can adsorb or dissolve oxygen with/without reaction and provide the stability and thereby increasing the shelf life of the product.

Powder X-ray Diffraction (PXRD)

The said polymorphs of the present invention are characterized by their X-ray powder diffraction pattern. Thus, the X-ray diffraction patterns of said polymorphs of the invention were measured on *PANalytical, X'Pert PRO* powder diffractometer equipped with goniometer of θ/θ configuration and *X'Celerator* detector. The Cu-

anode X-ray tube was operated at 40kV and 30mA. The experiments were conducted over the 2θ range of 2.0°-50.0°, 0.030° step size and 50 seconds step time.

In the foregoing section embodiments are described by way of examples to illustrate the process of invention. However, these are not intended in any way to limit the scope of the present invention and several variants of these examples would be evident to person ordinary skilled in the art.

Example 1

Process for the preparation of amorphous atorvastatin calcium

150 gms of Atorvastatin calcium Form M was taken in 750 mL of Ethyl acetate. Reaction mass was heated to 50-55 °C. Then reaction mass was cooled to 10-15 °C. Slowly 750 mL of n-Pentane was added. The obtained solid was filtered and dried to yield 135-138 gms of pure amorphous Atorvastatin calcium.

Certain modifications and improvements of the disclosed invention will occur to those skilled in the art without departing from the scope of invention, which is limited only by the appended claims.

We Claim:

1. An improved process for producing amorphous atorvastatin calcium comprising dissolving crystalline Form M of atorvastatin calcium in ester solvent, treating with an anti solvent and isolating amorphous atorvastatin calcium.

2. The process according to claim 1, wherein the ester solvent is ethyl acetate.

3. The process according to claim 1, wherein the anti solvent is a hydrocarbon.

4. The process according to claim 3, wherein the hydrocarbon is selected from hexane, pentane, heptane and cyclohexane or mixture thereof.

5. The process according to claim 3, wherein the hydrocarbon is pentane.

6. The process according to claim 1, wherein the amorphous atorvastatin calcium obtained is packaged to increase shelf life.

7. A method for packaging amorphous atorvastatin calcium comprising:

placing the amorphous atorvastatin calcium in low density polyethylene ("LDPE") sealed container under an inert atmosphere;

placing the sealed container, a desiccant and an oxygen adsorbent in a second sealed container;

placing the second sealed container in a triple laminated bag; and

sealing and enclosing the triple laminated bag in a closed high density polyethylene ("HDPE") container.

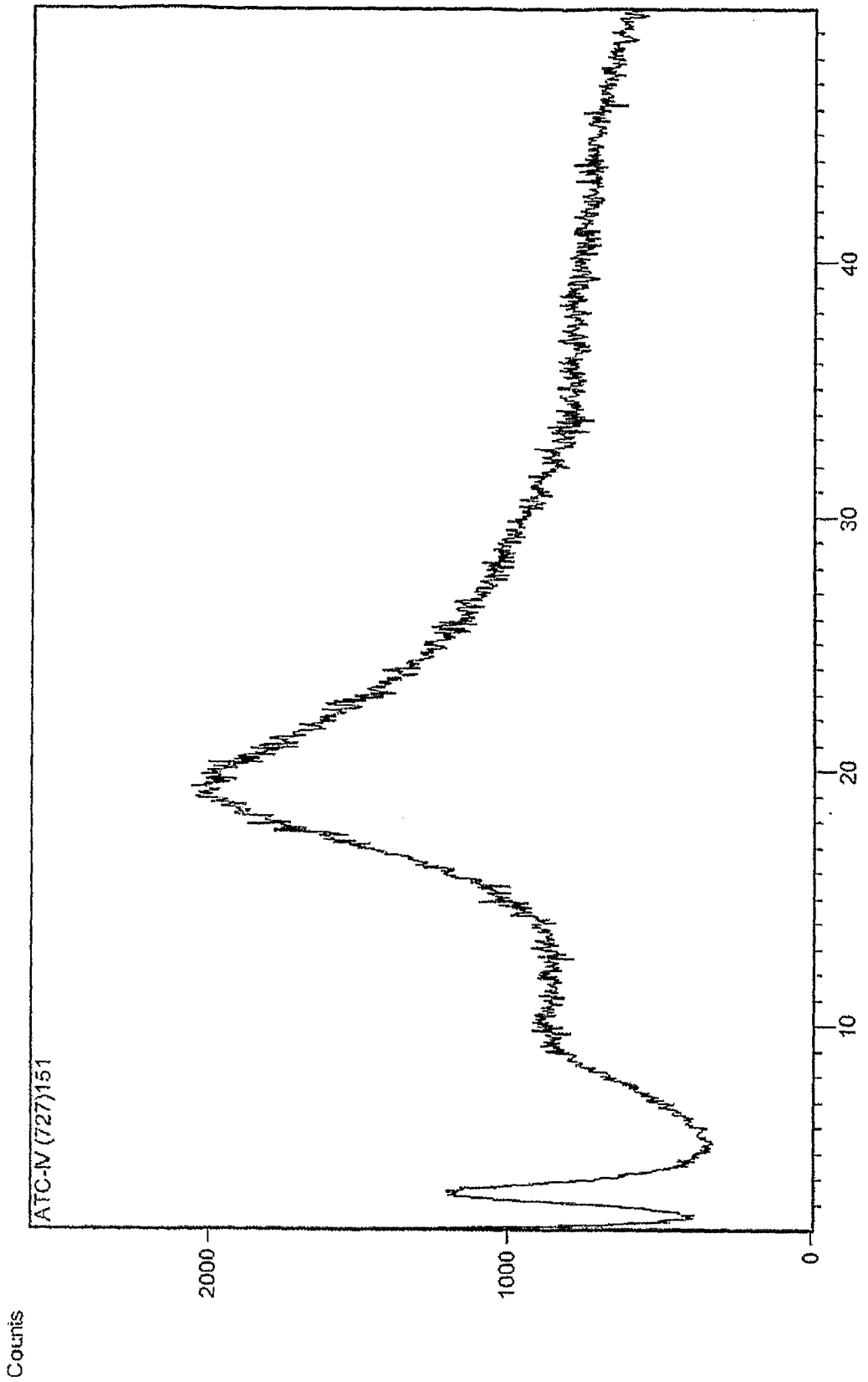


Figure 1