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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 May 2006 (04.05.2006)

PCT

(10) International Publication Number
WO 2006/046130 A2

(51) International Patent Classification:
C07C 67/52 (2006.01) *C07C 69/33* (2006.01)
C07C 69/013 (2006.01) *C12P 17/06* (2006.01)

(21) International Application Number:
PCT/IB2005/003270

(22) International Filing Date: 31 October 2005 (31.10.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2171/DEL/2004 29 October 2004 (29.10.2004) IN

(71) Applicant *(for all designated States except US)*: **RANBAXY LABORATORIES LIMITED** [IN/IN]; Plot No. 90, Sector - 32, Gurgaon 122001, Haryana (IN).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **KUMAR, Parveen** [IN/IN]; House No. 95, Sector - 11, Panchkula 134112, Haryana (IN). **MANDLECHA, Manish** [IN/IN]; Flat No. - 105, Paaschive, Plot No. - 11, Sector - 19, New Panvel 410206, New Bombay (IN). **MITRA, Ashoke** [IN/IN]; C 207, Sarita Vihar, New Delhi 110044 (IN).

(74) Common Representative: **RANBAXY LABORATORIES LIMITED**; c/o DESHMUKH, Jay R., 600 College Road East, Suite 2100, Princeton, NJ 08540 (US).

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2006/046130 A2

(54) Title: PROCESS FOR THE PREPARATION OF PRAVASTATIN

(57) Abstract: The invention relates to a process for the preparation of pure pravastatin or a salt thereof using adsorption matrices. The invention also relates to pharmaceutical compositions that include the pure pravastatin and the use of the compositions for treating hypercholesterolemia.

PROCESS FOR THE PREPARATION OF PRAVASTATIN

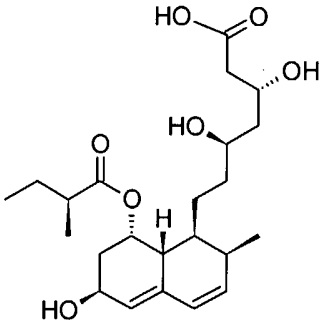
Field of the Invention

The field of the invention relates to a process for the preparation of pure pravastatin or a salt thereof using adsorption matrices. The invention also relates to pharmaceutical compositions that include the pure pravastatin and the use of the compositions for treating hypercholesterolemia.

Background of the Invention

The rate-limiting step in cholesterol biosynthesis is mediated by enzyme, 3- hydroxyl-3–methylglutaryl Coenzyme A (HMG-CoA) reductase. The statin family of compounds inhibits the enzyme and thereby limits the cholesterol formation in various mammalian species including humans.

Pravastatin of Formula I or salts thereof exhibit an important therapeutic advantage over other statins in that it selectively inhibits the cholesterol synthesis in the liver and small intestine but leaves cholesterol synthesis in the peripheral cells substantially unaffected. This selectivity is manifested due to the presence of a hydroxyl group at the C-6 position of hexahydronaphthalene nucleus, which increases its hydrophilic character.



FORMULA I

Various methods reported for the purification of pravastatin involve formation of crude pravastatin sodium salt via pravastatin lactone (U.S. Patent No. 5,272,174), or the ammonium salt route (U.S. Patent No. 6,689,590). The process of lactonization under heated conditions of reflux temperature for 40-50 hours is complicated by the formation of

impurities. This intermediate as well as the ammonium salt requires a crystallization step to improve upon the assay of the product before it is salified to sodium salt followed by its further purification to obtain the desired quality of the drug substance.

Several processes have been reported for the production of pravastatin sodium from compactin of Formula II by fermentation for example, in U.S. Patent Nos. 5,179,013; 4,346,227 and 4,537,859; U.S. Patent Application Publication Nos. 20020081675 and 20010026934; and European Patent No. 605230. In general, these processes involve microbial hydroxylation for the production of pravastatin from compactin. However, during the bioconversion step, depending on the microorganism, quality of starting material of Formula II and process conditions employed, purity profile and impurities present in pravastatin or a salt thereof may vary to a great extent.

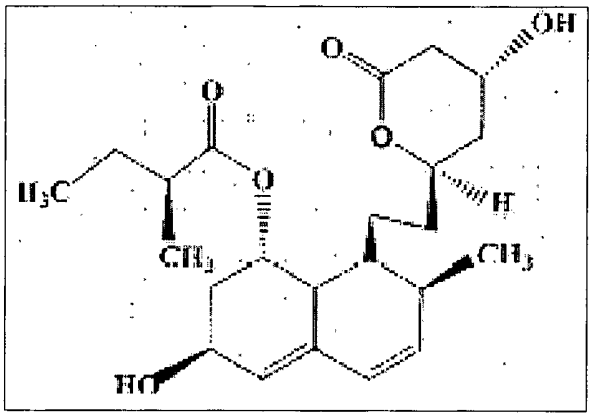
These impurities structurally have very close resemblance with that of pravastatin. Therefore once these impurities are formed during the fermentation process, their subsequent removal from the final product is very difficult. In order to obtain pure pravastatin or a salt thereof, several process are reported which suggest use of different solvents for crystallization of pravastatin, use of different chromatographic methods for purification of pravastatin and the like for example, in U.S. Patent Application Publication No. 20020082295; Korean Patent Application Nos. KR 2002071636; 2002071637; 2002071638; 2002071639; and International (PCT) Publication No. WO 02/30415.

The prior art processes for the preparation of pravastatin or salts thereof are not suitable from commercial point of view because these involve number of purification steps and the product is not obtained in high purity.

Thus, the present invention provides a process which does not result in impure pravastatin or salts thereof; rather pure pravastatin which is essentially free of pravastatin lactone impurity is obtained. The process of the present invention is simple with less number of purification steps and involves easily scalable unit operations to give pravastatin sodium, which is essentially free of pravastatin lactone.

Summary of the Invention

In one general aspect there is provided pure pravastatin or a salt thereof essentially free by HPLC of pravastatin lactone impurity of Formula II.



FORMULA II

In another general aspect there is provided a pharmaceutical composition that includes a therapeutically effective amount of the pure pravastatin or a salt thereof essentially free of pravastatin lactone impurity; and one or more pharmaceutically acceptable carriers, excipients or diluents.

In another general aspect there is provided a process for the preparation of pure pravastatin or a salt thereof essentially free of pravastatin lactone impurity. The process includes:

a) obtaining a solution of pravastatin or a salt thereof in one or more solvents;

b) adjusting pH of the resulting solution in the range of about 5.5 to about 7.5;

c) stirring the solution obtained in step b) with one or both of an adsorption matrix and activated carbon; and

d) recovering the pure pravastatin or a salt thereof from the solution thereof by the removal of the solvents.

In another aspect there is provided a process for removal of pravastatin lactone impurity from pravastatin or a salt thereof. The process includes stirring pravastatin or a salt thereof with one or both of an adsorption matrix and activated carbon in one or more solvents; adding a suitable anti-solvent; and recovering pravastatin or a salt thereof by the removal of the solvents.

The process may include further drying of the product obtained.

The process may produce the pure pravastatin essentially free of pravastatin lactone impurity.

In another general aspect there is provided a method for treating hypercholesterolemia in a warm-blooded animal, the method comprising providing a pharmaceutical composition to the warm-blooded animal that includes the pure pravastatin or a salt thereof essentially free of pravastatin lactone impurity.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

Detailed Description of the Invention

The inventors have developed a process for the preparation of pure pravastatin and salts thereof essentially free of pravastatin lactone impurity. The inventors have developed a process for the preparation of the pure pravastatin, by obtaining a solution of pravastatin or a salt thereof in one or more solvents; adjusting pH of the resulting solution in the range of about 5.5 to about 7.5; stirring the solution obtained in step b) with one or both of an adsorption matrix and activated carbon; and recovering the pure pravastatin or a salt thereof from the solution thereof by the removal of the solvents.

The term "essentially free" means that pravasatin lactone impurity is 0.05% or less or it is not detected in pravastatin or a salt thereof when determined by HPLC.

The inventors also have developed pharmaceutical compositions that contain the pure pravastatin or a salt thereof essentially free of pravastatin lactone impurity, in admixture with one or more solid or liquid pharmaceutical diluents, carriers, and/or excipients.

In general, the solution of pravastatin or a salt thereof may be obtained by dissolving pravastatin or a salt thereof in a suitable solvent. Alternatively, such a solution may be obtained directly from the fermentation broth.

In general, any of the methods known in the art can be employed for isolation of pravastatin or a salt thereof from the fermentation broth.

The term "solvent" includes any solvent or solvent mixtures, including, for example, lower alkanols, water and mixtures thereof. Examples of alkanols include methanol, ethanol, propanol, isopropanol, butanol and isobutanol. Mixtures of all of these solvents are also contemplated.

The solvent may be removed from the solution by a technique which includes, for example, distillation, distillation under vacuum, evaporation, filtration, filtration under vacuum, decantation and centrifugation.

The pH of the resultant solution can be adjusted in the range of about 5.5 to about 7.5 by addition of a suitable alkali or an acid. In particular, it may be adjusted in the range of about 6.1 to about 6.7, for example in the range of about 6.4 to about 6.7.

The solution may be stirred with an adsorption matrix and activated carbon for about 10 minutes to about 5 hours. The resultant mass may be filtered through a celite bed.

The adsorption matrices which may be used include silica gel, alumina, diatomaceous earth, kaolin, kieselguhr, or resins. The amount of adsorption matrix that may be used is from about 10% to about 50% by weight of the pravastatin sodium. In particular, the amount of the adsorption matrix may be about 25% by weight of the pravastatin sodium. The amount of activated carbon that may be used is from about 10% to about 20% by weight of the pravastatin sodium. In particular, the amount of the adsorption matrix may be about 15% by weight of the pravastatin sodium.

In another aspect, a suitable anti-solvent can be added to the clear solution to precipitate the pure pravastatin or a salt thereof. The term "anti-solvent includes any solvent in which pravastatin or a salt thereof is insoluble or poorly soluble or practically insoluble or partially soluble, including, for example, acetonitrile, ethyl acetate, acetone, ethyl methyl ketone and methyl isobutyl ketone.

The product may be further purified or additionally purified, by employing commonly practiced recrystallization techniques in solvent / anti-solvent mixture to obtain pravastatin or a salt thereof.

The product obtained may be further or additionally dried to achieve the desired moisture values. For example, the product may be further or additionally dried in a tray drier, dried under vacuum and/or in a Fluid Bed Dryer.

The resulting pure pravastatin or a salt thereof may be formulated into ordinary dosage forms such as, for example, tablets, capsules, pills, solutions, etc. In these cases, the medicaments can be prepared by conventional methods with conventional pharmaceutical excipients.

The pravastatin or a salt thereof can be administered for the prevention and treatment of hypocholesterolemia in a warm-blooded animal.

For the purpose of this disclosure, a warm-blooded animal is a member of the animal kingdom possessed of a homeostatic mechanism and includes mammals and birds.

The pravastatin or a salt thereof is generally administered as part of a pharmaceutical composition with a pharmaceutically acceptable carrier, diluent or excipient and optionally other therapeutic ingredients. The pravastatin or a salt thereof may be conventionally formulated into tablets, capsules, suspensions, dispersions, injectables and other pharmaceutical forms. Any suitable route of administration may be employed, such as, for example, peroral or parenteral.

The present invention is further illustrated by the following examples which are provided merely to be exemplary of the invention and do not limit the scope of the invention.

Certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Example 1:

Pravastatin sodium (10g, Assay 75%) isolated from the fermentation broth was dissolved in minimum amount of water (about 15 ml) and the pH was adjusted to 6.7. Activated carbon (1.5 g) and acetonitrile (15 ml) were added to the solution. It was stirred for 30 minutes, filtered through a celite bed and the bed was washed with water-acetonitrile mixture (30 ml) and the filtrate was collected. Acetonitrile (370 ml) was added to the filtrate to give a precipitate. The precipitate was stirred for 2 hours at about 28°C and the slurry was chilled to 15°C. The slurry was then filtered and wet cake was dried under vacuum to obtain 7.3 g of pravastatin sodium.

Assay: 83%.

Example 2:

Pravastatin sodium (10g Assay 75%), isolated from the fermentation broth, was dissolved in minimum amount of water (about 15ml) and the pH was adjusted to 6.7. Silica gel (2.5 g), activated carbon (1.5 g) and acetonitrile (15 ml) were added to the solution. It was stirred for 30 minutes, filtered through a celite bed and the bed was washed with water–acetonitrile mixture (30 ml) and the filtrate was collected. Acetonitrile (370 ml) was added to the filtrate. The precipitate was stirred for 2 hours at about 28°C and the slurry was chilled to 15°C. The slurry was then filtered and wet cake was dried under vacuum to obtain 6.7 g of pravastatin sodium.

Assay 87.6%

Example 3:

Pravastatin sodium (10g, Assay 81.8%), was dissolved in minimum amount of water (about 15 ml) and the pH was adjusted to 6.4. Alumina (2.5 g) was added instead of silica gel. The rest of the process was repeated exactly as described in example 2 to obtain 6.8 g of pravastatin sodium.

Assay: 91.1%

Example 4:

Pravastatin sodium (10g, Assay 82%), was dissolved in minimum amount of water (about 15 ml) and the pH was adjusted to 6.1. The rest of the process was exactly followed as described in example 2, to obtain 6.12 g of pravastatin sodium.

Assay: 93.7%

Example 5:

Pravastatin Sodium (10 gm, Assay 75%), was dissolved in minimum amount of water (about 15 ml) and the pH was adjusted to 6.4. The rest of the process was exactly followed as described in example 2, and 570 ml acetonitrile was added to the aqueous filtrate to obtain 6.7 g of pravastatin sodium.

Assay: 89.74%

Example 6:

Pravastatin sodium (10 g, Assay 75%), was dissolved in minimum amount of water (about 15 ml) and the pH was adjusted to 6.4. The rest of the process was exactly followed as described in example 2, to obtain 6.8 g dry powder.

Assay: 93.2%

Example 7:

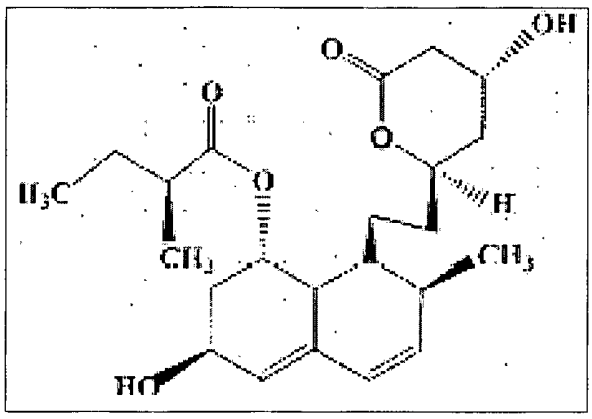
Pravastatin sodium (1g) obtained in example 6 was dissolved in water (1.5 ml) and the pH was adjusted to 6.4with 0.1 ml of 2N sodium hydroxide solution. Activated carbon (0.15 g), silica (0.25 g) and acetonitrile (1.5 ml) were added to the solution. It was stirred for 30 minutes, filtered through a celite bed and the bed was washed with a mixture of acetonitrile (1.5 ml) and water (1.4 ml). Acetonitrile (37 ml) was added and the solution was again stirred for 60 minutes at room temperature to give slurry. The slurry was chilled to 15°C, stirred, filtered and washed with acetonitrile. The wet cake was dried at 45° C till the moisture content was not more than 10% w/ w. The dry cake was dissolved in methanol (4 ml) at room

temperature. Activated carbon (0.1 g) was added, the contents were stirred for 30 minutes, filtered through a celite and the bed was washed with methanol (2ml). The solution was concentrated under vacuum. Acetonitrile (2ml) was added; the solution was concentrated under vacuum and dissolved in de-ionized water (3 ml). To the clear aqueous solution, acetonitrile (30 ml) was added to give slurry. The slurry was chilled to 10°C, stirred for 60 minutes, filtered, the wet cake thus obtained was washed with acetonitrile (2 ml) at 10°C, dried under vacuum at 45 °C till water content is NMT 10% w/w. De-ionized water (0.25 ml) was added to 0.25 g of dried pravastatin sodium and isopropyl alcohol (0.625 ml) were added and the contents were stirred at a temperature not more that 35°C to get a homogeneous solution. Acetonitrile (10 ml) was added at room temperature slowly in 2 hours. The contents were stirred for 2 hours at room temperature to give slurry. The slurry was chilled to 5°C and stirred for 15 hours, filtered and the wet cake was washed with chilled acetonitrile. The wet cake was dried under vacuum till moisture content was not more than 4% w/w to obtain pravastatin sodium essentially free of pravastatin lactone.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention.

We Claim:

1. Pure pravastatin or a salt thereof essentially free by HPLC of pravastatin lactone impurity of Formula II.



FORMULA II

2. A process for the preparation of pure pravastatin or a salt thereof essentially free by HPLC of pravastatin lactone impurity, the process comprising:

a) obtaining a solution of pravastatin or a salt thereof in one or more solvents;

b) adjusting pH of the resulting solution in the range of about 5.5 to about 7.5;

c) stirring the solution obtained in step b) with one or both of an adsorption matrix and activated carbon; and

d) recovering the pure pravastatin or a salt thereof from the solution thereof by the removal of the solvents.

3. The process of claim 2, wherein the solvent comprises one or more of lower alkanols water or mixtures thereof.

4. The process of claim 3, wherein the lower alkanol comprises one or more of methanol, ethanol, propanol, isopropanol, butanol and isobutanol.

5. The process of claim 2, wherein the pH is adjusted in the range of about 6.1 to about 6.7.

6. The process of claim 5, wherein the pH is adjusted in the range of about 6.4 to about 6.7.

7. The process of claim 2, wherein the adsorption matrix comprises one or more of silica gel, alumina, diatomaceous earth, kaolin, kieselguhr, and adsorption resins.

8. The process of claim 2, wherein the adsorption matrix is used in amount from about 10% to about 50% by weight of the pravastatin or a salt thereof.

9. The process of claim 8, wherein the adsorption matrix is used in amount about 25% by weight.

10. The process of claim 2, wherein the activated carbon is used in amount from about 10% to about 20% by weight of the pravastatin or a salt thereof.

11. The process of claim 10, wherein the activated carbon is used in amount about 15% by weight.

12. The process of claim 2, wherein removing the solvent comprises one or more of distillation, distillation under vacuum, evaporation, filtration, filtration under vacuum, decantation, and centrifugation.

13. The process of claim 12, further comprising adding anti-solvent before removing the solvent.

14. The process of claim 13, wherein the anti-solvent comprises one or more of acetonitrile, ethyl acetate, acetone, ethyl methyl ketone and methyl isobutyl ketone.

15. The process of claim 2, wherein the pure pravastatin or a salt thereof is recovered from the solution by filtration.

16. A process for removal of pravastatin lactone impurity from pravastatin or a salt thereof, the process comprising stirring pravastatin or a salt thereof with one or both of an adsorption matrix and activated carbon in one or more solvents; adding a suitable anti-solvent; and recovering pravastatin or a salt thereof by the removal of the solvents.

17. The process of claim 16, wherein the solvent comprises one or more of lower alkanols, water or mixtures thereof.

18. The process of claim 16, wherein the anti-solvent comprises one or more of acetonitrile, ethyl acetate, acetone, ethyl methyl ketone and methyl isobutyl ketone.

19. A pharmaceutical composition comprising:

a therapeutically effective amount of the pure pravastatin or a salt thereof essentially free of pravastatin lactone impurity by HPLC; and one or more pharmaceutically acceptable carriers, excipients or diluents.

20. A method of treating hypercholesterolemia in a warm-blooded animal, the method comprising providing a dosage form to the warm-blooded animal that includes pure pravastatin or a salt thereof essentially free of pravastatin lactone impurity by HPLC.