

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF TEXAS
MARSHALL DIVISION

FILED-CLERK
U.S. DISTRICT COURT
2006 DEC 29 AM 11:28
TX EASTERN-MARSHALL

LEK D.D.

Plaintiff,

vs.

BRISTOL-MYERS SQUIBB COMPANY and
WATSON PHARMACEUTICALS, INC.,

Defendants.

§
§
§
§
§
§
§
§
§
§
§
§

BY _____

CIVIL ACTION NO.

2 - 0 6 C V - 5 4 7

JURY TRIAL DEMANDED

Complaint for Patent Infringement

Plaintiff LEK D.D. alleges the following:

Parties

1 LEK D.D. ("LEK") is a foreign corporation duly organized and existing under the laws of the Republic of Slovenia. LEK is ultimately a wholly-owned subsidiary of Novartis AG, a recognized world leader in healthcare with core businesses in pharmaceuticals, consumer health, generics, eye care and animal health.

2 Upon information and belief, defendant Bristol-Myers Squibb Company ("Bristol-Myers") is a corporation duly organized and existing under the laws of the State of Delaware. Bristol-Myers may be served with process by serving CT Corp System, Bristol-Myers's registered agent in Texas, at 350 North St. Paul Street, Dallas, Texas 75201

3. Upon information and belief, defendant Watson Pharmaceuticals, Inc. ("Watson") is a corporation duly organized and existing under the laws of the State of Nevada. Watson may be served with process by serving Corporation Trust Company of Nevada, Watson's registered agent, at 6100 Neil Road, Suite 500, Reno, Nevada 89511.

Jurisdiction and Venue

4. This Court has subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338(a) because this action arises under the patent laws of the United States, 35 U.S.C. §§ 1, *et seq.*

5. Venue is proper in this District pursuant to 28 U.S.C. §§ 1391(b)-(c) and 1400(b) because Bristol-Myers and Watson have conducted business in this District, have committed acts of infringement in this District, and continue to commit acts of infringement in this District, entitling LEK to relief.

Infringement of U.S. Patent No. 6,740,775

6. On May 25, 2005, United States Patent No. 6,740,775 (the "'775 Patent") was duly and legally issued to LEK Pharmaceuticals D.D. for an invention titled "Crystalline Sodium Salt of Pravastatin." A true and correct copy of the '775 Patent is attached as Exhibit 1.

7. Plaintiff LEK owns the '775 Patent and has the right to make, have made, use, offer, and/or sell products covered by the '775 Patent. LEK has the right to enforce the '775 Patent against Bristol-Myers and Watson.

8. Bristol-Myers has infringed and continues to infringe the '775 Patent by its manufacture, use, sale, importation, and/or offer for sale of the drug it sells under the brand name Pravachol®. Bristol-Myers also has infringed and continues to infringe the '775 Patent by contributing to (and/or inducing) the conduct of others in manufacturing, using, selling, distributing, and/or offering to sell infringing products. Under 35 U.S.C. § 271, Bristol-Myers is liable for its infringement of the '775 Patent.

9. Watson has infringed and continues to infringe the '775 Patent by its manufacture, use, sale, importation, and/or offer for sale of its pravastatin sodium drug, which is marketed as a generic version of Bristol-Myers's Pravachol® product. Watson also has

infringed and continues to infringe the '775 Patent by contributing to (and/or inducing) the conduct of others in manufacturing, using, selling, distributing, and/or offering to sell infringing products. Under 35 U.S.C. § 271, Watson is liable for its infringement of the '775 Patent.

10. Bristol-Myers's acts of infringement have caused damage to LEK. LEK is entitled to recover from Bristol-Myers the damages it has sustained as a result of Bristol-Myers's wrongful acts in an amount subject to proof at trial. Unless enjoined by this Court, Bristol-Myers's infringement of LEK's exclusive rights under the '775 Patent will continue to damage LEK, causing irreparable harm for which there is no adequate remedy at law.

11. Upon information and belief, Bristol-Myers's infringement of the '775 Patent is willful and deliberate, and LEK is entitled to increased damages under 35 U.S.C. § 284 and to attorneys' fees and costs incurred in prosecuting this action under 35 U.S.C. § 285.

12. Upon information and belief, Bristol-Myers knew or should have known about the issuance of the '775 Patent. Because of the substantial volume of Pravachol® that Bristol-Myers sells, it should have known about any patents affecting it. Thus, Bristol-Myers's continued infringement of the '775 Patent is willful and reckless.

13. Watson's acts of infringement have caused damage to LEK. LEK is entitled to recover from Watson the damages it has sustained as a result of Watson's wrongful acts in an amount subject to proof at trial. Unless enjoined by this Court, Watson's infringement of LEK's exclusive rights under the '775 Patent will continue to damage LEK, causing irreparable harm for which there is no adequate remedy at law.

14. Upon information and belief, Watson's infringement of the '775 Patent is willful and deliberate, and LEK is entitled to increased damages under 35 U.S.C. § 284 and to attorneys' fees and costs incurred in prosecuting this action under 35 U.S.C. § 285.

15. Upon information and belief, Watson knew or should have known about the issuance of the '775 Patent. Because of the substantial volume of pravastatin sodium drug product that Watson sells, it should have known about any patents affecting it. Thus, Watson's continued infringement of the '775 Patent is willful and reckless.

Infringement of U.S. Patent No. 7,078,558

16. On July 18, 2006, United States Patent No. 7,078,558 (the "'558 Patent") was duly and legally issued to LEK Pharmaceuticals and Chemical Company D.D. for an invention titled "Crystals of the Sodium Salt of Pravastatin." A true and correct copy of the '558 Patent is attached as Exhibit 2.

17. Plaintiff LEK D.D. owns the '558 Patent and has the right to make, have made, use, offer, and/or sell products covered by the '558 Patent. LEK has the right to enforce the '558 Patent against Bristol-Myers and Watson.

18. Bristol-Myers has infringed and continues to infringe the '558 Patent by its manufacture, use, sale, importation, and/or offer for sale of the drug it sells under the brand name Pravachol®. Bristol-Myers also has infringed and continues to infringe the '558 Patent by contributing to (and/or inducing) the conduct of others in manufacturing, using, selling, distributing, and/or offering to sell infringing products. Under 35 U.S.C. § 271, Bristol-Myers is liable for its infringement of the '558 Patent.

19. Watson has infringed and continues to infringe the '558 Patent by its manufacture, use, sale, importation, and/or offer for sale of its pravastatin sodium drug, which is marketed as a generic version of Bristol-Myers's Pravachol® product. Watson also has infringed and continues to infringe the '558 Patent by contributing to (and/or inducing) the conduct of others in manufacturing, using, selling, distributing, and/or offering to sell infringing products. Under 35 U.S.C. § 271, Watson is liable for its infringement of the '558 Patent.

20. Bristol-Myers's acts of infringement have caused damage to LEK. LEK is entitled to recover from Bristol-Myers the damages it has sustained as a result of Bristol-Myers's wrongful acts in an amount subject to proof at trial. Unless enjoined by this Court, Bristol-Myers's infringement of LEK's exclusive rights under the '558 Patent will continue to damage LEK, causing irreparable harm for which there is no adequate remedy at law.

21. Upon information and belief, Bristol-Myers's infringement of the '558 Patent is willful and deliberate, and LEK is entitled to increased damages under 35 U.S.C. § 284 and to attorneys' fees and costs incurred in prosecuting this action under 35 U.S.C. § 285.

22. Upon information and belief, Bristol-Myers knew or should have known about the issuance of the '558 Patent. Because of the substantial volume of Pravachol® that Bristol-Myers sells, it should have known about any patents affecting it. Thus, Bristol-Myers's continued infringement of the '558 Patent is willful and reckless.

23. Watson's acts of infringement have caused damage to LEK. LEK is entitled to recover from Watson the damages it has sustained as a result of Watson's wrongful acts in an amount subject to proof at trial. Unless enjoined by this Court, Watson's infringement of LEK's exclusive rights under the '558 Patent will continue to damage LEK, causing irreparable harm for which there is no adequate remedy at law.

24. Upon information and belief, Watson's infringement of the '558 Patent is willful and deliberate, and LEK is entitled to increased damages under 35 U.S.C. § 284 and to attorneys' fees and costs incurred in prosecuting this action under 35 U.S.C. § 285.

25. Upon information and belief, Watson knew or should have known about the issuance of the '558 Patent. Because of the substantial volume of pravastatin sodium drug product that Watson sells, it should have known about any patents affecting it. Thus, Watson's continued infringement of the '558 Patent is willful and reckless.

Jury Demand

26. LEK demands a trial by jury on all issues.

Prayer for Relief

27. LEK requests entry of judgment in its favor and against defendants Bristol-Myers Squibb and Watson as follows:

a) Declaring that each defendant has infringed United States Patent Nos. 6,740,775 and 7,078,558;

b) Enjoining permanently each defendant and its respective officers, agents, employees, and those acting in privity with them, from further infringement, contributory infringement and/or inducing infringement of United States Patent Nos. 6,740,775 and 7,078,558;

c) Awarding damages to plaintiff arising out of defendants' willful, deliberate, and reckless infringement of United States Patent Nos. 6,740,775 and 7,078,558, including enhanced damages pursuant to 35 U.S.C. § 284, together with prejudgment and post-judgment interest, in an amount according to proof;

d) Awarding attorneys' fees pursuant to 35 U.S.C. § 285 or as otherwise permitted by law; and

e) For such other costs and further relief as this Court may deem just and proper.

DATED: December 29, 2006

Respectfully submitted,

By: Geoffrey L. Harrison by SCC by permission

Geoffrey L. Harrison
Attorney-in-Charge
State Bar No. 00785947
gharrison@susmangodfrey.com
Max L. Tribble, Jr.
State Bar No. 20213950
mtribble@susmangodfrey.com
Suyash Agrawal
State Bar No. 24036110
sagrawal@susmangodfrey.com
SUSMAN GODFREY L.L.P.
1000 Louisiana Street, Suite 5100
Houston, Texas 77002
Telephone: (713) 651-9366
Facsimile: (713) 654-6666

Robert M. Parker
State Bar No. 15498000
rmparker@cox-internet.com
Robert Christopher Bunt
State Bar No. 00787165
cbunt@cox-internet.com
PARKER & BUNT, P.C.
1000 East Ferguson, Suite 1114
Tyler, Texas 75702
Telephone: (903) 531-3535
Facsimile: (903) 533-9687

S. Calvin Capshaw
State Bar No. 03783900
ccapshaw@mailbmc.com
Elizabeth L. Derieux
State Bar No. 05770585
ederieux@mailbmc.com
BROWN McCARROLL, L.L.P.
1127 Judson Road, Suite 220
P.O. Box 3999
Longview, Texas 75601-5157
Telephone: (903) 236-9800
Facsimile: (903) 236-8787

Franklin Jones, Jr.
State Bar No. 00000055
maizieh@millerfirm.com
JONES AND JONES, INC., P.C.
201 West Houston Street
P.O. Drawer 1249
Marshall, TX 75671-1249
Telephone: (903) 938-4395
Facsimile: (903) 938-3360

Attorneys for Plaintiff LEK D.D.



US006740775B1

(12) **United States Patent**
Pflaum

(10) **Patent No.:** US 6,740,775 B1
(15) **Date of Patent:** May 25, 2004

(54) **CRYSTALLINE SODIUM SALT OF PRAVASTATIN**

(75) **Inventor:** Zlatko Pflaum, Domzale (SI)

(73) **Assignee:** LEK Pharmaceuticals d.d., Ljubljana (SI)

(*) **Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days

(21) **Appl No:** 10/408,012

(22) **Filed:** Apr. 4, 2003

Related U.S. Application Data

(63) Continuation of application No. 10/049,093, filed as application No. PC1-1B00/01103 on Aug. 4, 2000

(30) **Foreign Application Priority Data**

Aug 6 1999 (SI) P-9900191

(51) **Int. Cl.:** C07C 67/02; A01N 37/02

(52) **U.S. Cl.:** 560/256; 524 546; 524 548; 560 119

(58) **Field of Search:** 560,256 119; 514/546 548

(56) **References Cited**

U.S. PATENT DOCUMENTS

2002/0081675 A1 6 2002 Jekel et al

FOREIGN PATENT DOCUMENTS

EP	0457514 B1	8 1996
WO	99 45410	10 1998
WO	200017182	3 2000
WO	2000 46175	8 2000

OTHER PUBLICATIONS

Eguchi, I et al *Baioisaiensu To Indasutory* (1995) 53 (2) 113-16 *

* cited by examiner

Primary Examiner—Paul J. Killos

(74) *Attorney, Agent, or Firm*—Cohen, Pontani, Lieberman & Pavane

(57) **ABSTRACT**

A crystalline form of the sodium salt of pravastatin which is known by the chemical name 1-naphthalenecarboxylic acid 1,2,6,7,8,8a-hexahydro- β , δ -trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)-, mono sodium salt which is useful as a pharmaceutical substance. A method for its preparation and isolation, a pharmaceutical formulation containing the sodium salt of pravastatin in the crystalline form and a pharmaceutically acceptable carrier, and the pharmaceutical method of treatment are also disclosed.

20 Claims, 4 Drawing Sheets

EXHIBIT 1

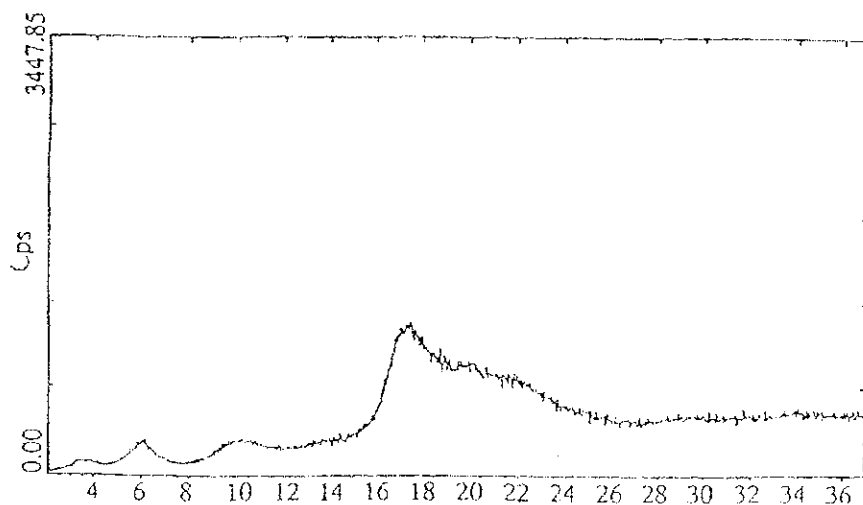
U.S. Patent

May 25, 2004

Sheet 1 of 4

US 6,740,775 B1

Figure 1



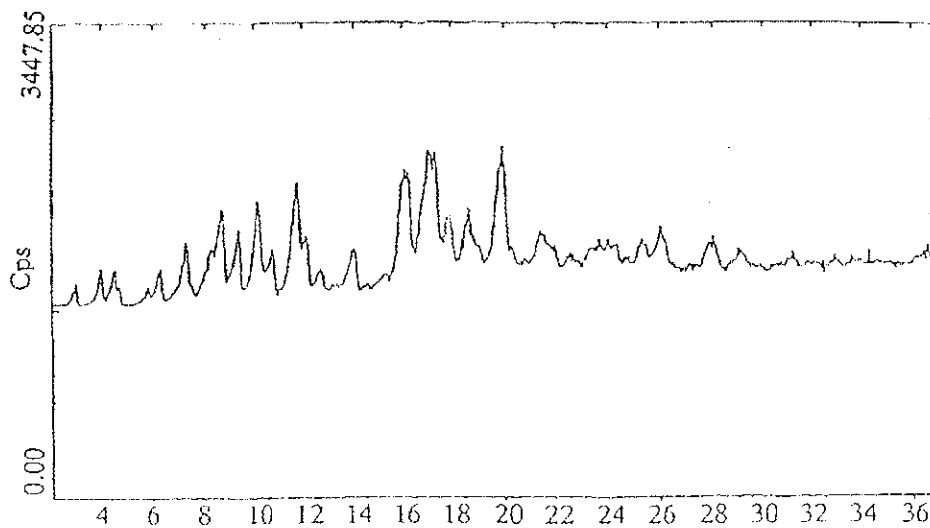
U.S. Patent

May 25, 2004

Sheet 2 of 4

US 6,740,775 B1

Figure 2



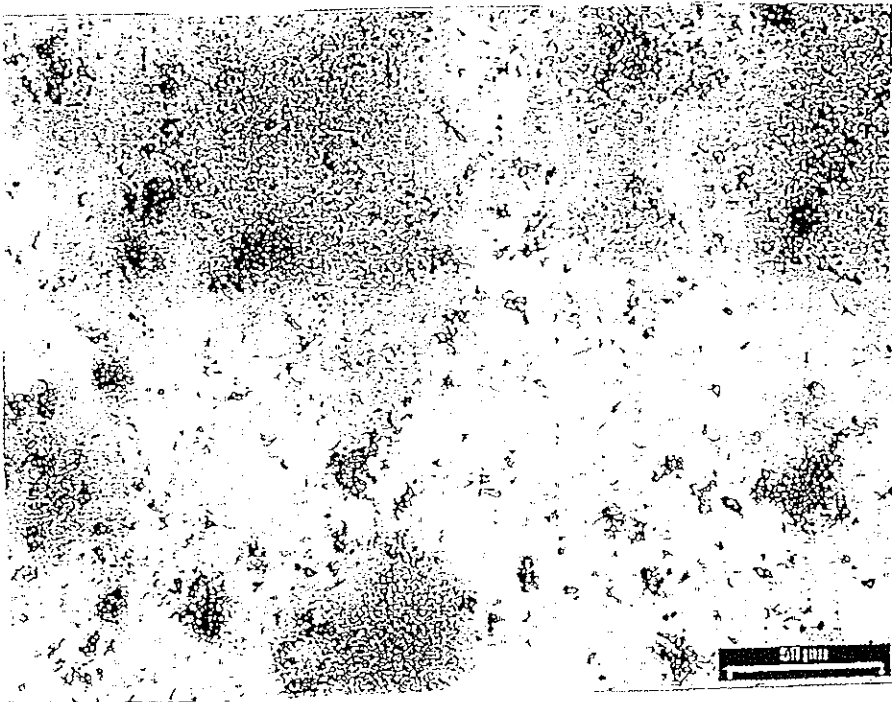
U.S. Patent

May 25, 2004

Sheet 3 of 4

US 6,740,775 B1

Figure 3



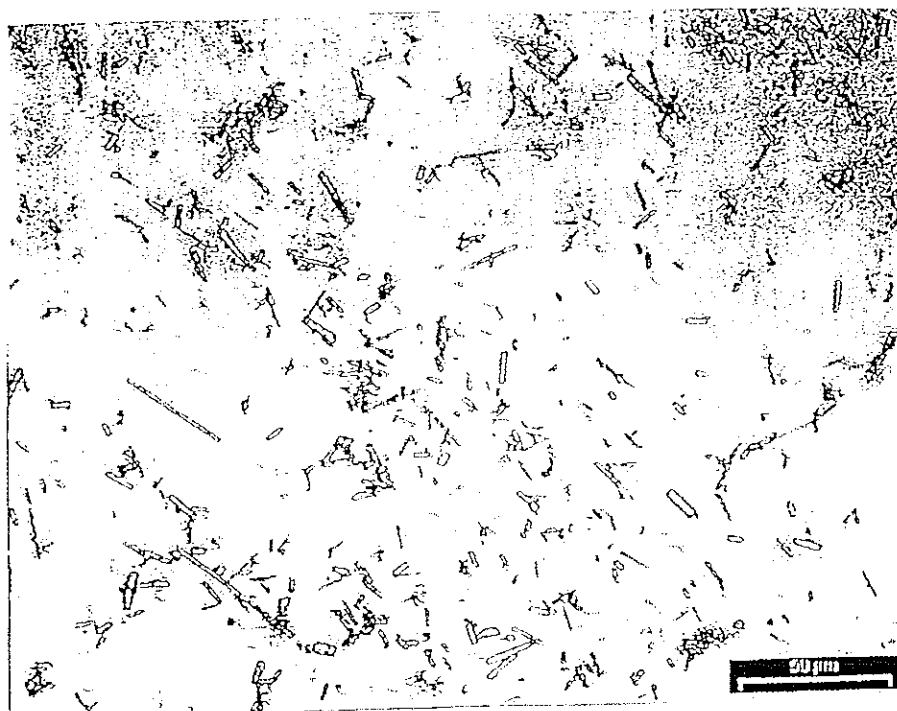
U.S. Patent

May 25, 2004

Sheet 4 of 4

US 6,740,775 B1

Figure 4



US 6,740,775 B1

1

CRYSTALLINE SODIUM SALT OF
PRAVASTATIN

PRIORITY CLAIM

This is as continuation of U.S. application Ser. No. 10/049,093, filed Apr. 22, 2002, which is a national phase application of PCT/IB00/01103, filed Aug. 4, 2000 claiming priority of Slovenian application No. P-9900191, filed Aug. 6, 1999.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a crystalline form of the sodium salt of pravastatin, which is known by the chemical name 1-naphthaleneheptanoic acid, 1,2,6,7,8-hexahydro- β , δ ,6-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)-, mono sodium salt, which is useful as a pharmaceutical substance. The present invention further relates to the method for its preparation and isolation, to a pharmaceutical formulation containing the sodium salt of pravastatin in the crystalline form and a pharmaceutically acceptable carrier, and to the pharmaceutical method of treatment.

2. Description of the Related Art

Lovastatin, pravastatin, simvastatin, mevastatin, atorvastatin, fluvastatin and cerivastatin and derivatives and analogs thereof are known as HMG-CoA reductase inhibitors and are used as antihypercholesterolemic agents. The majority of them are produced by fermentation using microorganisms of different species identified as species belonging to *Aspergillus*, *Monascus*, *Nocardia*, *Amycolatopsis*, *Mucor* or *Penicillium* genus, some are obtained by treating the fermentation products using the methods of chemical synthesis (simvastatin) or they are the products of total chemical synthesis (fluvastatin, atorvastatin and cerivastatin).

Processes for the preparation of the sodium salt of pravastatin in a solid form known from the prior art comprise, for example, the step of lyophilization. After lyophilization only the solvent is removed but impurities remain together with the sodium salt of pravastatin. Apart from the aforementioned, lyophilization is not very economical in large-scale production operations. During precipitation due to nonselectivity of the process, impurities precipitate together with the desired substance. Compared to both aforementioned processes for the preparation of pharmaceutical substances in the solid form, crystallization is the only selective process wherein the molecules of the desired substance are selectively incorporated into the crystal matrix. The possibility of inclusion of impurities into the crystal is minimal because only small size molecules are able to incorporate into the intermolecular space inside a crystal (related impurities, which are usually within the desired substance size range, may only be incorporated into this space with great difficulty). Incorporation of other molecules into the crystal matrix is not favored thermodynamically.

The advantage of substances in the crystal structures over those in amorphous structures is that their physical as well as chemical parameters are better defined and they are more stable. The latter is of particular importance for the substances which by nature are unstable and sensitive to different ambient influences, such as light, pH, atmosphere and temperature. Pravastatin sodium is particularly sensitive to these negative influences.

It has been known that thus far the sodium salt of pravastatin may only be present in an amorphous form. The

2

Merck Index 1996 describes the sodium salt of pravastatin as an amorphous substance.

Methods for the preparation of the sodium salt of pravastatin described in many patents, for example U.S. Pat. No. 4,537,859, U.S. Pat. No. 4,448,979, U.S. Pat. No. 4,410,629 and U.S. Pat. No. 4,316,227, afford only the preparation of an amorphous form. In the methods disclosed, after separation of the chromatographic columns, the fractions obtained comprising the sodium salt of pravastatin are lyophilized and the sodium salt in a solid amorphous form is obtained.

The WO-A-98/45110 discloses that after the sodium salt of pravastatin is purified using reverse-phase chromatography, alleged crystals may be obtained by precipitation in the ethanol/ethyl acetate mixture; however, the experiments we have carried out suggest that this combination of the solvents affords the preparation of pravastatin in the amorphous form and not in the crystalline form.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide the sodium salt of pravastatin in crystalline form which has improved purity and stability compared to the salts described in the prior art mentioned above.

Further, it is another object of the present invention to provide a process for the preparation of such a sodium salt of pravastatin.

These and further objects are accomplished by the present invention.

In a first aspect, the present invention provides the sodium salt of pravastatin in a crystalline form. Furthermore, the present invention also provides the sodium salt of pravastatin in a specific crystalline form, where in the crystals in an X-ray diffraction measurement produce a signal sufficiently comparable to that illustrated in the diffractogram shown in FIG. 2.

In a second aspect, the present invention provides a process for the preparation of the sodium salt of pravastatin in a crystalline form comprising the steps of: (a) dissolving the sodium salt of pravastatin in a lower aliphatic alcohol; (b) adding ethyl acetate to the alcoholic solution of the sodium salt of pravastatin; (c) cooling of said alcohol/ethyl acetate mixture; and (d) crystallizing the sodium salt of pravastatin.

According to a third aspect of the present invention, there is further provided a pharmaceutical formulation containing the sodium salt of pravastatin in the aforementioned crystalline forms.

The crystalline sodium salt of pravastatin according to the present invention is particularly suitable for the preparation of pharmaceutical products for the treatment of hypercholesterolemia and hyperlipidemia.

The various features of novelty which characterize the invention are pointed out with particularity in the claims annexed to and forming a part of the disclosure. For a better understanding of the invention, its operating advantages, and specific objects attained by its use, reference should be had to the drawing and descriptive matter in which there are illustrated and described preferred embodiments of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawings:

FIG. 1 is a diffractogram of a conventional amorphous sodium salt of pravastatin which is commercially available.

US 6,740,775 B1

3

scanned on the X-ray powder diffractometer within 2 to 42° 2 θ range with a 0.025° 2 θ step and an integration time of 1 second step

FIG 2 is a diffractogram of crystals of the sodium salt of pravastatin prepared according to Example 2 of the present invention, which are scanned on the X-ray powder diffractometer within 2 to 48° 2 θ range with a 0.035° 2 θ step and an integration time of 1 second step

FIG 3 is an image of the amorphous sodium salt of pravastatin used for the X-ray diffraction measurement shown in FIG. 1 which is obtained under the microscope under 400-fold magnification

FIG 4 is an image of crystals of the sodium salt of pravastatin prepared according to Example 2 of the present invention obtained under the microscope under 400-fold magnification

DETAILED DESCRIPTION OF THE PRESENTLY PREFERRED EMBODIMENTS

X-ray diffraction measurements were carried out with a X-ray powder diffractometer (Phillips PW 1710) using a Cu—K α (20 mA 40 kV, λ =1.5406 Å) light source. For microscopic observations, an OLYMPUS BX 50F microscope with a C/D Sony DXC-950-P camera was used with 400-fold magnification

In the following, the present invention will be illustrated in more detail by the description of preferred embodiments.

In our research work we have surprisingly found that by suitable selection of the solvents and adequate order of their use the sodium salt of pravastatin in a form having an improved crystallinity relative to the conventional solid form can be prepared. Thus, in contrast to the white appearance of the pravastatin sodium solid described in the WO-A-98/45410, it is possible according to the present invention to achieve crystals exhibiting a colorless or pale yellow appearance which clearly indicates the improved crystallinity and thus the clearly crystalline form of the sodium salt of pravastatin provided by the present invention.

Other physical properties of the crystals of the pravastatin sodium of the present invention further indicate the improved crystallinity obtained. Firstly, the crystals according to the present invention can be preferably obtained in the form of needles, sometimes in the form of radiating clusters. Such crystal shape can be readily observed under the microscope, for example when the observation is carried out under 400-fold magnification (see FIG. 4). By contrast, conventionally available amorphous pravastatin sodium appears in the shape of granular particles (see FIG. 3).

Secondly, the melting point of the pravastatin sodium crystals according to the present invention is preferably between 170 and 174° C., more preferably between 172 and 174° C. This melting point range achieved in the present invention is very small for such a complicated chemical structure and confirms the high crystallinity of the pravastatin sodium crystals obtained.

Thirdly, a further characteristic feature of the crystalline pravastatin sodium according to the present invention is that the signals obtained in an X-ray diffraction measurement (Cu—K α , 2 θ) have sharp and distinct peaks. In particular, the shape of the X-ray diffraction peaks of pravastatin sodium according to the present invention are defined by a small half-value width, which confirms a high degree of crystallinity. The term "half-value width" means the value of the 2 θ -range of one peak at the half height or magnitude of the respective peak. Accordingly, the signals obtained by

4

these measurements comprise distinct peaks (2 θ) having a half-value width preferably below 2°, more preferably below 1°, and most preferably below 0.5°.

Exemplary crystals of pravastatin sodium prepared according to the present invention produce a diffractogram in an X-ray diffraction measurement that is shown in FIG. 2. Due to its particularly improved crystallinity and, thus, purity and stability, such pravastatin sodium crystals which, in an X-ray diffraction measurement (Cu—K α) produce a signal sufficiently comparable to that, preferably essentially as that illustrated in the diffractogram shown in FIG. 2, constitute preferred embodiments of the present invention. Unit cells of this crystal could not be determined because of its size and high background at the angles >20° 2 θ . Comparison of the recorded diffractogram with the reference from the PDF and CSD databases (PDF—Powder Diffraction File issued by International Center for Diffraction Data, 12 Campus Boulevard, Newtown Square, Pa. 19073-3273 USA; CSD—Cambridge Structural Database System issued by Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, the United Kingdom) has shown that the crystals of the sodium salt of pravastatin according to the present invention are a novel and thus only known crystalline form of the sodium salt of pravastatin. For comparison, a diffractogram of amorphous pravastatin sodium which is commercially available is shown in FIG. 1.

The process for the preparation of crystals according to the present invention as described above comprises the following steps:

- (a) Providing a solution containing pravastatin and sodium cations in a lower aliphatic alcohol. This is suitably carried out by dissolution of an solid and/or amorphous sodium salt of pravastatin in a lower aliphatic alcohol having preferably 1 to 4 carbon atoms. More preferably, the alcohol used for the dissolution of pravastatin sodium is ethanol or methanol. The best crystallization results have been achieved when preparing a solution of pravastatin sodium in methanol.
- (b) Adding ethyl acetate into the alcoholic solution, preferably while the alcoholic solution obtained in step (a) is stirred continually. The addition of ethyl acetate into the alcoholic solution of pravastatin sodium is preferably carried out slowly, while the addition may be continuously or stepwise.
- (c) Cooling the resulting alcohol-ethyl acetate mixture; and
- (d) Crystallizing the sodium salt of pravastatin.

In step (d) from the cooled mixture crystals of the sodium salt of pravastatin which preferably have a colorless or pale yellow appearance and are in the form of needles or radiating clusters are formed.

Additionally, the crystals obtained by this process may preferably be filtered, ethyl acetate washed and dried.

The crystallization is carried out advantageously if the initial concentration of the sodium salt of pravastatin in the aliphatic alcohol used for the dissolution is preferably between 0.03 and 0.3 g/ml, more preferably between 0.05 and 0.2 g/ml, particularly about 0.1 g/ml, and if the volume of added ethyl acetate in step (b) does preferably not exceed the 15-fold volume, more preferably the 10-fold volume of the starting solution of the sodium salt of pravastatin in the aliphatic alcohol.

Furthermore, to achieve a higher crystallization rate, the preferred temperature of crystallization is below 15° C., more preferably below 10° C., particularly about 8° C.

For enforcing further crystallization, it is preferred to carry out the process according to the invention with additional steps of:

US 6,740,775 B1

5

(c) Further adding ethyl acetate to the mixture of step (d). This is done after an appropriate period of a first crystallization stage where crystallization occurs.

(f) then, crystallization of pravastatin sodium is continued while cooling.

With such an additional crystallization stage the yield of crystalline pravastatin sodium can be increased normally by 5 to 10%.

The volume of ethyl acetate additionally added to the cooled mixture in step (c) is preferably in the range of from 25 to 75% by volume, more preferably from 40 to 60% by volume based on the volume of ethyl acetate added in step (b).

Furthermore, the crystals are preferably formed within a total crystallization time of 3 to 20 hours. More preferably, the total crystallization time is between 4 and 12 hours, particularly about 4 hours.

The present invention also relates to pharmaceutical formulations containing the sodium salt of pravastatin in the form of crystals. The pharmaceutical formulation is present in the form which is suitable for oral and parenteral administration, respectively, and is useful for the treatment of hypercholesterolemia and hyperlipidemia. The pharmaceutical formulation of the present invention is available in the form of tablets, capsules, granules and suppositories as well as in the form of suspensions.

The pharmaceutical formulation of this invention may comprise, in addition to the sodium salt of pravastatin, one or more fillers, such as microcrystalline cellulose, lactose, sugars, starches, modified starch, mannitol, sorbitol and other polyols, dextrin, dextran and maltodextrin, calcium carbonate, calcium phosphate and/or hydrogen phosphate, sulphate, one or more binders, such as lactose, starches, modified starch, dextrin, dextran and maltodextrin, microcrystalline cellulose, sugars, polyethylene glycols, hydroxypropyl cellulose, hydroxypropyl methylcellulose, ethylcellulose, hydroxyethyl cellulose, methylcellulose, carboxymethyl cellulose, gelatin, acacia gum, tragacanth, polyvinylpyrrolidone, magnesium aluminium silicate, one or more disintegrating agents such as croscarmellose sodium, cross-linked polyvinylpyrrolidone, cross-linked carboxymethyl starch, starches and microcrystalline cellulose, magnesium aluminium silicate, polyacrylin potassium, one or more different glidants such as magnesium stearate, calcium stearate, zinc stearate, calcium behenate, sodium stearyl fumarate, talc, magnesium trisilicate, stearic acid, palmitic acid, carnauba wax, silicon dioxide, one or more buffering agents such as sodium or potassium citrate, sodium phosphate, dibasic sodium phosphate, calcium carbonate, hydrogen phosphate, phosphate sulphate, sodium or magnesium carbonate, sodium ascorbate, benzoate, sodium or potassium hydrogen carbonate, lauryl sulphate, or mixtures of such buffering agents.

If required, any the formulation may also comprise surfactants and other conventional components for solid, pharmaceutical formulations such as coloring agents, lakes, aromas and adsorbents. As surfactants the following may be used: ionic surfactants, such as sodium lauryl sulphate or non-ionic surfactants such as different poloxamers (polyoxyethylene and polyoxypropylene copolymers), natural or synthesized lecithins, esters of sorbitan and fatty acids (such as Span® manufactured by Atlas Chemie), esters of polyoxyethylenesorbitan and fatty acids (such as Tween® manufactured by Atlas Chemie), polyoxyethylated hydrogenated castor oil (such as Cremophor® manufactured by BASF), polyoxyethylene stearates (such as Brij® manufac-

6

tured by Atlas Chemie), dimethylpolysiloxane or any combination of the above mentioned surfactants.

If the solid pharmaceutical formulation is in the form of coated tablets, the coating may be prepared from at least one film-former such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, at least from one plasticizer such as polyethylene glycols, dibutyl sebacate, triethyl citrate, and other pharmaceutical auxiliary substances conventional for film coatings, such as pigments, fillers and others.

The pharmaceutical formulation can be prepared by conventional formulation methods known to those skilled in the art.

The present invention is illustrated but by no means limited by the following examples.

EXAMPLE 1

The sodium salt of pravastatin (1 g) was dissolved in methanol (10 ml) and while stirring ethyl acetate was added. The resulting clear yellow solution was cooled to 8° C and allowed to stand overnight. Formed radiating clusters of thin, long needle-like crystals were filtered, washed with ethyl acetate (20 ml) and dried. Yield: 0.87 g of pale yellow crystals, melting point 172–174° C.

EXAMPLE 2

The sodium salt of pravastatin (2 g) was dissolved in methanol (20 ml) and while stirring ethyl acetate (80 ml) was added. The clear, slightly yellow solution was cooled to 8° C and allowed to stand for 4 hours. Formed radiating clusters of thin, long needle-like crystals were filtered, washed with ethyl acetate (20 ml) and dried. Yield: 1.53 g of colorless crystals, melting point 172–174° C.

EXAMPLE 3

The sodium salt of pravastatin (2 g) was dissolved in methanol (20 ml) and while stirring ethyl acetate (150 ml) was added. The resulting clear, slightly yellow solution was cooled to 8° C and allowed to stand for 4 hours. Formed radiating clusters of thin, long needle-like crystals were filtered, washed with ethyl acetate (20 ml) and dried. Yield: 1.66 g of colorless crystals, melting point 172–174° C.

EXAMPLE 4

The sodium salt of pravastatin (2 g) was dissolved in methanol (20 ml) and while stirring ethyl acetate (170 ml) was added. The resulting clear, slightly yellow solution was cooled to 8° C and allowed to stand for 4 hours. Formed radiating clusters of thin, long needle-like crystals were filtered, washed with ethyl acetate (20 ml) and dried. Yield: 1.75 g of colorless crystals, melting point 172–174° C.

EXAMPLE 5

The sodium salt of pravastatin (2 g) was dissolved in methanol (12 ml) and while stirring ethyl acetate (100 ml) was added. The resulting clear, slightly yellow solution was cooled to 8° C and allowed to stand for 1 hour. After that further ethyl acetate (60 ml) was added, so that the pravastatin still dissolved in the solution was forced to crystallize. After 2 hours at 8° C the formed radiating clusters of thin, long needle-like crystals were filtered, washed with ethyl acetate (20 ml) and dried. Yield: 1.85 of colorless crystals, melting point 172–174° C.

The invention is not limited by the embodiments described above which are presented as examples only but can be modified in various ways within the scope of protection defined by the appended patent claims.

US 6,740,775 B1

7

1 claim:

1 A crystalline sodium salt of pravastatin having an X-ray diffraction pattern substantially in accordance with that shown in FIG. 2

2 The sodium salt of pravastatin according to claim 1, wherein the crystals exhibit a colorless or pale yellow appearance

3 The sodium salt of pravastatin according to claim 1, wherein the crystals clearly appear in the form of needles or radiating clusters

4 The sodium salt of pravastatin according to claim 1, having a melting point in the range of from 170° C. to 174° C.

5 The sodium salt of pravastatin according to claim 1, wherein the crystals in an X-ray diffraction measurement produce distinct peaks (2 θ) having a half-value width below 2°

6 A process for the preparation of the sodium salt of pravastatin in a crystalline form, comprising the steps of:

(a) providing a solution containing pravastatin and sodium cations in a lower aliphatic alcohol;

(b) adding ethyl acetate to said alcoholic solution;

(c) cooling said alcohol-ethyl acetate mixture; and

(d) crystallizing said sodium salt of pravastatin

7 The process according to claim 6 additionally comprising, after a first crystallization stage, the steps of:

(e) adding further ethyl acetate to the alcohol-ethyl acetate mixture; and

(f) further crystallizing the sodium salt of pravastatin

8 The process according to claim 6, wherein the lower aliphatic alcohol is ethanol or methanol

9 The process according to claim 6, wherein the lower aliphatic alcohol is methanol

10 The process according to claim 6, wherein the addition of ethyl acetate is performed while the alcoholic solution of the sodium salt of pravastatin is stirred continually

8

11 The process according to claim 6, wherein the concentration of the sodium salt of pravastatin in the alcoholic solution of step (a) is between 0.03 and 0.3 g/ml

12 The process according to claim 6, wherein the volume of added ethyl acetate in step (b) does not exceed the 15-fold volume of the initial alcoholic solution of the sodium salt of pravastatin

13 The process according to claim 7, wherein the volume of further added ethyl acetate in step (e) is in the range of from 25 to 75% by volume based on the volume of ethyl acetate added in step (b).

14 The process according to claim 7, wherein the alcohol-ethyl acetate mixture is cooled to a temperature below 15° C.

15 The process according to claim 6, wherein the total crystallization time is between 3 and 20 hours

16 the process according to claim 6, wherein the formed crystals are filtered, ethyl acetate washed and dried

17 A pharmaceutical formulation containing the sodium salt of pravastatin in a crystalline form

18 The pharmaceutical formulation according to claim 17, comprising the sodium salt of pravastatin in a crystalline form; the crystals being in the form of needles or radiating clusters having a melting point of from 170° C. to 174° C. and an X-ray diffraction pattern substantially in accordance with that shown in FIG. 2

19 A pharmaceutical formulation of the sodium salt of pravastatin in a crystalline form, wherein the crystals in an X-ray diffraction measurement produce a signal sufficiently comparable to that illustrated in the diffractogram shown in FIG. 2.

20 A method of treating hypercholesterolemia and hyperlipidemia comprising administering to a person in need of such treatment, a hypercholesterolemia and hyperlipidemia treating effective amount of a crystalline sodium salt of pravastatin

* * * * *



(12) **United States Patent**
Pflaum

(10) **Patent No.:** US 7,078,558 B1
(45) **Date of Patent:** *Jul. 18, 2006

(54) **CRYSTALS OF THE SODIUM SALT OF PRAVASTATIN**

FOREIGN PATENT DOCUMENTS

(75) **Inventor:** Zlatko Pflaum, Domzale (SI)

WO WO 98 45 410 * 10 1998
WO WO 00 17 150 3 2000

(73) **Assignee:** Lek Pharmaceutical and Chemical Company D.D., Ljubjana (SI)

OTHER PUBLICATIONS

Arai et al (1988) Annu Rep Sankyo, 40 pp 1-38 *

(*) **Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer

(Continued)

Primary Examiner: Cecilia J. Isang
Assistant Examiner: Taylor Victor Oh
(74) *Attorney Agent or Firm:* Cohen Pontani Lieberman & Pavane

(21) **Appl No.:** 10/049,093

(57) **ABSTRACT**

(22) **PCT Filed:** Aug 4, 2000

(86) **PCT No.:** PC/IB00/01103

§ 371 (c)(1)
(2) (4) **Date:** Apr. 22, 2002

(87) **PCT Pub No.:** WO01/10813

PCT Pub Date: Feb. 15, 2001

(30) **Foreign Application Priority Data**

Aug 6 1999 (SI) 9900191

(51) **Int. Cl.**

C07C 67/02 (2006 01)
C07C 69/74 (2006 01)

(52) **U.S. Cl.** 560/119; 560 256

(58) **Field of Classification Search** 560.256,
560/187, 188, 124, 123, 122, 119; 514, 460
See application file for complete search history

(56) **References Cited**

U.S. PATENT DOCUMENTS

6,740,775 B1 * 5 2004 Pflaum 560 256
2002 0081675 A1 * 6 2002 Jekkel et al 435 135

Lovastatin, pravastatin, simvastatin, mevastatin, atorvastatin, fluvastatin and cervastatin and derivatives and analogs thereof are known as HMG-Co A reductase inhibitors and are used as antihypercholesterolemic agents. The majority of them are produced by fermentation using microorganisms of different species identified as species belonging to an *Aspergillus*, *Monascus*, *Nocardia*, *Amiclatopsis*, *Mucor*, or *Trichoderma* genus; some are obtained by treating the fermentation products using the methods of chemical synthesis (simvastatin) or they are the products of total chemical synthesis (fluvastatin, atorvastatin and cervastatin). The present invention relates to a crystalline form of the sodium salt of pravastatin, which is known by the chemical name 1-naphthaleneheptanoic acid, 1,2,6,7,8,8a-hexahydro- β , δ ,6-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)-, mono sodium salt, which is useful as a pharmaceutical substance. The present invention further relates to the method for its preparation and isolation, to a pharmaceutical formulation containing the sodium salt of pravastatin in the crystalline form and a pharmaceutically acceptable carrier and to a pharmaceutical method of treatment. The novel crystalline form of the sodium salt of pravastatin is useful in the treatment of hypercholesterolemia and hyperlipidemia.

23 Claims, 4 Drawing Sheets

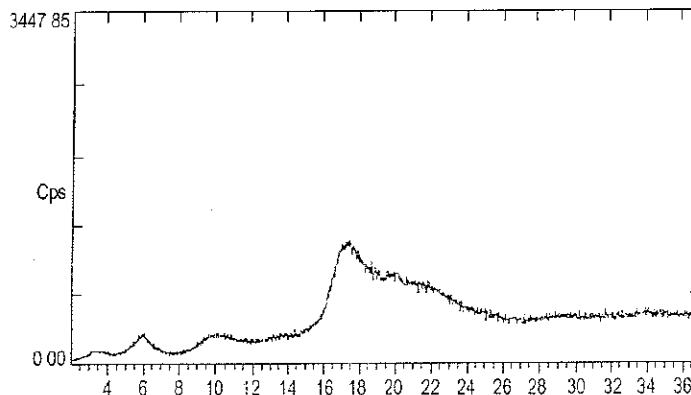


EXHIBIT 2

US 7,078,558 B1

Page 2

OTHER PUBLICATIONS

Harry G. Brittain, Polymorphism in Pharmaceutical Solids, Marcel Dekker, Inc. 1999, p. 236, lines 17-22.*
Sato et al. The Jnl of Antibiotics vol. XLI, No. pp. 1265-67 (1988)

Arai et al. Pravastatin Sodium(CS 5145): A Novel Cholesterol Lowering Agent Which Inhibits HMG-CoA Reductase (1988)

* cited by examiner

U.S. Patent

Jul. 18, 2006

Sheet 1 of 4

US 7,078,558 B1

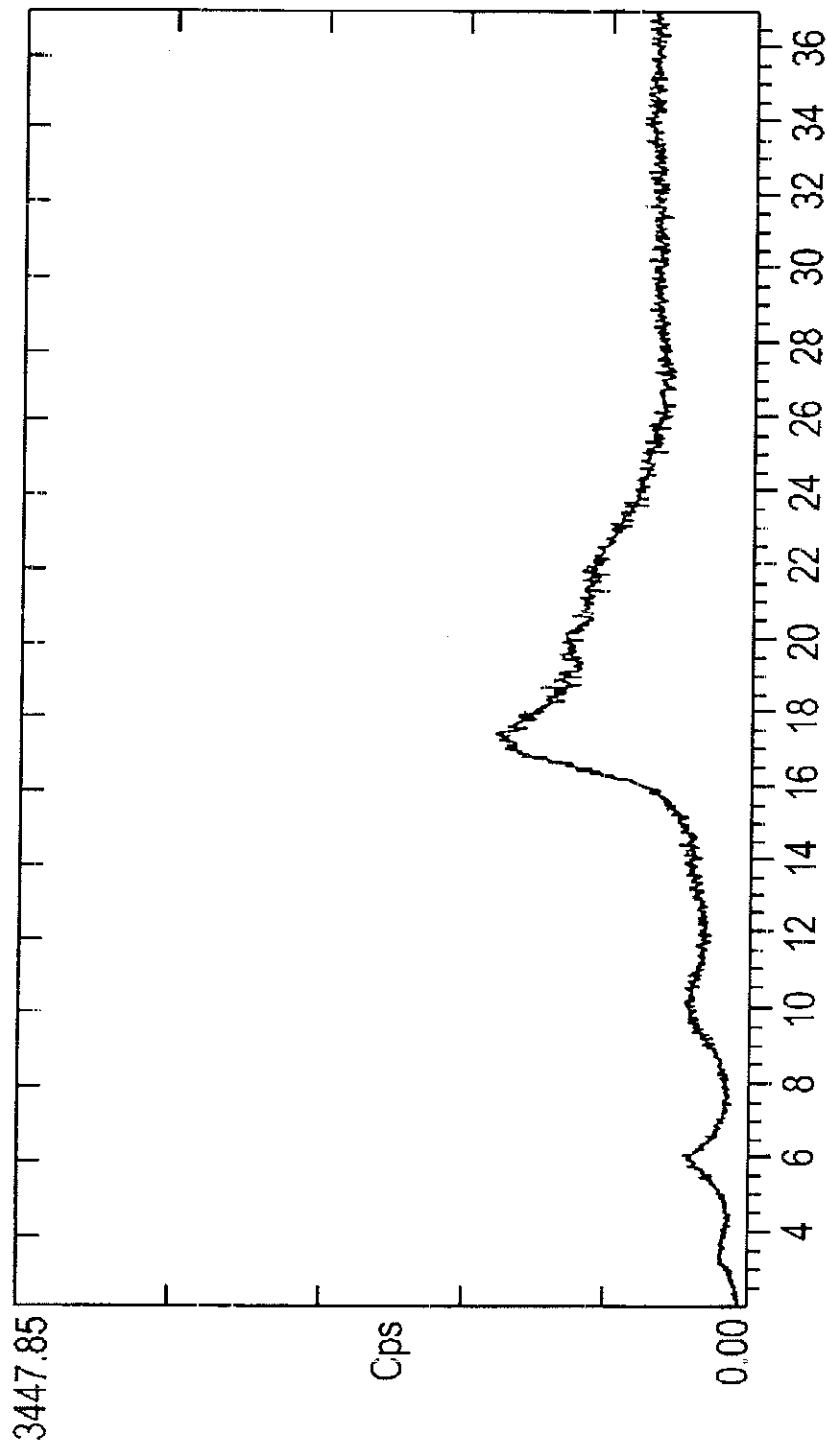


FIG. 1

U.S. Patent

Jul. 18, 2006

Sheet 2 of 4

US 7,078,558 B1

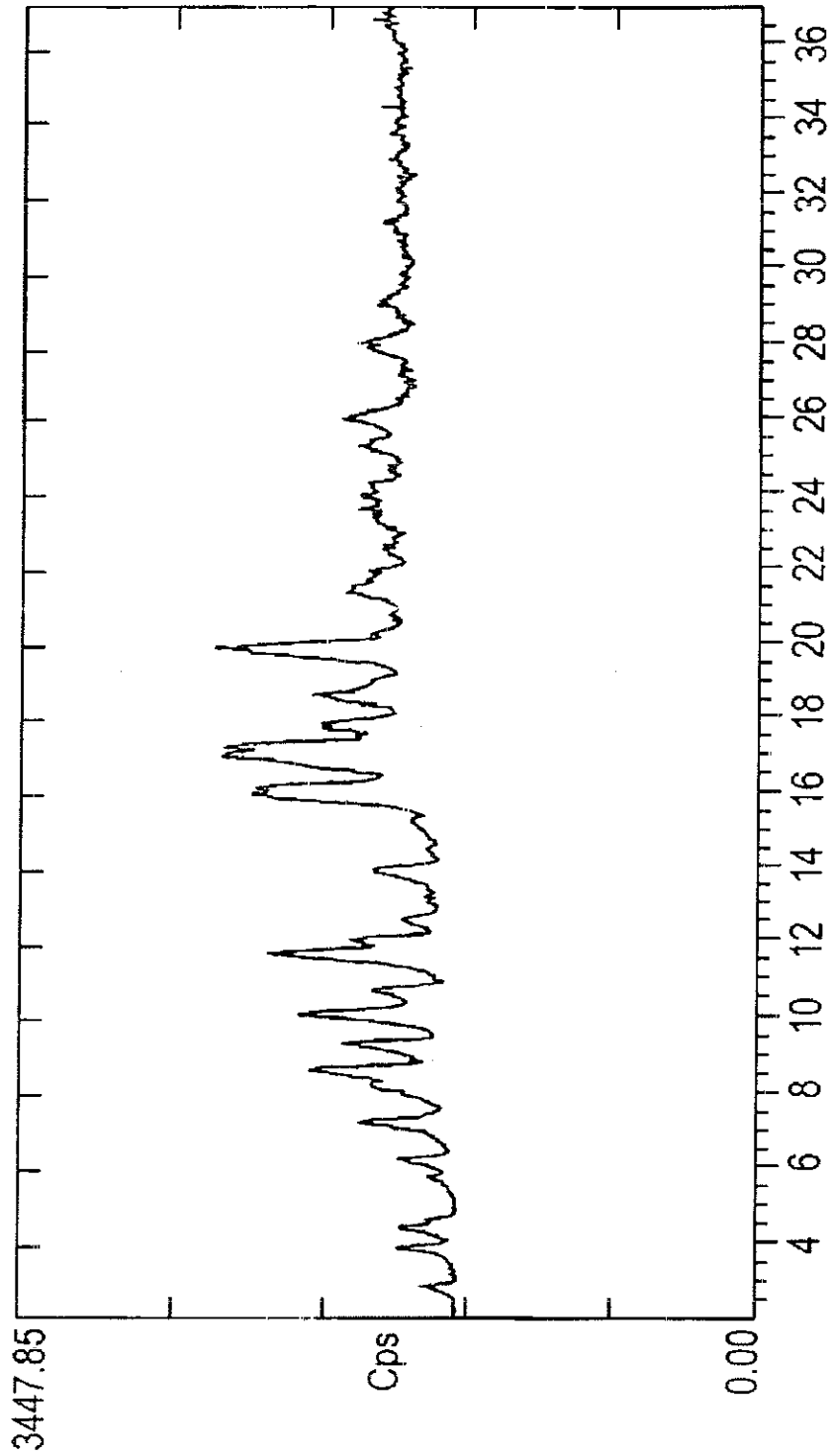


FIG. 2

U.S. Patent

Jul. 18, 2006

Sheet 3 of 4

US 7,078,558 B1

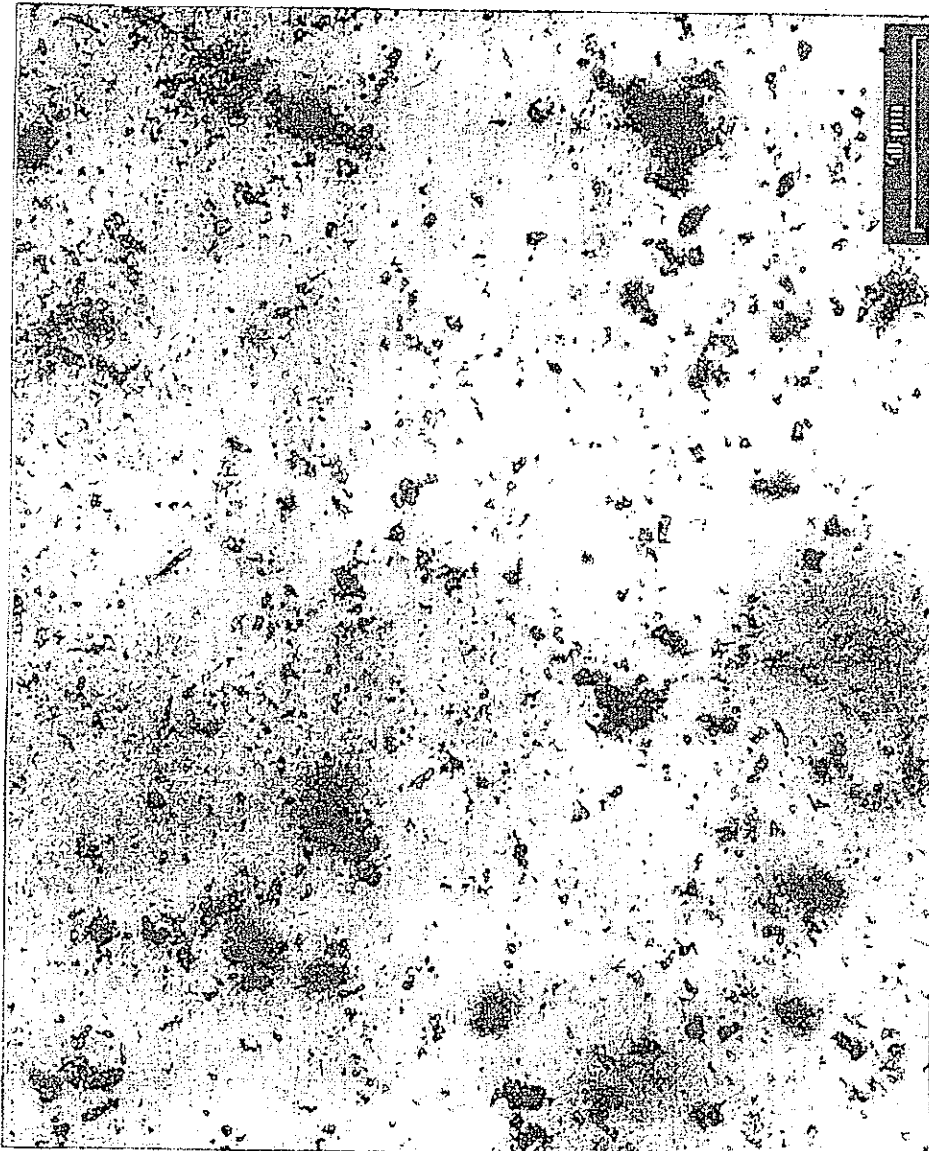


FIG. 3

U.S. Patent

Jul. 18, 2006

Sheet 4 of 4

US 7,078,558 B1

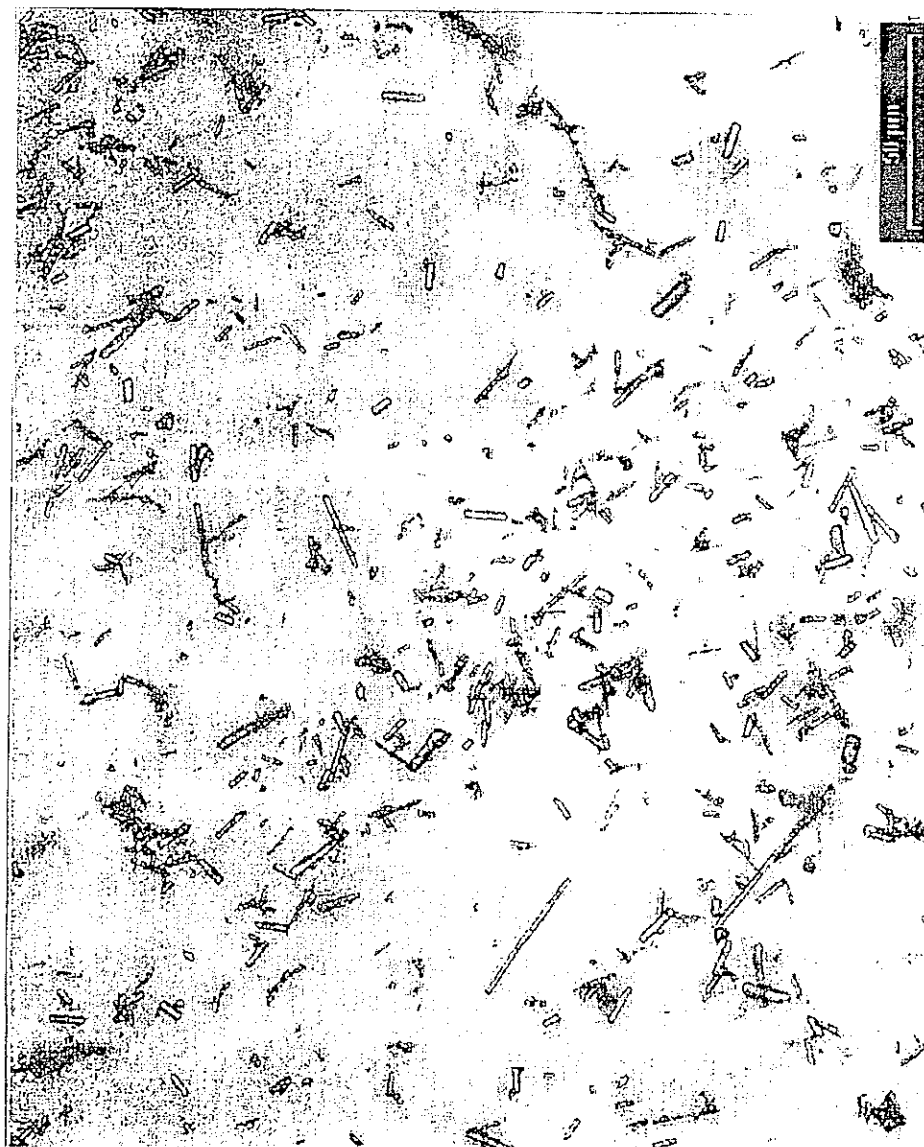


FIG. 4

US 7,078,558 B1

1

CRYSTALS OF THE SODIUM SALT OF
PRAVASTATIN

The present invention relates to a crystalline form of the sodium salt of pravastatin which is known by the chemical name 1-naphthaleneheptanoic acid 1,2,6,7,8,8a-hexahydro- β , δ -6-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)-mono sodium salt, which is useful as a pharmaceutical substance. The present invention further relates to the method for its preparation and isolation, to a pharmaceutical formulation containing the sodium salt of pravastatin in the crystalline form and a pharmaceutically acceptable carrier, and to a pharmaceutical method of treatment.

The present invention relates to a crystalline form of the sodium salt of pravastatin which is known by the chemical name 1-naphthaleneheptanoic acid 1,2,6,7,8,8a-hexahydro- β , δ -6-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)-mono sodium salt, which is useful as a pharmaceutical substance. The present invention further relates to the method for its preparation and isolation, to a pharmaceutical formulation containing the sodium salt of pravastatin in the crystalline form and a pharmaceutically acceptable carrier and to the pharmaceutical method of treatment.

Lovastatin, pravastatin, simvastatin, mevastatin, atorvastatin, fluvastatin and cerivastatin and derivatives and analogs thereof are known as HMG-CoA reductase inhibitors and are used as antihypercholesterolemic agents. The majority of them are produced by fermentation using microorganisms of different species identified as species belonging to *Aspergillus*, *Monascus*, *Noceoidia*, *Amycolatopsis*, *Mucor* or *Penicillium* genus; some are obtained by treating the fermentation products using the methods of chemical synthesis (simvastatin) or they are the products of total chemical synthesis (fluvastatin, atorvastatin and cerivastatin).

Processes for the preparation of the sodium salt of pravastatin in a solid form known from the prior art comprise, for example, the step of lyophilisation. After lyophilisation only the solvent is removed but impurities remain together with the sodium salt of pravastatin. Apart from the aforementioned, lyophilisation is not very economical in large-scale production operations. During precipitation due to nonselectivity of the process, impurities precipitate together with the desired substance. Compared to the both aforementioned processes for the preparation of pharmaceutical substances in the solid form, crystallization is the only selective process wherein the molecules of the desired substance are selectively incorporated into the crystal matrix. Possibility of inclusion of impurities into the crystal is minimal because only small size molecules are able to incorporate into intermolecular space inside a crystal (related impurities, which are usually within the desired substance size range may only be incorporated into this space with great difficulty) incorporation of other molecules into the crystal matrix is not favoured thermodynamically.

The advantage of substances in the crystal structures over those in amorphous structures is that their physical as well as chemical parameters are better defined and they are more stable. The latter is of particular importance for the substances which in their nature are unstable and sensitive to different ambient influences such as light, pH, atmosphere and temperature. Pravastatin sodium is particularly sensitive to these negative influences.

It has been known that thus far the sodium salt of pravastatin may only be present in an amorphous form. The Merck Index 1996 describes the sodium salt of pravastatin as an amorphous substance.

2

Methods for the preparation of the sodium salt of pravastatin described in many patents, for example U.S. Pat. No. 4,537,859, U.S. Pat. No. 4,448,979, U.S. Pat. No. 4,410,629 and U.S. Pat. No. 4,346,227, afford only the preparation of an amorphous form. In the methods disclosed, after separation on the chromatographic columns, the fractions obtained comprising the sodium salt of pravastatin are lyophilized and the sodium salt in a solid-amorphous form is obtained.

The WO-A-98/45410 discloses that after the sodium salt of pravastatin is purified using reverse-phase chromatography, alleged crystals may be obtained by precipitation in the ethanol/ethyl acetate mixture; however, the experiments we have carried out suggest that this combination of the solvents affords the preparation of pravastatin in the amorphous form and not in the crystalline form.

It is an object of the present invention to provide the sodium salt of pravastatin which is improved in purity and stability compared to the salts described in the prior art mentioned above.

Further, it is another object of the present invention to provide a process for the preparation of such a sodium salt of pravastatin.

These and further objects are accomplished by the present invention.

In a first aspect, the present invention provides the sodium salt of pravastatin in a crystalline form. Furthermore, the present invention also provides the sodium salt of pravastatin in a specific crystalline form, wherein the crystals in an X-ray diffraction measurement produce a signal sufficiently comparable to that illustrated in the diffractogram shown in FIG. 2.

In a second aspect, the present invention provides a process for the preparation of the sodium salt of pravastatin in a crystalline form comprising the steps of: (a) dissolution of the sodium salt of pravastatin in a lower aliphatic alcohol; (b) addition of ethyl acetate to the alcoholic solution of the sodium salt of pravastatin; (c) cooling of said alcohol/ethyl acetate mixture; and (d) crystallization.

According to a third aspect of the present invention, there is further provided a pharmaceutical formulation containing the sodium salt of pravastatin in the aforementioned crystalline forms.

The crystalline sodium salt of pravastatin according to the present invention is particularly suitable for the preparation of pharmaceutical products for the treatment of hypercholesterolemia and hyperlipidemia.

In the following, drawings will be briefly described.

FIG. 1: Diffractogram of a conventional amorphous sodium salt of pravastatin which is commercially available, scanned on the X-ray powder diffractometer within 2 to 42° 2 θ range with a 0.025° 2 θ step and an integration time of 1 second/step.

FIG. 2: Diffractogram of crystals of the sodium salt of pravastatin prepared according to Example 2 of the present invention, which are scanned on the X-ray powder diffractometer within 2 to 48° 2 θ range with a 0.035° 2 θ step and an integration time of 1 second/step.

FIG. 3: Image of the amorphous sodium salt of pravastatin used for the X-ray diffraction measurement shown in FIG. 1, which is obtained under the microscope under 400-fold magnification.

FIG. 4: Image of crystals of the sodium salt of pravastatin prepared according to Example 2 of the present invention, obtained under the microscope under 400-fold magnification.

US 7,078,558 B1

3

X-ray diffraction measurements were carried out with a X-ray powder diffractometer (Phillips PW 1710) using a $\text{Cu-K}\alpha$ (20 mA 40 kV, $\lambda=1.5406 \text{ \AA}$) light source. For microscopic observations an OLYMPUS BX 50F microscope with a CCD Sony DXC-950-P camera was used with 400-fold magnification.

In the following, the present invention will be illustrated in more detail by the description of preferred embodiments.

In our research work we have surprisingly found that by suitable selection of the solvents and adequate order of their use the sodium salt of pravastatin in a form having an improved crystallinity, relative to the conventional solid form, can be prepared. Thus, in contrast to the white appearance of the pravastatin sodium solid described in the WO-A-98/45410, it is possible according to the present invention to achieve crystals exhibiting a colorless or pale yellow appearance, which clearly indicates the improved crystallinity and, thus, the clearly crystalline form of the sodium salt of pravastatin provided by the present invention.

Other physical properties of the crystals of the pravastatin sodium of the present invention further indicate the improved crystallinity obtained. Firstly, the crystals according to the present invention can be preferably obtained in the form of needles, sometimes in the form of radiating clusters. Such crystal shape can be readily observed under the microscope, for example when the observation is carried out under 400-fold magnification (see FIG. 4). By contrast, conventionally available amorphous pravastatin sodium appear in the shape of granular particles (see FIG. 3).

Secondly, the melting point of the pravastatin sodium crystals according to the present invention is preferably between 170 and 174° C, more preferably between 172 and 174° C. This melting point range achieved in the present invention is very small for such a complicated chemical structure and confirms the high crystallinity of the pravastatin sodium crystals obtained.

Thirdly, a further characteristic feature of the crystalline pravastatin sodium according to the present invention is that the signal obtained in an X-ray diffraction measurement ($\text{Cu-K}\alpha$, 2 θ) have sharp and distinct peaks. In particular, the shape of the X-ray diffraction peaks of pravastatin sodium according to the present invention are defined by a small half-value width, which confirms a high degree of crystallinity. The term "half-value width" means the value of the 2 θ -range of one peak at the half height or magnitude of the respective peak. Accordingly, the signals obtained by these measurements comprise distinct peaks (2 θ) having a half-value width preferably below 2°, more preferably below 1°, and most preferably below 0.5°.

Exemplary crystals of pravastatin sodium prepared according to the present invention produce a diffractogram in an X-ray diffraction measurement that is shown in FIG. 2. Due to its particularly improved crystallinity and, thus, purity and stability, such pravastatin sodium crystals which, in an X-ray diffraction measurement ($\text{Cu-K}\alpha$), produce a signal sufficiently comparable to that, preferably essentially as that illustrated in the diffractogram shown in FIG. 2, constitute preferred embodiments of the present invention. Unit cells of this crystal could not be determined because of its size and high background at the angles $>20^\circ$ 2 θ . Comparison of the recorded diffractogram with the reference from the PDF and CSD databases (PDF—Powder Diffraction File issued by "International Center for Diffraction Data", 12 Campus Boulevard, Newtown Square, PA 19073-3273 USA; CSD—"Cambridge Structural Database System" issued by "Cambridge Crystallographic Data Centre", 12 Union Road, Cambridge CB2 1EZ, the United Kingdom)

4

has shown that the crystals of the sodium salt of pravastatin according to the present invention are really a novel and thus only known crystalline form of the sodium salt of pravastatin. For comparison, a diffractogram of amorphous pravastatin sodium which is commercially available is shown in FIG. 1.

The process for the preparation of crystals according to the present invention as described above comprises the following steps:

(a) Providing a solution containing pravastatin and sodium cations in a lower aliphatic alcohol. This is suitably carried out by dissolution of an solid and/or amorphous sodium salt of pravastatin in a lower aliphatic alcohol having preferably 1 to 4 carbon atoms. More preferably the alcohol used for the dissolution of pravastatin sodium is ethanol or methanol. The best crystallization results have been achieved when preparing a solution of pravastatin sodium in methanol.

(b) Addition of ethyl acetate into the alcoholic solution, preferably while the alcoholic solution obtained in step (a) is stirred continually. The addition of ethyl acetate into the alcoholic solution of pravastatin sodium is preferably carried out slowly, while the addition may be continuously or stepwise.

(c) Cooling of the resulting alcohol/ethyl acetate mixture.
(d) Crystallization.

In step (d), from the cooled mixture crystals of the sodium salt of pravastatin, which preferably have a colorless or pale yellow appearance and are in the form of needles or radiating clusters, are formed.

Additionally, the crystals obtained by this process may preferably be filtered, ethyl acetate washed and dried.

The crystallization is carried out advantageously if the initial concentration of the sodium salt of pravastatin in the aliphatic alcohol used for the dissolution is preferably between 0.03 and 0.3 g/ml, more preferably between 0.05 and 0.2 g/ml, particularly about 0.1 g/ml, and if the volume of added ethyl acetate in step (b) does preferably not exceed the 15-fold volume, more preferably the 10-fold volume of the starting solution of the sodium salt of pravastatin in the aliphatic alcohol.

Furthermore, to achieve a higher crystallization rate the preferred temperature of crystallization is below 15° C, more preferably below 10° C, particularly about 8° C, or enforcing further crystallization, it is preferred to carry out the process according to the invention with additional steps of:

(e) Further adding ethyl acetate to the mixture of step (d). This is done after an appropriate period of a first crystallization stage where crystallization occurs.

(f) then, crystallization of pravastatin sodium is continued while cooling.

With such an additional crystallization stage the yield of crystalline pravastatin sodium can be increased, normally by 5 to 10%.

The volume of ethyl acetate additionally added to the cooled mixture in step (e) is preferably in the range of from 25 to 75% by volume, more preferably from 40 to 60% by volume based on the volume of ethyl acetate added in step (b).

Furthermore, the crystals are preferably formed within a total crystallization time of 3 to 20 hours. More preferably, the total crystallization time is between 4 and 12 hours, particularly about 4 hours.

The present invention also relates to pharmaceutical formulations containing the sodium salt of pravastatin in the form of crystals. The pharmaceutical formulation is present

US 7,078,558 B1

5

in the form which is suitable for oral and parenteral administration, respectively, and is useful for the treatment of hypercholesterolemia and hyperlipidemia. The pharmaceutical formulation of the present invention is available in the form of tablets, capsules, granules and suppositories as well as in the form of suspensions.

The pharmaceutical formulation of this invention may comprise, in addition to the sodium salt of pravastatin, one or more fillers, such as microcrystalline cellulose, lactose, sugars, starches, modified starch, mannitol, sorbitol and other polyols, dextrin, dextran and maltodextrin, calcium carbonate, calcium phosphate and/or hydrogen phosphate, sulphate, one or more binders, such as lactose, starches, modified starch, dextrin, dextran and maltodextrin, microcrystalline cellulose, sugars, polyethylene glycols, hydroxypropyl cellulose, hydroxypropyl methylcellulose, ethylcellulose, hydroxyethyl cellulose, methylcellulose, carboxymethyl cellulose, gelatin, acacia gum, tragacanth, polyvinylpyrrolidone, magnesium aluminium silicate, one or more disintegrating agents such as croscarmellose sodium, cross-linked polyvinylpyrrolidone, cross-linked carboxymethyl starch, starches and microcrystalline cellulose, magnesium aluminium silicate, polyacrylin potassium, one or more diluent glidants such as magnesium stearate, calcium stearate, zinc stearate, calcium behenate, sodium stearyl fumarate, talc, magnesium trisilicate, stearic acid, palmitic acid, carnauba wax, silicon dioxide, one or more buffering agents such as sodium or potassium citrate, sodium phosphate, dibasic sodium phosphate, calcium carbonate, hydrogen phosphate, phosphate, sulphate, sodium or magnesium carbonate, sodium ascorbate, benzoate, sodium or potassium hydrogen carbonate, lauryl sulphate, or mixtures of such buffering agents.

If required, any the formulation may also comprise surfactants and other conventional components for solid pharmaceutical formulations such as coloring agents, lakes, aromas and adsorbents. As surfactants the following may be used: ionic surfactants, such as sodium lauryl sulphate or non-ionic surfactants such as different poloxamers (polyoxyethylene and polyoxypropylene copolymers), natural or synthesized lecithins, esters of sorbitan and fatty acids (such as Span® manufactured by Atlas Chemie), esters of polyoxyethylenesorbitan and fatty acids (such as Tween® manufactured by Atlas Chemie), polyoxyethylated hydrogenated castor oil (such as Cremophor®, manufactured by BASF), polyoxyethylene stearates (such as Brij®, manufactured by Atlas Chemie), dimethylpolysiloxane or any combination of the above mentioned surfactants.

If the solid pharmaceutical formulation is in the form of coated tablets, the coating may be prepared from at least one film-former such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, at least from one plasticizer such as polyethylene glycols, dibutyl sebacate, triethyl citrate, and other pharmaceutical auxiliary substances conventional for film coatings, such as pigments, fillers and others.

The pharmaceutical formulation can be prepared by conventional formulation methods known to those skilled in the art.

The present invention is illustrated but by no means limited by the following examples.

EXAMPLE 1

The sodium salt of pravastatin (1 g) was dissolved in methanol (10 ml) and while stirring ethyl acetate was added. The resulting clear yellow solution was cooked to 8° C. and allowed to stand overnight. Formed radiating clusters of

6

thin, long needle-like crystals were filtered, washed with ethyl acetate (20 ml) and dried. Yield: 0.87 g of pale yellow crystals, melting point 172–174° C.

EXAMPLE 2

The sodium salt of pravastatin (2 g) was dissolved in methanol (20 ml) and while stirring ethyl acetate (80 ml) was added. The clear, slightly yellow solution was cooled to 8° C. and allowed to stand for 4 hours. Formed radiating clusters of thin, long needle-like crystals were filtered, washed with ethyl acetate (20 ml) and dried. Yield: 1.53 g of colorless crystals, melting point 172–174° C.

EXAMPLE 3

The sodium salt of pravastatin (2 g) was dissolved in methanol (20 ml) and while stirring ethyl acetate (150 ml) was added. The resulting clear, slightly yellow solution was cooled to 8° C. and allowed to stand for 4 hours. Formed radiating clusters of thin, long needle-like crystals were filtered, washed with ethyl acetate (20 ml) and dried. Yield: 1.66 g of colorless crystals, melting point 172–174° C.

EXAMPLE 4

The sodium salt of pravastatin (2 g) was dissolved in methanol (20 ml) and while stirring ethyl acetate (170 ml) was added. The resulting clear, slightly yellow solution was cooled to 8° C. and allowed to stand for 4 hours. Formed radiating clusters of thin, long needle-like crystals were filtered, washed with ethyl acetate (20 ml) and dried. Yield: 1.75 g of colorless crystals, melting point 172–174° C.

EXAMPLE 5

The sodium salt of pravastatin (2 g) was dissolved in methanol (12 ml) and while stirring ethyl acetate (100 ml) was added. The resulting clear, slightly yellow solution was cooled to 8° C. and allowed to stand for 1 hour. After that further ethyl acetate (60 ml) was added, so the pravastatin still dissolved in the solution was forced to crystallize. After 2 hours at 8° C. the formed radiating clusters of thin, long needle-like crystals were filtered, washed with ethyl acetate (20 ml) and dried. Yield: 1.85 g of colorless crystals, melting point 172–174° C.

The invention claimed is:

1. The sodium salt of pravastatin in a crystalline form wherein the crystals in the X-ray diffraction measurement produce distinct peaks having a half-value width below 2° measured at the reflection angle 2 θ using CuK α radiation.

2. The sodium salt of pravastatin according to claim 1 wherein the melting point is in the range of from 170° C. to 174° C.

3. A process for preparing pharmaceutical products for the treatment of hypercholesterolemia and hyperlipidemia comprising the step of adding the active agent pravastatin as a crystalline sodium salt together with a pharmaceutically acceptable carrier, wherein the crystals in the X-ray diffraction measurement produce distinct peaks having a half-value width below 2° measured at the reflection angle 2 θ using CuK α radiation.

4. A process for the preparation of the sodium salt of pravastatin in crystalline form comprising the steps of:

(a) first preparing a solution of pravastatin and sodium cations in a lower aliphatic alcohol;

US 7,078,558 B1

7

- (b) thereafter adding ethyl acetate to said alcoholic solution so as to obtain a clear solution of the pravastatin sodium cations, aliphatic alcohol and ethyl acetate;
- (c) thereafter cooling said clear alcohol/ethyl acetate mixture of step (b); and
- (d) obtaining said sodium salt of pravastatin in crystalline form; wherein the crystals in the X-ray diffraction measurement produce distinct peaks having a half-value width below 2° measured at the reflection angle 2θ using $\text{CuK}\alpha$ radiation
5. The process according to claim 4, wherein the lower aliphatic alcohol is ethanol or methanol
6. The process according to claim 4 wherein the ethyl acetate is added while the alcoholic solution of the sodium salt of pravastatin is stirred continually
7. The process according to claim 4, wherein the concentration of the sodium salt of pravastatin in the alcoholic solution of step (a) is between 0.03 and 0.3 g/ml
8. The process according to claim 4, wherein the volume of added ethyl acetate in step (b) does not exceed the 15-fold volume of the initial alcoholic solution of the sodium salt of pravastatin
9. The sodium salt of pravastatin in crystalline form having an X-ray diffraction pattern comprising characteristic peaks at 4.0 ± 0.2 ; 10.2 ± 0.2 ; 16.3 ± 0.2 ; 17.4 ± 0.2 and 20.0 ± 0.2 degrees measured at reflection angle 2θ
10. The sodium salt of pravastatin in a crystalline form having an X-ray diffraction pattern comprising characteristic peaks at 4.0 ± 0.2 ; 6.3 ± 0.2 ; 10.2 ± 0.2 ; 16.3 ± 0.2 ; 17.4 ± 0.2 ; 18.0 ± 0.2 and 20.0 ± 0.2 degrees measured at reflection angle 2θ .
11. The sodium salt of pravastatin in a crystalline form having an X-ray diffraction pattern comprising characteristic peaks at 4.0 ± 0.2 ; 6.3 ± 0.2 ; 10.2 ± 0.2 ; 11.8 ± 0.2 ; 16.3 ± 0.2 ; 17.4 ± 0.2 ; 18.0 ± 0.2 and 20.0 ± 0.2 degrees measured at reflection angle 2θ
12. The crystalline form of the sodium salt of pravastatin having an X-ray diffraction pattern comprising characteristic peaks at 4.0 ± 0.2 ; 10.2 ± 0.2 ; 16.1 ± 0.2 (broad); 17.2 ± 0.2 (broad); and 20.0 ± 0.2

8

13. The crystalline form of the sodium salt of pravastatin of claim 12 wherein the broad peak at 16.1 ± 0.2 comprises a peak at 16.05 and at 16.3 and the broad peak at 17.2 ± 0.2 comprises a peak at 17.0 and 17.3.
14. The process according to claim 4 wherein the concentration of the sodium salt of pravastatin in the alcoholic solution of step (a) is between 0.05 and 0.2 g/ml.
15. The process according to claim 4 wherein the concentration of the sodium salt of pravastatin in the alcoholic solution of step (a) is about 0.1 g/ml.
16. The process according to claim 4 wherein the volume of added ethyl acetate in step (b) does not exceed the 10-fold volume of the initial alcoholic sodium of the sodium salt of pravastatin
17. The process according to claim 4 additionally comprising after a first crystallization stage the steps of:
- (e) adding further ethyl acetate to the alcohol/ethyl acetate mixture; and
- (f) causing further crystallization
18. The process according to claim 4 wherein the lower aliphatic alcohol is methanol
19. The process according to claim 4, wherein the concentration of the sodium salt of pravastatin in the alcoholic solution of step (a) is between 0.03 and 0.3 g/ml
20. The process according to claim 17, wherein the volume of further added ethyl acetate in step (e) is in the range of from 25 to 75% by volume based on the volume of ethyl acetate added in step (b)
21. The process according to claim 4, wherein the alcohol/ethyl acetate mixture is cooled to a temperature below 15°C .
22. The process according to claim 4 wherein the total crystallization time is between 3 and 20 hours
23. The process according to claim 4 wherein the formed crystals are filtered, washed with ethyl acetate and dried

* * * * *