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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

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WO 2009/139730 A1

(54) **Title**: PREPARATION OF NOVEL NON-CRYSTALLINE FORMS OF ATORVASTATIN CALCIUM

(57) **Abstract**: The invention relates to a process for producing non crystalline forms of Atorvastatin Calcium.

PREPERATION OF NON CRYSTALLINE FORMS OF ATORVASTATIN Ca

Field of Invention

This invention relates to a process for producing novel non crystalline forms of Atorvastatin Calcium which is known by the chemical name [R-(R*,R*)]-2-(4-Fluorophenyl) β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl)-1*H* pyrrole-1-heptanoic acid hemi calcium salt.

Background of the Invention

Atorvastatin Calcium is a drug that currently most therapeutically effective agent for reducing low density lipoprotein(LDL) particle concentration in the blood stream of patients at risk for cardiovascular diseases.

Atorvastatin works by inhibiting HMG-CoA reductase, an enzyme in the metabolic pathway for the synthesis of the cholesterol. This enzyme catalyses the conversion of HMG-CoA to mevalonate which is the rate determining step in the biosynthesis of cholesterol.

A decreased production of cholesterol stimulates low density lipoprotein (LDL) receptor and consequently reduces the concentration of LDL particles in the blood stream. This reduces the risk of coronary artery disease.

Processes for the preparation of Atorvastatin Calcium and its intermediates are described in the US patents 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; 5,273,995; 5,280,126; 5,298,627; 5,342,952; 5,385,929; 5,397,792; European Patent 409,281; and WO 89/07598 which are incorporated here as references.

Pharmaceutical substances can exist in more than one non crystalline form (Hancock et. al. Pharm Sci., **1997**, *86*, 1). Amorphous form of a substance offers practical advantage over crystalline form of the same substances, especially when the aqueous solubility of API is low. It is important to notice that depends on method of preparation non crystalline forms of a substances can have different thermodynamic and physical properties. Non crystalline forms which may affect the stability and bioavailability of the API and dosage

forms (*Bryn S.R. Solid-State Chemistry of Drugs, Academic Press, New York 1982, page 79*).

Amorphous Atorvastatin Calcium can be prepared following the US patents numbers 6,087,511 and 6,274,740. There are also many patent applications for the preparation of the amorphous Atorvastatin Calcium.

Besides amorphous forms of Atorvastatin Calcium WO 02/059087 A1 reports a method of preparing a non crystalline form of Atorvastatin Calcium starting from an intermediate in the synthesis of the Atorvastatin.

Some of the non crystalline forms and crystalline forms of Atorvastatin Calcium and their hydrates show stability problem due to the high surface area or high degree of hydration which can result formation of degradation product such as Atorvastatin lactone or oxidation products.

There is still a need for the stable non crystalline forms of Atorvastatin Calcium as drug substance and drug product.

Summary of the Invention

It is an object of the invention preparing new non crystalline forms of Atorvastatin Calcium following a simple, reproducible and industrially applicable process.

Amorphous crude Atorvastatin calcium is prepared following the patent application no TR 2007 07566 and US patent no 5,273,995. This crude amorph form has solubility problem for example it is not soluble in methanol and due to the low solubility it has low cell up take which is also affects bioavailability. So it was necessary to find new non crystalline forms of Atorvastatin Calcium which must show a better solubility and cell up take.

It is another object of the invention to use a binary system to produce novel non-crystaline forms of Atorvastatin Calcium. Non crystalline forms of Atorvastatin Calcium in this invention are obtained in an ethyl acetate/water system which helps to get a pure product. In literature non crystalline forms of Atorvastatin Calcium were prepared by using different methods but never a binary system is used. Thus in an industrial scale wet crude Atorvastatin Calcium containing some water and methanol is dissolved in ethyl acetate

and added into water at moderate temperature. In 30 min to 2 hours Amorph atorvastatin Calcium is precipitated, centrifuged and dried by using a Fluid Bed Drier (FBD). But Atorvastatin Calcium obtained this way contains 10,000 to 30,000 ppm ethyl acetate proved by Head-space GC and NMR). All attempts to drop residual solvent were unsuccessful. Even an effective system like FBD is not enough to drop the ethyl acetate below 5000 ppm.

It is an object of the invention to produce product containing less than 5000 ppm residual solvent. Two different ways are possible to get non crystalline form of atovastatin calcium containing ethyl acetate less than 5000 ppm. One of them is drying wet crude amorph Atorvastatin Calcium having methanol less than 2-3% and dissolving it in ethyl acetate then adding into water. The ethyl acetate/water ratio must be around 1/5.8 respectively. Second process is that taking directly crude wet amorph Atorvastatin Calcium and precipitating it in ethyl acetate/water then filtering and drying by using FBD. This product contains around 7,000 to 30,000 ppm ethyl acetate and then suspending it into ethyl acetate/water in a ratio of x/x v/v and removing ethyl acetate under reduced pressure to get novel non-crystaline form of Atorvastatin Calcium after drying in FBD.

It is another object of the invention to use ethyl acetate which stabilizes non crystalline form of Atorvastatin Calcium and prevents formation of the degradation product like Atorvastatin Lactone. One of the main problems with the non crystalline form of Atorvastatin Calcium is its instability as a drug product also as a drug substance when compared with crystalline form I of Atorvastatin Calcium. According to present invention it is found that presence of ethyl acetate stabilizes non crystalline form of Atorvastatin Calcium. When amorph form of Atorvastatin Calcium which is prepared following US patent no 5,273,995 and non crystalline form of Atorvastin Calcium prepared in this invention are dried at 50-60 °C under vacuum, Atorvastatin lacton impurity in Atorvastatin Calcium which is prepared according to US patent no 5,273,995 is increases from 0.03% to to 0.8-1% but no increase of the impurity is observed in non crystalline form of Atorvastatin Calcium produced in this invention (lacton impurity is around 0.03%).

BRIEF DESCRIPTION OF THE FIGURES

Fig 1 shows a representative X-ray diffractogram of amorphous form Atorvastatin Calcium produced following US patent no 5,298,627.

Fig 2 shows a representative X-ray diffractogram of solvated non crystaline form of Atorvastatin Calcium.

Fig 3 shows a representative X-ray diffractogram of novel non crystaline form of Atorvastatin Calcium which was obtained from solvated non crystaline form of Atorvastatin Calcium.

Fig 4 shows a representative X-ray diffractogram of novel non crystaline form of Atorvastatin Calcium

A Schmadzu RDX 6000 X-ray diffractometer is used for the measurements of X-ray diffractograms. The scanning range was 2-40 degrees two-theta. The samples were grounded before analysis.

Detailed Description of the Invention

Amorphous crude Atorvastatin Calcium is prepared following the patent application no TR 2007 07566 and US patent no 5,273,995. As described in the experimental part Atorvastatin intermediate (4R-cis)-1,1-Dimethylethyl-6-[2-[-(4-fluorophenyl)-5-(1-isopropyl)-3-phenyl-4-

[(phenylaminocarbonyl)-1H[pyrrol-1-yl]2,2-dimethylethyl-1,3-dixoane-4-acetate, namely diol protected tertiarybutyl ester of Atorvastatin is dissolved in a mixture of acetone/methanol/water containing hydroxylamin hydrochloride. The reaction is almost completed for 10-60 minutes to give a mixture of compounds Atorvastatin lacton, methyl ester of Atorvastatin and tertiary butyl ester of Atorvastatin. But still trace amount of diol protected Atorvastatin and diol protected tertiarybutyl ester of Atorvastatin remain as an impurity which affect the quality of the final product. To solve this problem acetone and methanol are distilled of under reduced pressure and fresh methanol and hydroxylamin hydrochloride are added to the residue. The solution is heated up to 50-70 ^{o}C and the progress of the reaction is followed by TLC (dichloromethane/methanol v/v 15:1) and HPLC. The reaction was completed in 30-45 minutes. The solution is concentrated under

reduced pressure to remove methanol. To the residue ethyl acetate is added and the phases are separated. The organic phase is washed three times with water, concentrated under reduced pressure to give a solid containing tertiary butyl ester, methyl ester and lacton of Atorvastatin. To this solid methanol is added together with 1-3 equivalent of NaOH. The solution is stirred at 38-42 °C for 30-60 minutes. The TLC analysis showed that all the esters were hydrolyzed. A $CaCl_2 \cdot 2H_2O$ solution in water is added. The solution is stirred for 15-30 minutes and filtered to remove any solid material and added in to water within 5-15 minutes while stirring. The product is filtered and 63 kg wet product is obtained. From this wet product 63 g sample was taken dried in fume hood under air stream over night and 23.6 g Atorvastatin Calcium was obtained in 85% overall yield with a purity of 99.75% determined by HPLC. The XRD is given in Figure 1.

Non crystalline forms of Atorvastatin Calcium can be obtained following two different processes from this crude wet product. According to first process, after suspension of the wet crude Atorvastatin Calcium into water, the product is taken and used directly in the next step without drying. Thus wet crude product is precipitated in a binary system of ethyl acetate/water, centrifuged and dried by using FBD. This product contains around 15,000-30,000 ppm ethyl acetate and has the following XRD diffractogram as shown in Figure 2. This solvated product is taken into a ethyl acetate/water mixture and ethyl acetate is removed under reduced pressure to give final product containing less than 5,000 ppm ethyl acetate after drying in FBD and having non crystalline form as shown in Figure 3. According to second process crude wet Atorvastatin Calcium (without drying) obtained above is suspended into water to remove methanol which lead the product to precipitate as ethyl acetate solvated form. Then the product is dried until LOD is below 30%, dissolved in ethyl acetate, filtered over celite and added into water. In this process ethyl acetate water ratio must be 1/6 especially 1/4.6 to get non crystalline form of Atorvastatin calcium having ethyl acetate below 5,000 ppm. The XRD is given in Figure 4.

It is understood that the above features and the features described below can be used not only in their described combination but also in other combinations or in isolation without departing from the scope of the invention.

The invention is now further illustrated by means of examples. These examples are not intended to limit the scope of the invention any way.

Example 1

Preparation of non crystalline form of [R-(R*,R*)]-2-(4-Fluorophenyl),β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl)-1*H* pyrrole-1-heptanoicacid hemi calcium salt starting from diol protected tertiarybutyl ester in large scale

A 2000 L GLR was charged with 137 kg methanol, 63 kg of aceton, 27.5 kg of water and 26.6 kg of (4R-cis)-1,1-Dimethylethyl-6-[2-[-(4-fluorophenyl)-5-(1-isopropyl)-3-phenyl-4-[(phenylaminocarbonyl)-1H[pyrrol-1-yl]2,2-dimethylethyl-1,3-dixoane-4-acetate, namely diol protected tertiarybutyl ester of Atorvastatin at room temperature. To this suspension was added 2.84 kg (1 eqv.) of hydroxylamine hydrochloride. The suspension was heated to 55-°65 C and became a clear solution. The mixture was stirred at this temperature for 35-45 minutes. TLC analysis showed that most of the starting material was converted to the corresponding acid and esters. Acetone and methanol was removed under reduced pressure. To the residue 137 kg of methanol and 6.5 kg of hydroxylamine hydrochloride was added. The solution was heated to 55-°65 °C and stirred at this temperature for 15-30 minutes. TLC analysis showed that all the starting material was consumed. The solution was concentrated under reduced pressure. To the residue 246 kg of ethyl acetate and 267 kg of water was added and the phases were separated. The organic phase was washed with two times 267 kg of water. The organic phase containing mixture of the compound of the formula (II) and (III) was concentrated under reduced pressure. To the residue 95 kg of methanol and NaOH solution (2 eqv. 3.28 kg NaOH was dissolved in 26.7 kg of water) were added. The mixture was stirred at 35-45 °C for 30-40 minutes. TLC analysis showed that all the starting materials were converted into the sodium salt of Atorvastatin. A $CaCl_2$ solution (0.5 eqv., 3 kg of $CaCl_2 \cdot 2H_2O$ dissolved in 26 kg of water) was added to the Atorvastatin sodium solution at 35-45 °C. The solution was stirred for 10-30 minutes and filtered over 0.5 micron filter to remove any solid particles. To the filtered solution containing Atorvastatin Calcium 750 kg of water was added in 5-10 minutes while stirring. The product was immediately precipitated to get amorphous form by fast addition of water. After waiting 30-60 minutes, the product was centrifuged and washed with a 18 kg mixture of methanol water

(1:1). Then suspended into 100 kg of water and centrifuged to give a wet product 63 kg. A 63 g sample was taken dried in fume hood under air stream over night and Atorvastatin Calcium was obtained 23.6 g in 85% overall yield with a purity of 99.75% determined by HPLC. The XRD is given in Figure 1.

A 1000 L GLR was charged with 153 kg ethyl acetate and 887 kg water at 22 - 27 °C. To this mixture 59 kg wet Atorvastatin Calcium obtained above was added. The solution was stirred for 10-60 minutes. After precipitation it was filtered through the stainless centrifuge. The cake was washed with 30 kg water. Wet Atorvastatin Calcium was obtained 47 kg. The product was dried in fluid bed drier and obtained as a white solid 20.2 kg. Ethyl acetate content of the product was around 18,000 ppm determined by head space GC. The XRD is given in Figure 2.

To drop ethyl acetate content below 5000 ppm a 1000 L GLR was charged with 72 kg ethyl acetate and 205 kg water at room temperature. 20.2 kg of Atorvastatin Ca was added to this solution. The mixture was stirred at 24–28 °C for 10–15 minutes and ethyl acetate is removed under reduced pressure. The precipitate was filtered centrifuged. Wet Atorvastatin Calcium 43 kg of was obtained and dried in fluid bed drier to give 17.5 kg non crystalline form of Atorvastatin Calcium which has ethyl acetate content below 5000 ppm. The XRD is given in Figure 3.

Example 2

Preparation of [R-(R*,R*)]-2-(4-fluorophenyl),β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl -4-[(phenylamino)carbonyl)-1Hpyrrole-1-heptanoic acid hemi calcium salt starting from diol protected tertiarybutyl ester

A 1000 mL round bottom flask was charged with 256.75 g methanol, 118.5 g of aceton, 75 g of water and 50 g of (4R-cis)-1,1-Dimethylethyl-6-[2-[-(4-fluorophenyl)-5-(1-isopropyl)-3-phenyl-4-[(phenylaminocarbonyl)-1H[pyrrol-1-yl]2,2-dimethylethyl-1,3-dixoane-4-acetate, namely diol protected tertiarybutyl ester of Atorvastatin at room temperature. To this suspension was added 5.3 g (1 eqv.) of hydroxylamine hydrochloride. The suspension was heated to 60-65 °C and became a clear solution. TLC analysis showed that most of the starting material was converted to the corresponding acid and esters. Acetone and methanol was removed under reduced pressure. To the residue

256.75 g of methanol and 12.25 g of hydroxylamine hydrochloride was added. The solution was heated to 60-°65 °C . TLC analysis showed that all the starting material was consumed. The solution was concentrated under reduced pressure. To the residue 461.5 g of ethyl acetate and 500 g of water was added and the phases were separated. The organic phase was washed with three times 500 g of water. The organic phase containing mixture of the compound of the formula (II) and (III) was concentrated under reduced pressure. To the residue 256.75 g of methanol and NaOH solution (2 eqv. 6.15 g NaOH was dissolved in 25 g of water) were added. The mixture was stirred at 38-42 °C TLC analysis showed that all the starting materials were converted into the sodium salt of Atorvastatin. A $CaCl_2$ solution (0.5 eqv., 6.16 g of $CaCl_2 \cdot 2H_2O$ dissolved in 25 g of water) was added to the Atorvastatin sodium solution at 38-42 °C. The solution was stirred for 10-30 minutes and filtered over celite to remove any solid particles. To 350 g of water, filtered solution containing Atorvastatin Calcium was added rapidly while stirring. The product precipitated while adding the solution to water. After waiting 30-60 minutes, the product was filtered and washed with a 80–100 ml mixture of methanol water (1:1) and then washed with 100 g of water. The wet product was dried and obtained 73g as a white powder.

A 2000 mL flask was charged with 230 g ethyl acetate and 73 g wet crude Atorvastatin Calcium at room temperature. Water content of the product was calculated by weighing wet crude product assuming that with a quantitative yield around 46 g Atorvastatin Calcium can be obtained. The ratio of ethyl acetate: water was adjusted to 1:4.6 (w/w). Thus to the ethyl acetate containing Atorvastatin calcium 1050 g of water was added. The precipitation was completed in 1.0 – 1.5 hrs. The suspension was filtered and dried at 50-60 °C for 12 -15 hrs and 33 g in 75 % yield non crystalline Atorvastatin Calcium having an ethyl acetate content 2908 ppm is obtained as a white powder. The XRD is given in Figure 4.

CLAIMS

1. The process for the preparation of non-crystaline form of Atorvastatin Calcium having X-ray diffractogram as depicted in Figure 3 and comprising steps of:

a) dissolving wet Atorvastatin Calcium which can contain water and more than 5-30% methanol in ethyl acetate;

b) filtering the solution to remove any solid particles

c) adding ethyl acetate containing Atorvastatin Calcium into water having a binary solvent system

d) precipitating Atorvastatin Calcium solvated with ethyl acetate

e) isolating Atorvastatin Calcium solvated form having X-ray diffractogram as depicted in Figure 2 after drying in FBD

f) suspending Atorvastatin Calcium solvated form into a binary system of ethyl acetate-water to drop ethyl acetate below 5,000 ppm

g) removing ethyl acetate under reduced pressure

h) isolating non crystalline form of Atorvastatin Calcium after drying in FBD.

2. Processes according to the claim 1, characterized in that wet Atorvastatin Calcium contains 1 to 5 fold of water based on its dry weight.

3. Processes according to the claim 1, characterized in that wet Atorvastatin Calcium contains 5 to 30% of methanol based on its dry weight.

4. Processes according to the claim 1, characterized in that the mixture of solvents comprises at least one ester and water.

5. Process according to claim 4, characterized in that the ester is selected from the group consisting of methyl, ethyl, propyl, isopropyl and butyl acetate.

6. Process according to claim 1, characterized in that the binary solvents system comprises 1-30 % by weight of ester.

7. Method according to claim 6, characterized in that the binary solvents system comprises 15-20 % by weight of ester.

8. The process for the preparation of non-crystaline form of Atorvastatin Calcium having X-ray diffractogram as depicted in Figure 4 and comprising steps of:

a) dissolving wet Atorvastatin Calcium which can contain water and less than 5% methanol in ethyl acetate;

b) filtering the solution to remove any solid particles

c) adding ethyl acetate containing Atorvastatin Calcium into water having a binary solvent system

d) precipitating Atorvastatin Calcium solvated with ethyl acetate

e) isolating non crystalline form of Atorvastatin Calcium having ethyl acetate below 5,000 ppm after drying in FBD.

9. Processes according to the claim 8, characterized in that wet Atorvastatin Calcium contains 1 to 5 fold of water based on its dry weight.

10. Processes according to the claim 8, characterized in that wet Atorvastatin Calcium contains less than 5% of methanol based on its dry weight.

11. Processes according to the claim 8, characterized in that the mixture of solvents comprises at least one ester and water.

12. Process according to claim 11, characterized in that the ester is selected from the group consisting of methyl, ethyl, propyl, isopropyl and butyl acetate.

13. Process according to claim 8, characterized in that the binary solvents system comprises 5-30 % by weight of ester.

14. Method according to claim 13, characterized in that the binary solvents system comprises 15-20 % by weight of ester.

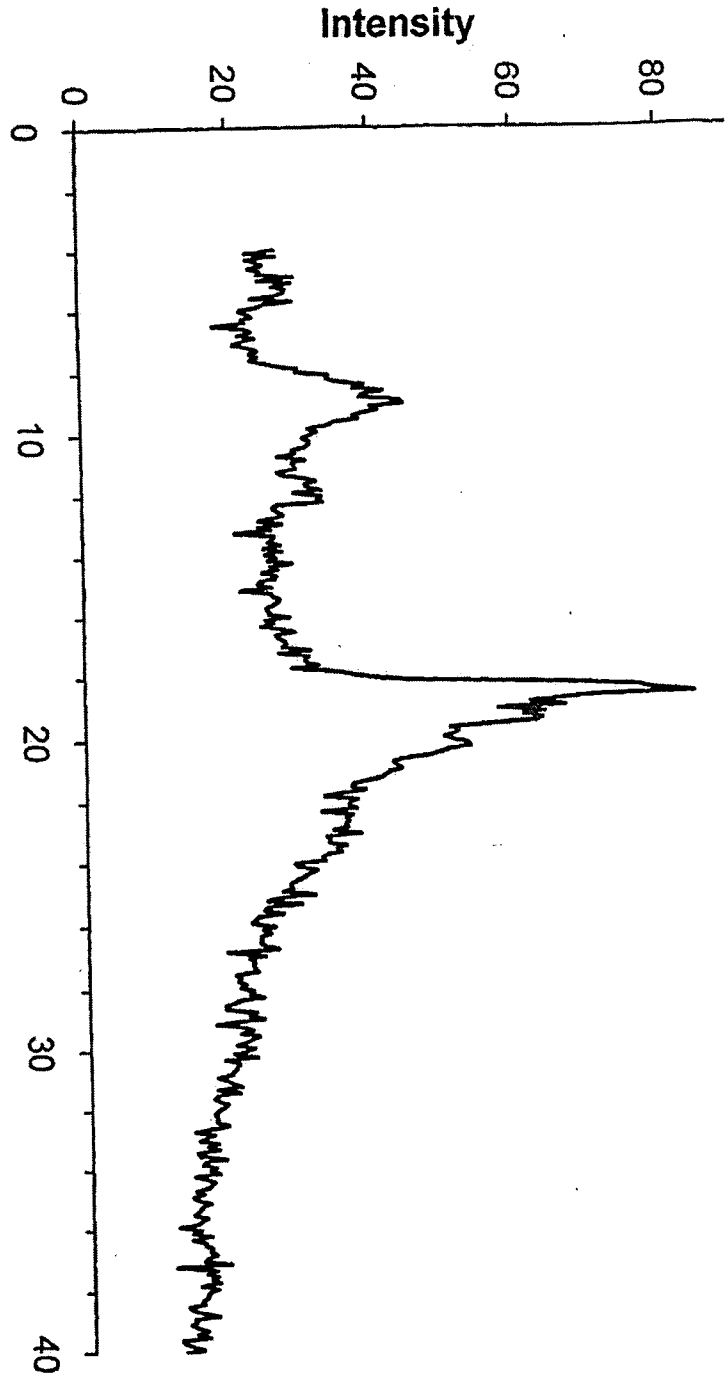


Fig. 1

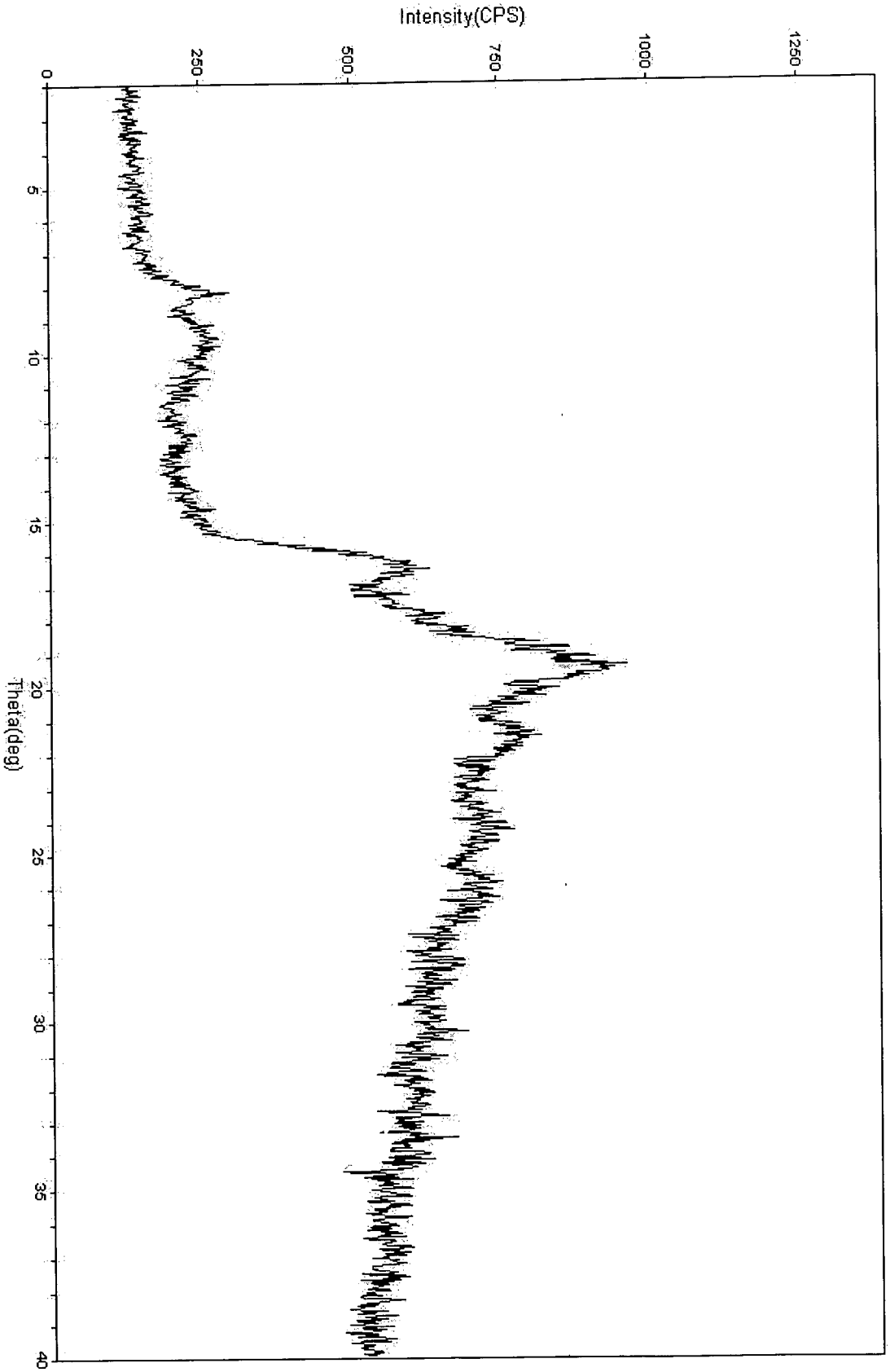

Intensity(CPS)
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Theta(deg)

FIG : 2

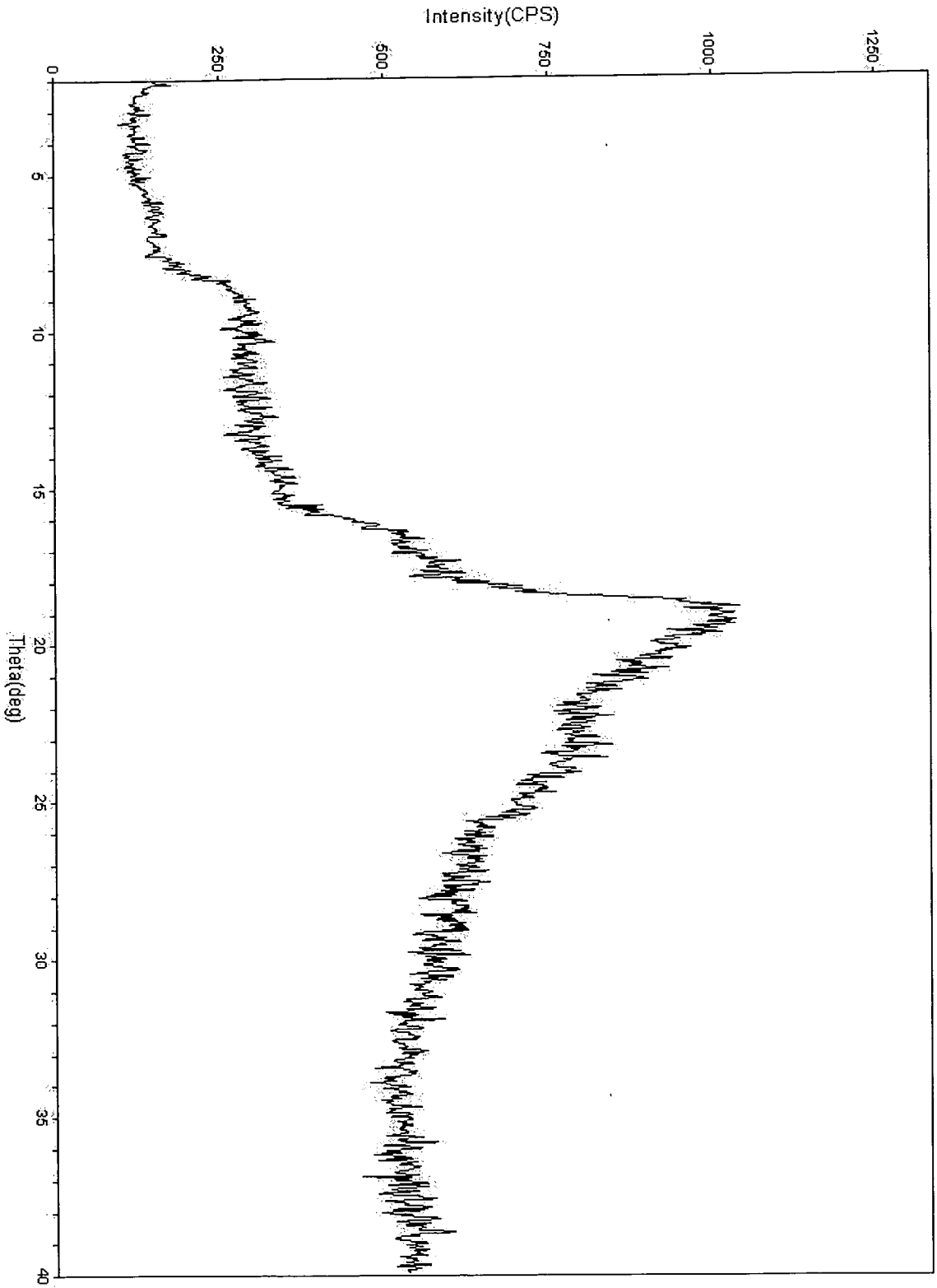

Intensity(CPS)
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40

FIG : 3

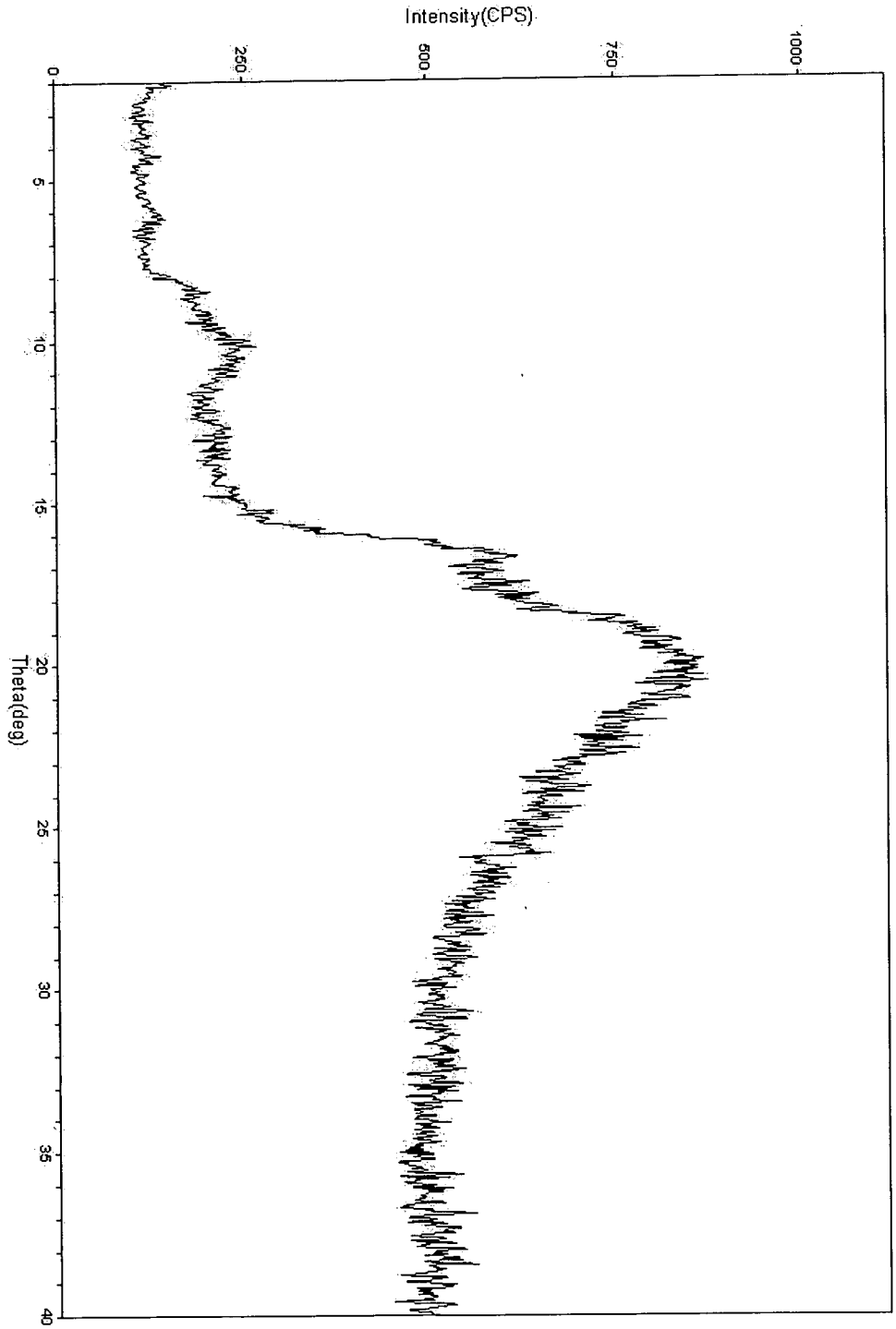

Intensity(CPS)
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1000
0
5
10
15
20
25
30
35
40
Theta(deg)

FIG :4

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2008/000050

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D207/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/059087 A (LEK TOVARNA FARMACEVTSKIH [SI]; SORSAK GORAZD [SL]) 1 August 2002 (2002-08-01) cited in the application example 2	1-14
A	WO 03/068739 A (LECIVA A S [CZ]; RADL STANISLAV [CZ]; STACH JAN [CZ]) 21 August 2003 (2003-08-21) example 1	1-14
A	WO 02/083638 A (CADILA HEALTHCARE LTD [IN]; AGARWAL VIRENDRA KUMAR [IN]; VAKIL MANISH) 24 October 2002 (2002-10-24) example 2	1-14

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
21 January 2009	27/01/2009

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/TR2008/000050

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