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[IN/IN]; c/o Sh P P Jindal, House N° 206, Sector 44/A, 160047 Chandigarh, Chandigarh (IN). **KUMAR, Yaten-dra** [IN/IN]; U-26/5, Phase - III/DLF Qutab Enclave, Gurgaon, Haryana 122001 (IN).

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

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(71) Applicant (*for all designated States except US*): **RANBAXY LABORATORIES LIMITED** [IN/IN]; 19, Nehru Place, New Delhi, Delhi 110019 (IN).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **DE, Shantanu** [IN/IN]; G-1220, Ghittaranjan Park, New Delhi, Delhi 110070 (IN). **TRIPATHI, Vinayak** [IN/IN]; D-35, Mahanagar Extension, 226006 Lucknow, Uttar Pradesh (IN). **SATHYANARAYANA, Swargam** [IN/IN]; H.No. 9-6-95 /2 (Old), 9-6-194 (New), Ram Nager, Karim Nager, Andhra Pradesh 505002 (IN). **JINDAL, Shantanu**

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(54) Title: NOVEL FORMS OF FLUVASTATIN SODIUM, PROCESSES FOR PREPARATION AND PHARMACEUTICAL COMPOSITIONS THEREOF

(57) Abstract: Provided are substantially amorphous fluvastatin sodium and amorphous Form R6 and R-14 of fluvastatin sodium. Also provided are crystalline forms of fluvastatin sodium designated as Forms R-1, R-2, R-3, R-4, R-5, R-7, R-8, R-9, R-10, R-11, R-12, R-13, R-15 and R-16 and an anhydrous crystalline form. Also provided are processes for preparing such polymorphic forms and pharmaceutical compositions thereof. Also provided are methods for antagonizing HMG-CoA comprising administering to a mammal therapeutically effective amounts of the compounds described herein.

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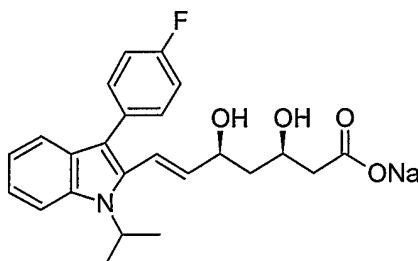
NOVEL FORMS OF FLUVASTATIN SODIUM, PROCESSES FOR PREPARATION AND PHARMACEUTICAL COMPOSITIONS THEREOF

Field of the Invention

5 Provided herein are substantially amorphous fluvastatin sodium and amorphous Form R-6 and R-14 of fluvastatin sodium. Also provided are crystalline forms of fluvastatin sodium designated as Forms R-1, R-2, R-3, R-4, R-5, R-7, R-8, R-9, R-10, R-11, R-12, R-13, R-15 or R-16 and an anhydrous crystalline form. Also provided are processes for preparing polymorphic forms of fluvastatin sodium, as well as
10 pharmaceutical compositions thereof, which can be used as HMG-CoA antagonists.

Background of the Invention

 Fluvastatin sodium is chemically a monosodium salt of a racemic mixture of (3R,5S) and (3S,5R) erythro-7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-3,5-
15 dihydroxy-6-heptenoic acid of Formula I.



FORMULA I

 Fluvastatin sodium is a cholesterol lowering agent, which acts inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. It is indicated as an adjunct to diet to reduce elevated total cholesterol (Total-C), LDL-C, TG and Apo B levels, and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson Type IIa and IIb) whose response to dietary restriction of saturated fat and cholesterol and other non-pharmacological measures has not been adequate. It is also indicated to slow the progression of coronary atherosclerosis in
20 patients with coronary heart disease as part of a treatment strategy to lower total and LDL
25 cholesterol to target levels. Fluvastatin sodium is the first entirely synthetic HMG-CoA

reductase inhibitor, and is in part structurally distinct from the fungal derivatives of this therapeutic class.

A process for preparing fluvastatin sodium involving lyophilization of aqueous solution of fluvastatin sodium has been disclosed. Also previously disclosed is
5 lyophilization of racemic fluvastatin sodium to form a mixture of a crystalline form, designated as Form A, and amorphous material, and disclose a new crystalline form, designated as Form B. The estimated amount of Form A obtained by lyophilization is reportedly about 50 %. It is disclosed that crystalline Form B is obtained either by transformation of material containing Form A in a slurry of a mixture of an organic
10 solvent and water, or by crystallization from an organic solvent and water mixture. Also described is that Form B is less hygroscopic than Form A or the amorphous form of fluvastatin sodium, which allegedly improves handling and storage of the compound.

Crystalline forms of racemic fluvastatin sodium hydrates, referred to as polymorphic Forms C, D, E and F, processes for preparing these crystalline forms and
15 pharmaceutical compositions comprising the crystalline forms have also been disclosed. In particular, it was reported that fluvastatin sodium has estimated water content in range from 3-6 % for Form C, 6-12 % for Form D, 15-22 % for Form E and 24-32 % for Form F of fluvastatin sodium.

Also previously disclosed are crystalline hydrates of enantiomerically enriched
20 (3R,5S) or (3S,5R) of fluvastatin sodium referred to as Forms A, B1, B2, C, D and E. These forms are characteristically different from the other known crystalline forms as these belong to enantiomerically enriched either (3R, 5S) or (3S,5R) enantiomers of fluvastatin sodium.

However, in view of the above, there remains a need for novel forms of fluvastatin.
25

Brief Description of the Drawings

Figure 1 depicts an X-Ray Powder Diffraction (XRPD) pattern of substantially amorphous fluvastatin sodium.

Figure 2 depicts an FTIR spectrum of substantially amorphous fluvastatin sodium.

Figure 3 depicts an X-Ray Powder Diffraction (XRPD) pattern of substantially amorphous fluvastatin sodium obtained by spray drying.

Figure 4 depicts an X-Ray Powder Diffraction (XRPD) pattern of mixture of crystalline and amorphous fluvastatin sodium.

5 Figure 5 depicts an X-Ray Powder Diffraction (XRPD) pattern of Form R-1 of fluvastatin sodium.

Figure 6 depicts an FTIR spectrum of Form R-1 of fluvastatin sodium.

Figure 7 depicts an X-Ray Powder Diffraction (XRPD) pattern of Form R-2 of fluvastatin sodium.

10 Figure 8 depicts an FTIR spectrum of Form R-2 of fluvastatin sodium.

Figure 9 depicts an X-Ray Powder Diffraction (XRPD) pattern of Form R-3 of fluvastatin sodium.

Figure 10 depicts an FTIR spectrum of Form R-3 of fluvastatin sodium.

15 Figure 11 depicts an X-Ray Powder Diffraction (XRPD) pattern of Form R-4 of fluvastatin sodium.

Figure 12 depicts an X-Ray Powder Diffraction (XRPD) pattern of Form R-5 of fluvastatin sodium.

Figure 13 depicts an FTIR spectrum of Form R-5 of fluvastatin sodium.

20 Figure 14 depicts an X-Ray Powder Diffraction (XRPD) pattern of Form R-6 of fluvastatin sodium.

Figure 15 depicts an FTIR spectrum of Form R-6 of fluvastatin sodium.

Figure 16 depicts an X-Ray Powder Diffraction (XRPD) pattern of Form R-7 of fluvastatin sodium.

Figure 17 depicts an FTIR spectrum of Form R-7 of fluvastatin sodium.

25 Figure 18 depicts an X-Ray Powder Diffraction (XRPD) pattern of Form R-8 of fluvastatin sodium.

Figure 19 depicts an FTIR spectrum of Form R-8 of fluvastatin sodium.

Figure 20 depicts an X-Ray Powder Diffraction (XRPD) pattern of Form R-9 of fluvastatin sodium.

Figure 21 depicts an FTIR spectrum of Form R-9 of fluvastatin sodium.

Figure 22 depicts an X-Ray Powder Diffraction (XRPD) pattern of Form R-10 of fluvastatin sodium.

Figure 23 depicts an FTIR spectrum of Form R-10 of fluvastatin sodium.

Figure 24 depicts an X-Ray Powder Diffraction (XRPD) pattern of Form R-11 of fluvastatin sodium.

Figure 25 depicts an FTIR spectrum of Form R-11 of fluvastatin sodium.

Figure 26 depicts an X-Ray Powder Diffraction (XRPD) pattern of Form R-12 of fluvastatin sodium.

Figure 27 depicts an X-Ray Powder Diffraction (XRPD) pattern of Form R-13 of fluvastatin sodium.

Figure 28 depicts an X-Ray Powder Diffraction (XRPD) pattern of Form R-14 of fluvastatin sodium.

Figure 29 depicts an X-ray diffractogram of Form R-15 of fluvastatin sodium.

Figure 30 depicts an X-Ray Powder Diffraction (XRPD) pattern of Form R-16 of fluvastatin sodium.

Figure 31 depicts an FTIR spectrum of Form R-16 of fluvastatin sodium.

Figure 32 depicts a DSC of Form R-16 of fluvastatin sodium.

Figure 33 depicts an X-Ray Powder Diffraction (XRPD) pattern of anhydrous crystalline form of fluvastatin sodium.

Figure 34 depicts an FTIR spectrum of anhydrous crystalline form of fluvastatin sodium.

Figure 35 depicts a DSC of Form anhydrous crystalline form of fluvastatin sodium.

Summary of the Invention

It has been surprisingly discovered that racemic fluvastatin sodium can be isolated in substantially amorphous form. In contrast, a mixture of amorphous form and other polymorphic forms are isolated when using all previously known methods. Also provided
5 are methods of isolating racemic fluvastatin sodium in novel amorphous forms (for example, Form R-6 and Form-14 of fluvastatin sodium by crystallization processes that do not require lyophilization or freeze-drying.

Also provided are methods of isolating racemic fluvastatin sodium novel crystalline forms (for example, Form R-1, R-2, R-3, R-4, R-5, R-7, R-8, R-9, R-10, R-11,
10 R-12, R-13, R-15 and R-16 of fluvastatin sodium) and an anhydrous crystalline form by processes, which can include lyophilization, crystallization, spray-drying or combinations thereof.

In one aspect, provided is substantially amorphous fluvastatin sodium having about 15 % or less of crystallinity. Substantially amorphous fluvastatin sodium can include one
15 or more of the following embodiments. For example, substantially amorphous fluvastatin sodium can exhibit an XRPD pattern as depicted in Figure 1. Substantially amorphous fluvastatin sodium can also exhibit an FTIR spectrum as depicted in Figure 2. Substantially amorphous fluvastatin sodium can also have water content of less than about 1.5 % w/w.

20 In another aspect, provided are processes for preparing substantially amorphous fluvastatin sodium comprising the steps of:

- a) contacting fluvastatin sodium having a moisture content of about 5 % w/w with tetrahydrofuran to form a first mixture,
- b) optionally removing water from the first mixture obtained in step a) to form
25 a concentrated mixture and contacting the concentrated mixture with tetrahydrofuran to form a second mixture,
- c) removing the solvent from the second mixture obtained in step c) to form a resultant mass,
- d) contacting the resultant mass obtained in step c) with one or more organic
30 solvents selected from one or more C₅₋₈ alkanes, one or more C₅₋₇

cycloalkanes, one or more halogenated hydrocarbons, one or more aliphatic ethers, one or more petroleum ethers, one or more ketones or mixtures thereof to form a third mixture, and

e) isolating amorphous fluvastatin sodium from the third mixture thereof,

5 The process can include the following embodiment. In particular, the water can be removed azeotropically in step b).

In another aspect, provided are processes for preparing substantially amorphous fluvastatin sodium comprising the steps of:

10 a) dissolving fluvastatin sodium having a moisture content of about 5 % w/w or less in a one or more organic solvents, and

b) removing the one or more organic solvents from the solution thereof.

The process can include one or more of the following embodiments. For example, the one or more organic solvents can be removed by spray drying in step b). The one or more organic solvents can be one or more of C₁₋₄ alcohols, C₃₋₈ ketones, C₃₋₆ esters, C₄₋₈ ethers, polar aprotic solvents, or mixtures thereof.

15 In another aspect, provided is amorphous fluvastatin sodium having about 15 % or less of crystallinity prepared by a process comprising the steps of:

a) dissolving fluvastatin sodium having a moisture content 5 % w/w or less in a one or more organic solvents, and

20 b) removing the one or more organic solvents from the solution thereof.

Also provided is amorphous Form R-6 of fluvastatin sodium. Form 6 of fluvastatin sodium can have one or more of the following embodiments. For example, Form R-6 of fluvastatin sodium can exhibit an XRPD pattern as depicted in Figure 14. Form R-6 of fluvastatin sodium can also have water content of about 0.5 to 2.0 % as determined by Karl Fischer analysis. Form R-6 of fluvastatin sodium can also exhibit a FTIR spectrum in potassium bromide as depicted in Figure 15.

25 In another aspect, provided are processes for preparing polymorphic Form R-6 of fluvastatin sodium comprising the steps of:

- a) contacting fluvastatin sodium with tetrahydrofuran to form a mixture,
- b) adding a seed amount of amorphous Form R-6 of fluvastatin sodium to the mixture obtained in step a), and to form a seeded mixture
- c) isolating Form R-6 of fluvastatin sodium from the seeded mixture thereof.

5 The process can include the following embodiments. For example, the mixture of step a) can be stirred for about 10 to 30 hours. Seed amounts of amorphous Form R-6 of fluvastatin sodium can range from about 0.1 % w/w to about 50 % w/w of the initial fluvastatin sodium amount, preferably from about 0.5 % w/w to about 10 % w/w, more preferably from about 1 % w/w to about 2.5 % w/w.

10 In another aspect, provided is anhydrous crystalline fluvastatin sodium. Anhydrous crystalline fluvastatin sodium can include one or more of the following embodiments. For example, anhydrous crystalline fluvastatin sodium can exhibit an XRPD pattern as depicted in Figure 33. Anhydrous crystalline fluvastatin sodium can exhibit an XRPD pattern having 2θ values at about 4.2, 10.4, 18.6, 21.3 and 24.5.

15 Anhydrous crystalline fluvastatin sodium can also exhibit a FTIR spectrum in potassium bromide as depicted in Figure 34. Anhydrous crystalline fluvastatin sodium can also exhibit a Differential Scanning Calorimetric thermogram as depicted in Figure 35. Anhydrous crystalline fluvastatin sodium can also have water content of less than about 0.1 % w/w.

20 In another aspect, provided are processes for preparing anhydrous crystalline fluvastatin sodium comprising the steps of:

- a) contacting fluvastatin sodium with one or more organic solvents and optionally water to form a first mixture, and acidifying the first mixture with an acid to form an acidified first mixture, wherein the one or more organic solvents is selected from one or more C₅₋₈ alkanes, one or more C₅₋₇ cycloalkanes, one or more halogenated hydrocarbons, one or more aliphatic ethers, one or more petroleum ethers, one or more ketones or mixtures thereof,
- b) isolating a solid residue from the acidified first mixture obtained in step a),

- c) forming a second mixture by contacting the solid residue of step b) with one or more sodium-containing alkali compounds in the presence of one or more ethers,
- d) isolating anhydrous crystalline fluvastatin sodium from the second mixture thereof.

The one or more sodium-containing alkali compounds can be selected from sodium hydroxide, sodium carbonate, sodium bicarbonate, sodium alkoxide, sodium alkanoate or mixtures thereof.

Also provided are pharmaceutical compositions comprising therapeutically effective amounts of substantially amorphous fluvastatin sodium and optionally one or more pharmaceutically acceptable diluents or excipients.

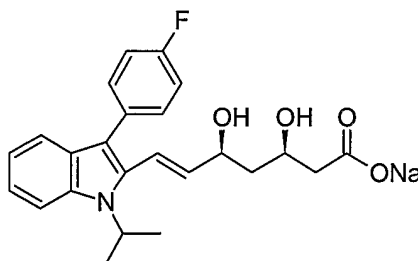
Also provided are pharmaceutical compositions comprising therapeutically effective amounts of Form R-6 of fluvastatin sodium and optionally one or more pharmaceutically acceptable diluents or excipients.

Also provided are pharmaceutical compositions comprising therapeutically effective amounts of anhydrous crystalline fluvastatin sodium and optionally one or more pharmaceutically acceptable diluents or excipients.

In another aspect, provided are methods of antagonizing HMG-CoA in mammal comprising administering to the mammal therapeutically effective amounts of one or more of anhydrous crystalline fluvastatin sodium, substantially amorphous fluvastatin sodium, Form R-6 of fluvastatin sodium or mixtures thereof.

Detailed Description of the Invention

The term "racemic fluvastatin sodium," as used herein, refers to fluvastatin sodium of Formula I,



FORMULA I

which is a racemic mixture of (3R,5S) and (3S,5R) enantiomers, wherein fluvastatin sodium has an *erythro* confirmation with reference to the double bond geometry.

The term "substantially amorphous fluvastatin sodium," as used herein, refers to amorphous fluvastatin sodium having about 15 % w/w or less crystallinity.

The term "anhydrous," as used herein, refers to water content of about 0.5 % w/w or less. Preferably, the water content of anhydrous fluvastatin sodium is about 0.1 % w/w or less.

Provided herein is substantially amorphous fluvastatin sodium. Substantially amorphous fluvastatin sodium can have about 15 % or less crystallinity. Substantially amorphous fluvastatin sodium can also have about 10 % or less crystallinity and even from about 0.1 to 5 % crystallinity. Substantially amorphous fluvastatin sodium can be characterized as having water content of about 1.5 % w/w or less as determined by, for example, Karl Fischer analysis. Typical procedures for Karl Fischer analyses, as used herein, may be used. (For example, Karl Fischer analyses can comprise the steps of placing dehydrated alcohol, *e.g.*, methanol, in a titration vessel to a level sufficient to contact electrodes. Karl Fischer reagent can be added until a characteristic electrometric end point is reached. The target compound, *e.g.*, fluvastatin sodium, can be quickly added to the titration vessel, the solution stirred and titrated using Karl Fischer reagent.) An example of an X-Ray Powder Diffraction (XRPD) of substantially amorphous fluvastatin sodium is depicted in Figure 1. An example of a Fourier Transform Infrared (FTIR)

spectrum of substantially amorphous fluvastatin sodium in potassium bromide is depicted in Figure 2.

Also provided herein is storage-stable, non-hygroscopic, substantially amorphous fluvastatin sodium. In particular, such storage-stable, non-hygroscopic, substantially
5 amorphous form of fluvastatin sodium showed no conversion to crystalline form when stored at about 25 °C and about 45 % relative humidity.

Also provided are processes for preparing substantially amorphous fluvastatin sodium comprising the steps of:

- 10 a) contacting fluvastatin sodium having a moisture content of about 5 % w/w with tetrahydrofuran to form a first mixture,
- b) removing water from the first mixture obtained in step a) to form a concentrated mixture,
- c) contacting the concentrated mixture obtained in step b) with tetrahydrofuran to form a second mixture,
- 15 d) removing the solvent from the second mixture obtained in step c) to form a resultant mass,
- e) contacting the resultant mass obtained in step d) with one or more organic solvents selected from one or more C₅₋₈ alkanes, one or more C₅₋₇ cycloalkanes, one or more halogenated hydrocarbons, one or more aliphatic
20 ethers, petroleum ether, one or more ketones or mixtures thereof, to form a third mixture, and
- f) isolating substantially amorphous fluvastatin sodium from the third mixture thereof.

Fluvastatin sodium can be contacted with tetrahydrofuran and the resulting first
25 mixture can be stirred (at ambient temperatures to about 50 °C, preferably from about 30 °C to about 40 °C) to dissolve solid material. Water can be removed from the first mixture azeotropically to form a concentrated mixture. Tetrahydrofuran can be added to the concentrated mixture to form a second mixture. The second mixture can be further concentrated to remove solvent and form a resultant mass. The resultant mass can be
30 contacted with one or more organic solvents to form a third mixture. Suitable organic

solvents can be, for example, one or more of C₅₋₈ alkanes, C₅₋₇ cycloalkanes, halogenated hydrocarbons, aliphatic ethers, petroleum ether, ketones or mixtures thereof. The third mixture can be stirred and a formed precipitate can be filtered and dried under vacuum to yield substantially amorphous fluvastatin sodium. Each step can be carried out under inert atmosphere (for example, nitrogen, helium, argon, and the like) and under anhydrous conditions.

Also provided herein are processes for preparing substantially amorphous fluvastatin sodium comprising the steps of:

- a) contacting fluvastatin sodium with tetrahydrofuran to form a first mixture,
- 10 b) removing the solvent from the first mixture obtained in step a) to form a resultant mass,
- c) contacting the resultant mass obtained in step b) with one or more organic solvents selected from one or more C₅₋₈ alkanes, one or more C₅₋₇ cycloalkanes, one or more halogenated hydrocarbons, one or more aliphatic ethers, petroleum ether, one or more ketones or mixtures thereof, to form a second mixture, and
- 15 d) isolating substantially amorphous fluvastatin sodium from the second mixture thereof.

Fluvastatin sodium can be contacted with tetrahydrofuran to form a first mixture and the first mixture can be stirred (at ambient temperatures to about 50 °C, preferably from about 30 °C to about 40 °C) to dissolve solid material. The first mixture can be concentrated to remove solvent and the resultant mass thus obtained can be redissolved in one or more organic solvent to form a second mixture. Organic solvents include, for example, one or more C₅₋₈ alkanes, one or more C₅₋₇ cycloalkanes, one or more halogenated hydrocarbons, one or more aliphatic ethers, petroleum ether, one or more ketones or mixtures thereof. The second mixture can be stirred and solids therein can be filtered, suitably dried under vacuum to yield substantially amorphous fluvastatin sodium. Each step can be carried out under inert atmosphere (for example, nitrogen, helium, argon, and the like) and under anhydrous conditions.

Also provided are processes for preparing substantially amorphous fluvastatin sodium comprising the steps of:

- a) dissolving fluvastatin sodium having a moisture content of about 5 % w/w or less in one or more organic solvents to form a solution, and
- 5 b) removing the one or more organic solvents from the solution thereof to form substantially amorphous fluvastatin sodium.

Fluvastatin sodium having a moisture content of about 5 % or less can be prepared according to the present disclosure, as well as by techniques known to one of ordinary skill in the art. After dissolving fluvastatin sodium (less than about 5 % moisture) in one
10 or more suitable organic solvents, the solution so obtained can be concentrated to yield amorphous fluvastatin sodium having about 15 % or less crystallinity. Suitable organic solvents include, for example, C₁₋₄ alcohols, C₃₋₈ ketones, C₃₋₆ esters, C₄₋₈ ethers, polar aprotic solvents or mixtures thereof. Solutions of fluvastatin sodium can be concentrated, for example, by spray drying or by vacuum evaporation.

15 Also provided is amorphous fluvastatin sodium having about 15 % or less crystallinity prepared by processes comprising spray drying a solution of fluvastatin sodium, wherein the starting fluvastatin sodium has about 5 % or less of moisture content.

Also provided is novel polymorphic Form R-1 of fluvastatin sodium. Form R-1 of fluvastatin sodium can exhibit an X-Ray Powder Diffraction (XRPD) pattern having one
20 or more 2θ values at about 3.8, 11.3, 17.7 and/or 18.3. Form R-1 of fluvastatin sodium can also exhibit an XRPD pattern having one or more 2θ values at about 10.5, 12.0, 14.2, 14.4, 14.7, 21.4, 21.5, 22.2 and/or 22.4. Form R-1 of fluvastatin sodium can also exhibit an XRPD pattern having one or more 2θ values at about 13.6, 16.5, 19.2, 19.5, 19.7, 20.0, 23.54, 23.7, 23.9, 25.3, 25.9, 26.1, 26.3, 26.9, 27.1, 27.2, 27.9, 28.1, 28.3, 28.8, 29.0, 29.4,
25 29.8, 30.1, 31.1, 32.1, 32.5 and/or 33.2. An example of an XRPD of Form R-1 of fluvastatin sodium is depicted in Figure 5.

Form R-1 of fluvastatin sodium can have water content of about 1.5 to 3 % as determined by, for example, Karl Fischer analysis. Form R-1 of fluvastatin sodium can exhibit one or more FTIR absorption peaks at about: 1574, 1500, 1456, 1403, 1371, 1346,
30 1216, 1155, 1106, 1068, 1019, 970, 944, 926, 886, 838, 814, 740, 718, 688, 651, 565

and/or 522 (all values in cm^{-1}). An example of a Fourier Transform Infrared (FTIR) spectrum of Form R-1 of fluvastatin sodium in potassium bromide is depicted in Figure 6.

Also provided are processes for preparing novel polymorphic Form R-1 of fluvastatin sodium comprising the steps of:

- 5 a) lyophilizing a solution of fluvastatin sodium in water and optionally one or more organic solvents to form a lyophilized product,
- b) slurrying the lyophilized product in a mixture of one or more lower alcohols and water to form a slurry, and
- 10 c) isolating novel polymorphic Form R-1 of fluvastatin sodium from the slurry thereof followed by drying the product by conventional means.

A solution of fluvastatin sodium in water and optionally one or more organic solvents can be lyophilized using a freeze-dryer under conditions to facilitate lyophilization. The obtained lyophilized product can be slurried in a mixture of one or more lower alcohols and water. The lyophilized product can be separated/isolated and
15 dried by conventional means (for example, under vacuum and at ambient temperatures to about 60 °C, preferably between about 30 °C to about 50 °C, more preferably between about 35 °C to about 40 °C) to yield Form R-1 of fluvastatin sodium. Suitable organic solvents include alcohols (*e.g.*, methanol, ethanol, isopropanol), acetonitrile, acetone, tetrahydrofuran, 1,4-dioxane or mixtures thereof. Suitable lower alcohols include
20 methanol, ethanol, n-propanol, isopropanol, tert-butanol and the like, or mixture thereof.

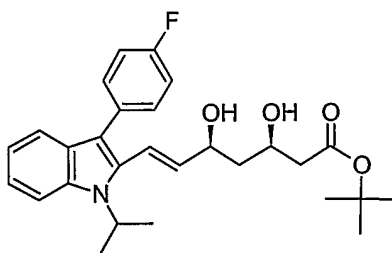
Also provided is novel polymorphic Form R-2 of fluvastatin sodium. Form R-2 of fluvastatin sodium can exhibit an XRPD pattern having one or more 2θ values at about 3.4, 9.3, 10.1, 10.8, 17.2 and/or 25.2. Form R-2 of fluvastatin sodium can also exhibit an XRPD pattern having one or more 2θ values at about 13.5, 14.8, 15.7, 17.3, 17.9, 19.3,
25 20.0, 21.9, 22.4 and/or 34.1. Form R-2 of fluvastatin sodium can also exhibit an XRPD pattern having one or more 2θ values at about 6.2, 7.9, 11.6, 11.7, 11.8, 12.2, 12.3, 15.5, 15.8, 16.0, 17.8, 18.1, 18.9, 19.0, 19.4, 20.4, 20.5, 21.0, 21.7, 22.5, 22.9, 23.4, 23.6, 23.9, 24.5, 25.9, 26.2, 26.5, 26.7, 27.0, 27.3, 27.5, 27.8, 28.3, 28.8, 28.9, 29.0, 29.3, 29.7, 30.1, 30.5, 30.9, 31.3, 31.7, 32.1, 32.4 and/or 32.5. An example of an XRPD pattern of Form R-
30 2 of fluvastatin sodium is depicted in Figure 7.

Form R-2 of fluvastatin sodium can have water content of about 5.0 to 6.5 % as determined by, for example, Karl Fischer analysis. Form R-2 of fluvastatin sodium can exhibit one or more FTIR absorptions at about: 1574, 1500, 1456, 1418, 1371, 1345, 1215, 1156, 1107, 1070, 1021, 973, 840, 814, 740, 655, 565 and/or 523. An example of a
5 Fourier Transform Infrared (FTIR) spectrum of Form R-2 of fluvastatin sodium in potassium bromide is depicted in Figure 8.

Also provided are processes for preparing form R-2 of fluvastatin sodium comprising the steps of:

- 10 a) dissolving fluvastatin sodium in water and one or more organic solvents to form a first mixture,
- b) adding one or more additional organic solvents to the first mixture to precipitate fluvastatin sodium from the first mixture thereof,
- c) dissolving the precipitate in water and optionally one or more organic solvents to form a second mixture,
- 15 d) lyophilizing the second mixture obtained in step c), and
- e) isolating Form R-2 of fluvastatin sodium from the second mixture thereof.

Fluvastatin sodium can be dissolved in one or more organic solvents and water to form a first mixture. Alternatively, the first mixture can be prepared, for example, by following procedure. *Tert*-butyl ester of fluvastatin of Formula II



20 **FORMULA II**

can be contacted with sodium hydroxide in water and one or more organic solvents. Suitable organic solvents can be one or more of alcohols (*e.g.*, methanol, ethanol, isopropanol), acetonitrile, acetone, tetrahydrofuran, 1,4-dioxane or mixtures thereof. The

volume of the solvent can be reduced a specific volume (for example, solvent can be removed completely or partially removed).

One or more additional organic solvents in which fluvastatin sodium is slightly soluble, sparingly soluble, practically insoluble or insoluble can be added to the first
5 mixture to form a precipitate of fluvastatin sodium. Such additional organic solvents can be one or more aliphatic ethers, hexane, heptane, petroleum ethers or mixtures thereof.

The precipitate of fluvastatin sodium can be isolated and dissolved in water and optionally one or more organic solvents to form a second mixture. Suitable organic solvents can be one or more of methanol, ethanol, isopropanol, acetonitrile, acetone,
10 tetrahydrofuran, 1,4-dioxane or mixtures thereof. The second mixture can be lyophilized using a freeze-dryer under conditions sufficient to facilitate lyophilization. For example, the freeze dryer can be operated under vacuum at about 150 mT (mTorr) at about -20 to -80 °C for about 2 to 12 hours followed by maintaining temperature at about -10 to 10 °C for about 2 to 12 hours. The freeze dryer can then be maintained at about 20-30 °C for
15 about 2 to 8 hours, followed by raising the temperature to about 40 °C for about 2 to 10 hours and finally maintained at about 25 °C for about 2 to 8 hours. After lyophilization, the product obtained is Form R2 of fluvastatin sodium.

Also provided herein is novel polymorphic Form R-3 of fluvastatin sodium. Form R-3 of fluvastatin sodium can exhibit an XRPD pattern having one or more 2θ values at
20 about 3.4, 10.3, 17.7 and/or 18.2. Form R-3 of fluvastatin sodium can also exhibit an XRPD pattern having one or more 2θ values at about 10.8, 12.3, 13.7 and/or 25.3. Form R-3 of fluvastatin sodium can also exhibit an XRPD pattern having one or more 2θ values at about 6.8, 14.4, 15.2, 16.1, 16.4, 16.7, 19.3, 19.9, 20.2, 20.8, 21.3, 21.5, 21.7, 21.9, 22.1, 22.8, 23.3, 23.4, 23.6, 24.1, 24.3, 26.0, 26.4, 27.7, 28.0, 28.3, 29.3, 29.9, 30.9, 31.3
25 and/or 31.5. An example of an XRPD pattern of Form R-3 of fluvastatin sodium is depicted in Figure 9.

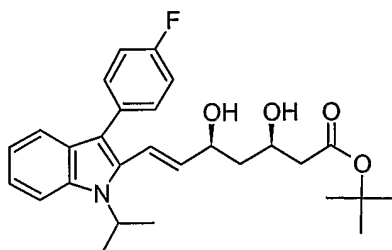
Form R-3 of fluvastatin sodium can have water content of about 13 to 16 %, as determined by, for example, Karl Fischer analysis. Form R-3 of fluvastatin sodium can exhibit one or more FTIR absorption peaks at about: 1567, 1499, 1456, 1402, 1372, 1347,
30 1215, 1156, 1138, 1107, 1095, 1071, 970, 943, 888, 839, 813, 740, 718, 656, 565 and/or

523 (all values in cm^{-1}). An example of a FTIR spectrum of Form R-3 of fluvastatin sodium in potassium bromide is depicted in Figure 10.

Also provided are processes for preparing novel polymorphic Form R-3 of fluvastatin sodium comprising the steps of:

- 5 a) dissolving fluvastatin sodium in water and one or more organic solvents to form a first mixture,
- b) adding one or more additional organic solvents to the first mixture to precipitate fluvastatin sodium from the first mixture thereof,
- c) dissolving the precipitate in one or more organic solvents and optionally
10 water to form a second mixture,
- d) spray-drying the second mixture obtained in step c), and
- e) isolating Form R-3 of fluvastatin sodium followed by drying by conventional means.

Fluvastatin sodium can be dissolved in one or more organic solvents and water to
15 form a first mixture. Alternatively, the first mixture can be prepared, for example, by following procedure. *Tert*-butyl ester of fluvastatin of Formula II



FORMULA II

can be contacted with sodium hydroxide in water and one or more organic solvents.
20 Suitable organic solvents can be one or more of alcohols (*e.g.*, methanol, ethanol, isopropanol), acetonitrile, acetone, tetrahydrofuran, 1,4-dioxane or mixtures thereof. The volume of the solvent can be reduced a specific volume (for example, solvent can be removed completely or partially removed).

One or more additional organic solvents, in which fluvastatin sodium is slightly
25 soluble, sparingly soluble, practically insoluble or insoluble, can be added to the first

mixture to form a precipitate of fluvastatin sodium. Such additional solvents include diethyl ether, diisopropyl ether, methyl isobutyl ether, methyl tert-butyl ether, hexane, heptane, petroleum ether or mixtures thereof.

The precipitate can be isolated and dissolved in one or more organic solvents and optionally water to form a second mixture. The second mixture can be subjected to spray-drying. The spray drying may be accomplished using a spray-dryer, which operates on the principle of nozzle spraying in a parallel flow, *i.e.*, the sprayed material and the drying gas each flow in the same direction. The drying gas can be air or one or more inert gases, for example, nitrogen, argon or carbon dioxide. The gas inlet temperature can be about 30-50 °C, about 35-45 °C, or even about 40 °C. The gas outlet temperature can be about 50-80 °C, 60-70 °C, or even about 65 °C. The product obtained is dried by conventional means to yield form R-3 of fluvastatin sodium.

Also provided is novel polymorphic Form R-4 of fluvastatin sodium. Form R-4 of fluvastatin sodium can exhibit an XRPD pattern having one or more 2θ at about 3.7, 10.5, 10.8, 17.6 and/or 18.2. Form R-4 of fluvastatin sodium can also exhibit an XRPD pattern having one or more 2θ values at about 11.8, 13.9, 21.4, 22.3 and/or 25.3. Form R-4 of fluvastatin sodium can also exhibit an XRPD pattern having one or more 2θ values at about 11.0, 13.4, 13.8, 14.5, 14.7, 15.9, 16.1, 17.6, 18.2, 19.2, 19.7, 20.4, 21.1, 21.7, 22.7, 23.0, 23.8, 24.0, 24.2, 25.1, 25.6, 26.3, 29.8, 30.2, 30.4, 30.7, 31.8, 32.6 and/or 33.0. Form R-4 of fluvastatin sodium can have water content of about 5.0 to 6.5 % as determined by, for example, Karl Fischer analysis. An example of an XRPD pattern of Form R-4 of fluvastatin sodium is depicted in Figure 11.

Also provided are processes for preparing Form R-4 of fluvastatin sodium comprising the steps of:

- a) lyophilizing a mixture of fluvastatin sodium in water and optionally one or more organic solvents,
- b) isolating Form R-4 of fluvastatin sodium from the mixture thereof, and
- c) drying Form R-4 of fluvastatin sodium by conventional means.

A mixture of fluvastatin sodium in water and optionally one or more organic solvents can be lyophilized using a freeze dryer under conditions sufficient to facilitate

lyophilization. For example, the freeze dryer can be operated under vacuum of about 150 mT (mTorr) at about -20 to -80 °C for about 2 to 12 hours followed by maintaining at about -10 to 10 °C for about 2 to 12 hours. The freeze dryer can then be maintained at about 20 to 30 °C for about 2 to 8 hours followed by raising the temperature to about 40 °C for about 2 to 10 hours, and finally maintained at about 25 °C for about 2 to 8 hours. Suitable organic solvents can be one or more of alcohols (*e.g.*, methanol, ethanol, isopropanol), acetonitrile, acetone, tetrahydrofuran, 1,4-dioxane or mixtures thereof.

The product obtained after lyophilization can be dried by conventional means to yield Form R-4 of fluvastatin sodium.

Also provided is novel polymorphic Form R-5 of fluvastatin sodium. Form R-5 of fluvastatin sodium can exhibit an XRPD pattern having one or more 2θ at about 3.3, 10.0, 13.4, 17.6 and/or 18.1. Form R-5 of fluvastatin sodium can also exhibit an XRPD pattern having one or more 2θ values at about 6.7, 20.3, 21.6, 21.7, 25.2 and/or 25.3. Form R-5 of fluvastatin sodium can also exhibit an XRPD pattern having one or more 2θ values at about 10.9, 12.0, 12.6, 13.4, 14.3, 14.8, 15.1, 16.2, 16.6, 17.6, 18.1, 19.0, 19.2, 19.6, 20.3, 20.7, 21.3, 21.6, 21.7, 22.1, 24.1, 24.3, 24.6, 24.8, 25.1, 25.2, 25.3, 25.8, 27.1, 27.7, 27.9, 28.3, 28.8, 29.3, 29.5, 29.9, 30.2, 31.5, 32.0, 32.2, 32.7 and 33.0. An example of an XRPD pattern of Form R-5 of fluvastatin sodium is depicted in Figure 12.

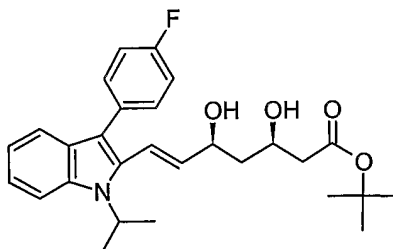
Form R-5 of fluvastatin sodium can have water content of about 12 to 14 % as determined by, for example, Karl Fischer analysis. An example of a FTIR spectrum of Form R-5 of fluvastatin sodium in potassium bromide is depicted in Figure 13.

Also provided are processes for preparing Form R-5 of fluvastatin sodium comprising the steps of:

- a) dissolving fluvastatin sodium in water and one or more organic solvents to form a first mixture,
- b) adding one or more additional organic solvents to the first mixture to precipitate fluvastatin sodium from the first mixture thereof,
- c) dissolving the precipitate in water and optionally one or more organic solvents to form a second mixture,
- d) lyophilizing the second mixture obtained in step c),

- e) isolating Form R-5 of fluvastatin sodium from the second mixture thereof.

Fluvastatin sodium can be dissolved in one or more organic solvents and water to form a first mixture. Alternatively, the first mixture can be prepared, for example, by following procedure. *Tert*-butyl ester of fluvastatin of Formula II



FORMULA II

can be contacted with sodium hydroxide in water and one or more organic solvents. Suitable organic solvents can be one or more of alcohols (*e.g.*, methanol, ethanol, isopropanol), acetonitrile, acetone, tetrahydrofuran, 1,4-dioxane or mixtures thereof. The volume of the solvent can be reduced a specific volume (for example, solvent can be removed completely or partially removed).

One or more additional organic solvents, in which fluvastatin sodium is slightly soluble, sparingly soluble, practically insoluble or insoluble, can be added to the first mixture to form a precipitate of fluvastatin sodium. Such additional solvents include diethyl ether, diisopropyl ether, methyl isobutyl ether, methyl *tert*-butyl ether, hexane, heptane, petroleum ether or mixtures thereof.

The precipitate of fluvastatin sodium can be isolated and dissolved in water and optionally one or more organic solvents to form a second mixture. Suitable organic solvents can be one or more of alcohols (*e.g.*, methanol, ethanol, isopropanol), acetonitrile, acetone, tetrahydrofuran, 1,4-dioxane or mixtures thereof. The second mixture can be lyophilized using a freeze-dryer under conditions sufficient to facilitate lyophilization. For example, the freeze dryer can be operated under vacuum of about 150 mT (mTorr) at about -20 to -80 °C for about 2 to 12 hours followed by maintaining temperature at about -10 to 10 °C for about 2 to 12 hours. The freeze dryer can then be maintained at about 20 to 30 °C for about 2 to 8 hours followed by raising the temperature to about 40 °C for

about 2 to 10 hours, and finally at about 25 °C for about 2 to 8 hours. After lyophilization, the product obtained is Form R-5 of fluvastatin sodium.

Also provided is novel amorphous Form R-6 of fluvastatin sodium. Form R-6 of fluvastatin sodium can have an XRPD pattern as depicted, for example, in Figure 14.

- 5 Form R-6 of fluvastatin sodium can have water content of about 0.5 to 2.0 % as determined by, for example, Karl Fischer analysis. A FTIR spectrum of Form R-6 of fluvastatin sodium in potassium bromide is depicted, for example, in Figure 15.

Also provided are processes for preparing novel polymorphic Form R-6 of fluvastatin sodium comprising the steps of:

- 10 a) contacting fluvastatin sodium with tetrahydrofuran to form a mixture,
b) adding a seed amount of amorphous Form R-6 of fluvastatin sodium to the mixture obtained in step a),
c) isolating Form R-6 of fluvastatin sodium from the reaction mass thereof.

- 15 Fluvastatin sodium can be contacted with tetrahydrofuran to form a mixture. The resultant mixture can be seeded with the addition of amorphous Form R-6 of fluvastatin sodium and then stirred at ambient temperature. The seed amounts of amorphous Form R-6 of fluvastatin sodium can range from to about 0.1 % to 50 % w/w of the initial amount of fluvastatin sodium in the mixture, preferably from about 0.5 % to about 10 % w/w, more preferably from about 1 % to about 2.5 % w/w. After the mixture is seeded, it can
20 be stirred for a time sufficient to precipitate Form R-6 of fluvastatin sodium (for example, for about 6 to about 96 hours, preferably from about 24 to about 72 hours, more preferably for about 48 hours). The mixture can then be filtered under inert atmosphere (*e.g.*, nitrogen, argon, helium) and solid obtained can be dried by conventional means (for example, under vacuum and at ambient temperatures to about 60 °C) to yield Form R-6 of
25 fluvastatin sodium.

- Fluvastatin sodium used in step a) can be prepared by the following procedure. Fluvastatin *tert*-butyl ester can be contacted with sodium hydroxide in water and one or more organic solvents to form a reaction mixture. Suitable organic solvents can be one or more of alcohols (*e.g.*, methanol, ethanol, isopropanol), acetonitrile, acetone,
30 tetrahydrofuran, 1,4-dioxane or mixtures thereof. After the reaction is completed, the

reaction mixture can be concentrated and the residue can be contacted with tetrahydrofuran. After stirring for about 10 to 30 hours, fluvastatin sodium is filtered, and can be used to prepare amorphous Form R-6 of fluvastatin sodium, as described above.

Also provided is novel polymorphic Form R-7 of fluvastatin sodium. Form R-7 of fluvastatin sodium can exhibit an XRPD pattern having one or more 2θ values at about 3.3, and/or 11.5. Form R-7 of fluvastatin sodium can also exhibit an XRPD pattern having one or more 2θ values at about 6.5, 8.2, 9.6, 19.9, 22.0, 22.1, 22.3 and/or 25.8. Form R-7 of fluvastatin sodium can also exhibit an XRPD pattern having one or more 2θ values at about 16.6, 17.5, 18.1, 18.5, 18.9, 19.2, 19.6, 20.5, 21.0, 21.3, 23.1, 23.2, 23.8, 24.0, 24.6, 24.9, 25.1, 26.9, 27.4, 27.9, 28.6, 29.2, 29.5, 29.8 and/or 30.1. An example of an XRPD pattern of Form R-7 of fluvastatin sodium is depicted in Figure 16.

Form R-7 of fluvastatin sodium can have water content of about 0.7 to 1.5 % as determined by, for example, Karl Fischer analysis. Form R-7 of fluvastatin sodium can exhibit one or more FTIR absorption peaks at about: 1578, 1536, 1500, 1456, 1418, 1371, 1341.92, 1217, 1156, 1106, 1068, 975, 940, 887, 839, 813, 740, 690, 655, 565 and/or 523 (all values are in cm^{-1}). An example of a FTIR spectrum of Form R-7 of fluvastatin sodium in potassium bromide is depicted in Figure 17.

Also provided are processes for preparing novel polymorphic Form R-7 of fluvastatin sodium comprising the steps of:

- a) contacting amorphous form of fluvastatin sodium with tetrahydrofuran to form a mixture, and
- b) isolating Form R-7 of fluvastatin sodium from the mixture thereof.

Amorphous form of fluvastatin sodium can be contacted with tetrahydrofuran and the resultant mixture can be stirred at ambient temperature for a time sufficient for the amorphous form to completely convert to Form R-7 of fluvastatin sodium. The mixture can then be filtered under inert atmosphere (for example, nitrogen, argon, helium) and solid obtained can be dried using conventional means (for example, under vacuum and at ambient temperatures to about 60 °C) to yield Form R-7 of fluvastatin sodium.

Also provided is novel polymorphic Form R-8 of fluvastatin sodium. Form R-8 of fluvastatin sodium can exhibit an XRPD pattern having 2θ values at about 3.7, 4.0, 12.1,

18.3, 19.6, 20.3 and/or 37.1. Form R-8 of fluvastatin sodium can also exhibit an XRPD pattern having 2θ values at about 15.6, 16.2, 19.6, 21.4, 22.5, 25.4, 26.2 and/or 28.6.

Form R-8 of fluvastatin sodium can also exhibit an XRPD pattern having 2θ values at about 11.0, 11.3, 12.9, 14.0, 14.3, 14.8, 17.8, 18.8, 21.7, 23.2, 23.4, 23.8, 24.2, 24.8, 26.9, 5 32.1, 32.4, 32.8 and/or 33.0. An example of an XRPD of Form R-8 of fluvastatin sodium is depicted in Figure 18.

Form R-8 of fluvastatin sodium can have water content of about 2.5 to 4.5 % as determined by, for example, Karl Fischer analysis. Form R-8 of fluvastatin sodium can exhibit one or more FTIR absorptions at about 1587, 1535, 1497, 1455, 1385, 1336, 1238, 10 1215, 1156, 1138, 1104, 1058, 1041, 1012, 966, 943, 912, 877, 841, 815, 740, 692, 603, 564, 536 and/or 483 (all values are in cm^{-1}). An example of a FTIR spectrum of Form R-8 of fluvastatin sodium in potassium bromide is depicted in Figure 19.

Also provided are processes for preparing form R-8 of fluvastatin sodium comprising the steps of:

- 15 a) dissolving fluvastatin sodium in a solvent mixture of water and one or more lower alcohols to form a mixture,
- b) removing the solvent mixture completely from the mixture obtained in step a) to form a residue,
- c) 20 contacting the residue obtained in step b) with tetrahydrofuran to form a second mixture, and
- d) isolating Form R-8 of fluvastatin sodium from the second mixture thereof.

Fluvastatin sodium can be dissolved in a solvent mixture water and one or more lower alcohols to form a mixture. Lower alcohols include, for example, C_1 - C_6 alcohols. The mixture obtained can be concentrated under vacuum to completely remove the solvent 25 mixture, leaving a residue. The residue can be contacted with tetrahydrofuran to form a second mixture, which can be stirred at ambient temperature for sufficient time to form Form R-8 of fluvastatin sodium. The solids thus obtained are filtered and dried using conventional means (for example, under vacuum and at ambient temperatures to about 60 °C) to yield Form R-8 of fluvastatin sodium.

Also provided is novel polymorphic Form R-9 of fluvastatin sodium. Form R-9 of fluvastatin sodium can exhibit an XRPD pattern having one or more 2θ values at about: 12.9, 20.3, 22.1, 22.5 and/or 23.8. Form R-9 of fluvastatin sodium can also exhibit an XRPD pattern having one or more 2θ values at about 4.0, 12.2, 15.7, 16.3, 21.3 and/or
5 28.7. Form R-9 of fluvastatin sodium can also exhibit an XRPD pattern having one or more 2θ values at about 11.0, 11.2, 17.7, 18.2, 18.8, 19.3, 19.6, 21.7, 24.3, 25.4, 25.6, 26.1, 26.3, 27.0, 29.9, 30.8, 34.7, 35.1 and 37.1. An example of an XRPD pattern is depicted in Figure 20. An example of a FTIR spectrum of Form R-9 of fluvastatin sodium in potassium bromide is depicted in Figure 21.

10 Also provided are processes for preparing Form R-9 of fluvastatin sodium comprising the steps of:

- a) dissolving fluvastatin sodium in a solvent mixture of water and one or more lower alcohols to form a first mixture,
- b) adjusting the pH of the first mixture obtained in step a) to about 7 to 8
15 using an acid to form a second mixture,
- c) contacting one or more lower ketones with the second mixture obtained in step b), and
- d) isolating Form R-9 of fluvastatin sodium from the second mixture thereof.

Fluvastatin sodium can be dissolved in a solvent mixture of one or more lower
20 alcohols and water to form a first mixture. The pH of the first mixture can be adjusted to a slightly basic condition (*i.e.*, pH of about 7 to 8), forming a second mixture. One or more lower ketones can be added to the second mixture and stirred for, for example, about 6-24 hours, preferably about 12 to 20 hours, more preferably about 15 to 18 hours. The obtained solid can then be filtered and dried using conventional means (for example, under
25 vacuum and at ambient temperatures to about 60 °C) to yield Form R-9 of fluvastatin sodium.

Also provided is novel crystalline Form R-10 of fluvastatin sodium. Form R-10 of fluvastatin sodium can exhibit an XRPD pattern having one or more 2θ values at about: 4.0, 12.1 and/or 20.3. Form R-10 of fluvastatin sodium can also exhibit an XRPD pattern
30 having one or more 2θ values at about: 12.9, 15.7, 16.2, 19.6, 22.5, 25.3, 26.3, 28.6 and/or

37.1. Form R-10 of fluvastatin sodium can also exhibit an XRPD pattern having one or more 2θ values at about: 14.9, 17.7, 18.2, 18.8, 21.3, 21.7, 23.8, 24.3, 27.0, 29.9, 30.8, 32.2, 32.8, 35.1, 36.1 and/or 36.5. An example of an XRPD pattern of Form R-10 of fluvastatin sodium is depicted in Figure 22. An example of an FTIR spectrum of Form R-10 of fluvastatin sodium in potassium bromide is depicted in Figure 23.

Also provided are processes for preparing Form R-10 of fluvastatin sodium comprising the steps of:

- a) dissolving fluvastatin sodium in a solvent mixture of one or more lower alcohols and water to form a first mixture,
- 10 b) contacting one or more lower ketones to the first mixture obtained in step a),
- c) isolating Form R-10 of fluvastatin sodium from the first mixture thereof.

Fluvastatin sodium can be dissolved in a solvent mixture of one or more lower alcohols and water to form a first mixture. One or more lower ketones can be contacted with the first mixture and stirred for, for example, about 6-24 hours, preferably about 12 to 20 hours, more preferably about 15 to 18 hours. The obtained solid can then be filtered and dried using conventional means (for example, under vacuum and at ambient temperatures to about 60 °C) to yield Form R-10 of fluvastatin sodium.

Also provided is novel crystalline Form R-11 of fluvastatin sodium. Form R-11 of fluvastatin sodium can exhibit an XRPD pattern having one or more 2θ values at about: 3.4, 10.1, 13.5, 17.7, 18.1 and/or 21.6. Form R-11 of fluvastatin sodium can also exhibit an XRPD pattern having one or more 2θ values at about: 11.9, 21.7, 25.2 and/or 25.6. Form R-11 of fluvastatin sodium can also exhibit an XRPD pattern having one or more 2θ values at about: 12.2, 20.2, 23.8, 26.1, 26.4, 27.4, 27.9, 28.1, 28.5, 29.8, 31.1, 31.6, 32.1 and/or 33.0. An example of an XRPD pattern of Form R-11 of fluvastatin sodium is depicted in Figure 24.

Form R-11 of fluvastatin sodium can have a moisture content of about 9 to 10.5 % w/w. An example of a FTIR spectrum of Form R-11 of fluvastatin sodium in potassium bromide is depicted in Figure 25.

Also provided are processes for preparing Form R-11 of fluvastatin sodium comprising the steps of:

- a) suspending fluvastatin sodium in water to form a suspension,
- b) contacting one or more ketones, alcohols, ethers or mixtures thereof to the suspension obtained in step a) to form a first mixture,
- c) contacting a salt solution with the first mixture obtained in step b) and forming a precipitate,
- d) isolating the precipitate,
- e) contacting the precipitate obtained in step d) with one or more ethers, C₅₋₇ alkanes, C₅₋₇ cycloalkanes, petroleum ethers, alcohols or mixtures thereof to form a second mixture.
- f) isolating Form R-11 of fluvastatin sodium from the second mixture thereof.

Fluvastatin sodium can be suspended in water to form a suspension. One or more ketones, alcohols, ethers or mixtures thereof can be contacted with the suspension to form a first mixture. The first mixture is typically a clear solution. A salt solution can be contacted with the first mixture to form a precipitate. The salt solution can comprise from about 1 to 35 % w/v of a sodium salt, for example sodium chloride. The precipitate can be filtered and washed with water and ether. The isolated precipitate can be contacted with one or more ethers, C₅₋₇ alkanes, C₅₋₇ cycloalkanes, petroleum ethers, alcohols or mixtures thereof to form a second mixture, stirred, filtered and dried using conventional means (for example, under vacuum and at ambient temperatures to about 60 °C) to yield Form R-11 of fluvastatin sodium.

Also provided is novel crystalline Form R-12 of fluvastatin sodium. Form R-12 of fluvastatin sodium can exhibit an XRPD pattern having one or more 2θ values at about: 3.7, 11.0, 12.9, 17.7, 18.4 and/or 20.3 25.5. Form R-12 of fluvastatin sodium can also exhibit an XRPD pattern having one or more 2θ values at about: 9.2, 14.7, 15.7, 21.3, 21.7 and/or 25.5. Form R-12 of fluvastatin sodium can also exhibit an XRPD pattern having one or more 2θ values at about: 7.2, 10.4, 12.2, 13.5, 15.3, 16.3, 16.8, 18.9, 19.4, 19.5, 22.0, 24.2, 24.4, 25.9, 26.8, 27.1, 28.0, 28.1, 29.7, 29.9, 31.9, 32.2, 33.0, 34.9 and/or 35.3. An example of an XRPD pattern of Form R-12 of fluvastatin sodium is depicted in Figure

26. Novel crystalline Form R-12 of fluvastatin sodium can have a moisture content of about 4.5 to 6.5 % w/w.

Also provided are processes for preparing Form R-12 of fluvastatin sodium comprising the steps of:

- 5 a) contacting fluvastatin sodium with one or more ethers to form a first mixture and stirring the first mixture,
- b) contacting water, one or more ethers and one or more ketones to the first mixture obtained in step a) to form a second mixture, and
- c) isolating Form R-12 of fluvastatin sodium from the second mixture thereof.

10 Fluvastatin sodium can be stirred with one or more ethers to form a first mixture. After stirring the first mixture, water, one or more ethers and one or more ketones can be contacted with the first mixture to form a second mixture. A solid thus obtained can then be filtered and dried using conventional means (for example, under vacuum and at ambient temperatures to about 60 °C) to yield Form R-12 of fluvastatin sodium.

15 Also provided is novel crystalline Form R-13 of fluvastatin sodium. Form R-13 of fluvastatin sodium can exhibit an XRPD pattern having one or more 2θ values at about: 4.2, 5.2, 6.6, 8.5 and/or 16.6. Form R-13 of fluvastatin sodium can also exhibit an XRPD pattern having one or more 2θ values at about: 3.3, 10.0, 12.7, 14.4 and/or 32.2. Form R-13 of fluvastatin sodium can also exhibit an XRPD pattern having one or more 2θ values
20 at about: 13.3, 13.4, 15.3, 16.9, 18.0, 18.5, 21.2, 22.2, 22.8, 23.6, 33.2 and/or 33.42. An example of an XRPD pattern of Form R-13 of fluvastatin sodium is depicted in Figure 27.

Also provided are processes for preparing Form R-13 of fluvastatin sodium comprising the steps of:

- 25 a) contacting fluvastatin sodium with one or more water-miscible solvents and water to form a first mixture and stirring the first mixture,
- b) contacting one or more ethers with the first mixture obtained in step a) to form a second mixture,
- c) isolating Form R-13 of fluvastatin sodium from the second mixture thereof.

Fluvastatin sodium can be contacted with one or more water miscible solvents and water to form a first mixture, and the first mixture can be stirred. One or more ethers can be contacted with the first mixture to form a second mixture and a solid thus obtained can be filtered and dried using conventional means (for example, under vacuum and at ambient temperatures to about 60 °C) to yield Form R-13 of fluvastatin sodium.

Also provided is a significantly amorphous Form R-14 of fluvastatin sodium. Form R-14 of fluvastatin sodium can exhibit an XRPD pattern having 2θ values at about 4.0 and/or 5.4. An example of an XRPD pattern of Form R-14 of fluvastatin sodium is depicted in Figure 28.

Also provided are processes for preparing Form R-14 of fluvastatin sodium comprising the steps of:

- a) dissolving fluvastatin sodium in one or more halogenated hydrocarbons to form a first mixture,
- b) contacting water and one or more ketones to the first mixture obtained in step a) to form a second mixture, and
- c) isolating Form R-14 of fluvastatin sodium from the second mixture thereof.

Fluvastatin sodium can be dissolved in one or more halogenated hydrocarbons to form a first mixture. Water and one or more ketones can be added to the first mixture to form a second mixture. A solid thus obtained can then be filtered and dried using conventional means (for example, under vacuum and at ambient temperatures to about 60 °C) to yield Form R-14 of fluvastatin sodium.

Also provided is novel crystalline Form R-15 of fluvastatin sodium. Form R-15 of fluvastatin sodium can exhibit an XRPD pattern having one or more 2θ values at about: 5.7, 10.8, 13.7 and/or 14.7. Form R-15 of fluvastatin sodium can also exhibit an XRPD pattern having one or more 2θ values at about: 18.3, 18.8, 20.9, 21.3 and/or 22.6. Form R-15 of fluvastatin sodium can exhibit an XRPD pattern having one or more 2θ values at about: 5.4, 8.7, 9.9, 11.2, 14.2, 15.2, 16.2, 16.7, 19.2, 20.1, 22.9, 23.5, 25.1, 26.2, 26.7, 27.2, 27.7, 28.5, 28.9, 29.7, 30.9, 32.1, 33.4 and 37.8. An example of an XRPD pattern of Form R-15 of fluvastatin sodium is depicted in Figure 29.

Also provided are processes for preparing Form R-15 of fluvastatin sodium comprising the steps of:

- a) dissolving fluvastatin sodium in one or more lower alcohols to form a first mixture,
- 5 b) contacting water and one or more ketones with the first mixture obtained in step a), and
- c) isolating Form R-15 of fluvastatin sodium from the first mixture thereof.

Fluvastatin sodium can be dissolved in one or more lower alcohols. Water and one or more ketones can be added to the first mixture followed by seeding with a seed amount
10 of Form R-15 of fluvastatin sodium. Seed amounts of amorphous Form R-15 of fluvastatin sodium can range from about 0.2 % w/w to about 50 % w/w of the initial fluvastatin sodium amount, preferably from about 0.5 % w/w to about 10 % w/w, more preferably from about 1 % w/w to about 2.5 % w/w. The solid thus obtained can then be filtered and dried using conventional means (for example, under vacuum and at ambient
15 temperatures to about 60 °C) to yield Form R-15 of fluvastatin sodium.

Also provided is novel crystalline Form R-16 of fluvastatin sodium. Form R-16 of fluvastatin sodium can exhibit an XRPD pattern having one or more 2θ values at about: 3.6, 14.3, 18.3, 21.4 and/or 24.4. Form R-16 of fluvastatin sodium can also exhibit an XRPD pattern having one or more 2θ values at about: 10.7, 11.4, 12.1, 15.5, 26.5 and/or
20 27.0. Form R-16 of fluvastatin sodium can exhibit an XRPD pattern having one or more 2θ values at about: 14.7, 16.0, 16.6, 18.8, 19.1, 20.3, 21.9, 23.4, 24.8, 25.5, 28.9, 29.6, 30.2, 30.8, 31.8, 32.4 and 39.6. An example of an XRPD pattern of Form R-16 of fluvastatin sodium is depicted in Figure 30.

Form R-16 of fluvastatin sodium can have a moisture content of about 3.5 to 4.5 %
25 w/w. An example of an FTIR spectrum of Form R-16 of fluvastatin sodium in potassium bromide is depicted in Figure 31. An example of a DSC thermogram of Form R-16 of fluvastatin sodium is depicted in Figure 32. The DSC thermogram shows two endothermic peaks at about 105-130 °C and about 150-165 °C.

Also provided are processes for preparing Form R-16 of fluvastatin sodium
30 comprising the steps of:

- a) contacting one or more esters of fluvastatin with one or more water miscible organic solvents to form a first mixture,
- b) contacting one or more sodium-containing alkali compounds with the first mixture obtained in step a) to form a second mixture,
- 5 c) removing the solvent from the second mixture obtained in step b) and forming a residue,
- d) contacting the residue obtained in step c) with tetrahydrofuran to form a third mixture,
- e) partially concentrating the third mixture obtained in step d),
- 10 f) isolating Form R-16 of fluvastatin sodium from the partially concentrated third mixture thereof.

Fluvastatin sodium can be contacted with one or more water miscible organic solvents and one or more sodium-containing alkali compound is added. Sodium-containing alkali compounds include sodium hydroxide, sodium carbonate, sodium bicarbonate, sodium alkoxide, sodium alkanoate or mixtures thereof. The solvent in the
15 second mixture can be removed, leaving a residue, which can be contacted with tetrahydrofuran to form a third mixture. The third mixture can be partially concentrated and, if required, the previous steps are repeated. The partially concentrated third mixture can be stirred and a solid thus obtained can be dried using conventional means (for
20 example, under vacuum and at ambient temperatures to about 60 °C) to yield form R-16 of fluvastatin sodium.

Also provided is an anhydrous crystalline fluvastatin sodium. Anhydrous crystalline fluvastatin can exhibit an XRPD pattern having one or more 2θ values at about: 4.2, 10.4, 18.6, 21.3 and/or 24.5. Anhydrous crystalline fluvastatin can also exhibit an
25 XRPD pattern having one or more 2θ values at about: 5.2, 8.5, 10.9, 15.4, 16.5, 19.5, 22.3, 22.0, 23.0 and/or 26.3. Anhydrous crystalline fluvastatin can exhibit an XRPD pattern having one or more 2θ values at about: 6.2, 7.2, 13.6, 14.4, 14.8, 17.2, 17.6, 18.0, 18.8, 20.9, 22.8, 23.5, 24.0, 25.0, 25.8, 27.0, 28.1, 28.4, 29.1, 29.2, 29.7, 30.4, 30.6, 31.4, 31.6, 32.2, 32.4, 32.9, 33.7, 34.0, 34.8 and 38.0. An example of an XRPD pattern exhibited by
30 anhydrous crystalline fluvastatin is depicted in Figure 33.

An example of a FTIR spectrum of anhydrous crystalline fluvastatin sodium in potassium bromide is depicted in Figure 34. An example of a DSC thermogram of anhydrous crystalline fluvastatin sodium is depicted in Figure 35. The DSC thermogram exhibits an endothermic peak at about 198-210 °C. The anhydrous crystalline fluvastatin sodium of the present invention can have moisture content of about 0.5 % w/w or less as determined by, for example, Karl-Fischer Analysis.

Also provided are processes for preparing anhydrous crystalline fluvastatin sodium comprising the steps of:

- a) contacting fluvastatin sodium with one or more organic solvents and optionally water to form a first mixture, and acidifying the first mixture with an acid to form an acidified first mixture,
- b) isolating a solid residue from the acidified first mixture obtained in step a),
- c) forming a second mixture by contacting the solid residue of step b) with one or more sodium-containing alkali compounds in the presence of one or more ethers,
- d) isolating anhydrous crystalline fluvastatin sodium from the second mixture thereof.

Fluvastatin sodium can be suspended in one or more organic solvents and optionally water to form a first mixture. The first mixture can be acidified with an acid to a pH of about 1.5 to 3 to form an acidified first mixture. The acidified first mixture can be concentrated by removing solvent, leaving a residue. The residue obtained can be contacted with one or more sodium-containing alkali compounds in presence of one or more ethers to form a second mixture. Sodium-containing alkali compounds can be selected from sodium hydroxide, sodium carbonate, sodium bicarbonate, sodium alkoxide (e.g., sodium methoxide), sodium alkanoate (e.g., sodium 2-ethylhexanoate) or mixtures thereof.

The second mixture can be stirred and crystals of anhydrous crystalline fluvastatin sodium thus obtained can be separated from the second mixture. The crystalline fluvastatin sodium can be dried under vacuum to yield anhydrous crystalline fluvastatin sodium.

Also provided herein are pharmaceutical compositions comprising the described forms of fluvastatin sodium. Thus, for example, provided are pharmaceutical compositions comprising:

a) one or more:

- 5 substantially amorphous fluvastatin sodium;
 Form R-1 of fluvastatin sodium;
 Form R-2 of fluvastatin sodium;
 Form R-3 of fluvastatin sodium;
 Form R-4 of fluvastatin sodium;
10 Form R-5 of fluvastatin sodium;
 Form R-6 of fluvastatin sodium;
 Form R-7 of fluvastatin sodium;
 Form R-8 of fluvastatin sodium;
 Form R-9 of fluvastatin sodium;
15 Form R-10 of fluvastatin sodium;
 Form R-11 of fluvastatin sodium;
 Form R-12 of fluvastatin sodium;
 Form R-13 of fluvastatin sodium;
 Form R-14 of fluvastatin sodium;
20 Form R-15 of fluvastatin sodium;
 Form R-16 of fluvastatin sodium;
 anhydrous crystalline fluvastatin sodium; or
 mixtures thereof;

 and optionally comprising one or more pharmaceutically acceptable diluents or
25 excipients.

Also provided herein are methods of antagonizing HMG-CoA in a mammal, which comprises administering to the mammal therapeutically effective amounts of one or more of the following:

- substantially amorphous fluvastatin sodium;
- 5 Form R-1 of fluvastatin sodium;
- Form R-2 of fluvastatin sodium;
- Form R-3 of fluvastatin sodium;
- Form R-4 of fluvastatin sodium;
- Form R-5 of fluvastatin sodium;
- 10 Form R-6 of fluvastatin sodium;
- Form R-7 of fluvastatin sodium;
- Form R-8 of fluvastatin sodium;
- Form R-9 of fluvastatin sodium;
- Form R-10 of fluvastatin sodium;
- 15 Form R-11 of fluvastatin sodium;
- Form R-12 of fluvastatin sodium;
- Form R-13 of fluvastatin sodium;
- Form R-14 of fluvastatin sodium;
- Form R-15 of fluvastatin sodium;
- 20 Form R-16 of fluvastatin sodium;
- anhydrous crystalline fluvastatin sodium; or
- mixtures thereof.

Powder XRD of the samples can be determined by using X-Ray Diffractometer, Rigaku Corporation, RU-H3R, Goniometer CN2155A3, X-Ray tube with Cu target anode, 25 Divergence slits 1°, Receiving slit 0.15mm, Scatter slit 1°, Power: 40 KV, 100 mA, Scanning speed: 2 deg/min step: 0.02 deg, Wave length: 1.5406 Å

FT-IR of the samples can be determined by using Instrument: Perkin Elmer, 16 PC, SCAN: 16 scans, 4.0 cm^{-1} , according to the USP 25, general test methods page 1920, infrared absorption spectrum by potassium bromide pellet method.

While the present invention has been described in terms of its specific
5 embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention. The examples are provided to illustrate particular aspects of the disclosure and do not limit the scope of the present invention as defined by the claims.

10

EXAMPLES

Example 1: Preparation of Substantially Amorphous Fluvastatin Sodium

Crude fluvastatin sodium (50 g) having a moisture content about 4.0 % w/w was suspended in tetrahydrofuran (1000 mL) at room temperature. The mixture obtained was heated to 40 °C and stirred until the solids were entirely dissolved. The solvent was
15 slowly evaporated from the mixture to remove water azeotropically. The volume of mixture was concentrated to approximately 125 mL followed by the subsequent addition and removal of tetrahydrofuran (100 mL). The resultant solution (volume about 125 mL) was cooled to room temperature, cyclohexane (750 mL) was added dropwise and the mixture was stirred at room temperature for 30 minutes. The precipitated product was
20 filtered and dried under vacuum at 35 °C to 40°C to yield the title compound. All steps were carried out under nitrogen atmosphere and anhydrous conditions.

Yield: 40.0 g

Water (% w/w by KF): 0.06 %

XRD and FTIR as per Figure 1 and 2 respectively.

25 Example 2: Preparation of Substantially Amorphous Fluvastatin Sodium

Crude fluvastatin sodium (50 g) having a moisture content about 4.0 % w/w was suspended in tetrahydrofuran (1000 mL) at room temperature. The mixture obtained was heated to 40 °C and stirred until the solids were completely dissolved. The solvent was slowly evaporated from the mixture to remove water azeotropically. The volume of the

mixture was concentrated to approximately 125 mL followed by the subsequent addition and removal of tetrahydrofuran (100 mL). The residue obtained as oil was dissolved in dichloromethane (100 mL). The resultant solution was cooled to room temperature, cyclohexane (750 mL) was added dropwise and the mixture was stirred at room
5 temperature for 30 minutes. The precipitated product was filtered and dried under vacuum at 35 °C to 40 °C to yield the title compound. All steps were carried out under nitrogen atmosphere and anhydrous conditions.

Yield: 38.0 g

Water (% w/w by KF): 0.06 %

10 XRD and FTIR as per Figure 1 and 2 respectively.

Example 3: Preparation of Substantially Amorphous Fluvastatin Sodium

Crude fluvastatin sodium (50 g) having a moisture content about 4.0 % w/w was suspended in tetrahydrofuran (1000 mL) at room temperature. The mixture obtained was
15 heated to 40 °C and stirred until the solids were completely dissolved. The solvent was evaporated slowly from the mixture to remove water azeotropically and the volume of mixture was concentrated to approximately 125 mL followed by subsequent addition and removal of tetrahydrofuran (100 mL). The residue obtained was an oil, which was dissolved in dichloromethane (100 mL). The resultant solution was cooled to room
20 temperature and subjected to spray drying. The product was further dried under vacuum at 35 to 40 °C to yield the title compound. All steps were carried out under nitrogen atmosphere and anhydrous conditions.

Yield: 35.0 g

Water (% w/w by KF): 1.3 %

25 XRD and FTIR as per Figure 1 and 2 respectively.

Example 4: Preparation of Substantially Amorphous Fluvastatin Sodium

Crude fluvastatin sodium (5 g) having a moisture content about 4.0 % w/w was suspended in tetrahydrofuran (50 mL) at room temperature. The mixture was then heated to 40 °C and stirred until the solids were completely dissolved. The solvent was then

evaporated slowly from the mixture to remove water azeotropically and the volume of mixture was concentrated to approximately 10 mL followed by subsequent addition and removal of tetrahydrofuran (10 mL). The solution obtained (volume about 10 mL) was cooled to room temperature and added dropwise to n-heptane (50 mL), followed by
5 stirring at room temperature for 30 minutes. The precipitated product was filtered and dried under vacuum at 35° to 40°C to yield the title compound. All steps were carried out under nitrogen atmosphere and anhydrous conditions.

Yield: 3.50 g

Water (% w/w by KF): 0.06 %

10 XRD and FTIR as per Figure 1 and 2 respectively.

Example 5: Preparation of Substantially Amorphous Fluvastatin Sodium

Crude fluvastatin sodium (5 g) having a moisture content about 4.0 % w/w was suspended in tetrahydrofuran (50 mL) at room temperature. The mixture obtained was
15 heated to 40 °C and stirred until the solids were completely dissolved. The solvent was evaporated slowly from the mixture to remove water azeotropically and the volume of mixture was concentrated to approximately 10 mL followed by subsequent addition and removal of tetrahydrofuran (10 mL). The solution obtained (volume about 10 mL) was cooled to room temperature and added dropwise to n-heptane (50 mL) followed by stirring
20 at room temperature for 30 minutes. The precipitated product was filtered and dried under vacuum at 35 to 40 °C to yield the title compound. All steps were carried out under nitrogen atmosphere and anhydrous conditions.

Yield: 4.1 g

Water (% w/w by KF): 0.05 %

25 XRD and FTIR as per Figure 1 and 2 respectively.

Example 6: Preparation of Substantially Amorphous Fluvastatin Sodium

Crude fluvastatin sodium (5 g) having a moisture content about 4.0 % w/w was suspended in tetrahydrofuran (50 mL) at room temperature. The mixture obtained was

heated to 40 °C and stirred until the solids were completely dissolved. The solvent was evaporated slowly from the mixture to remove water azeotropically and the volume of mixture was concentrated to approximately 10 mL followed by subsequent addition and removal of tetrahydrofuran (10 mL). The solution obtained (volume about 10 mL) was cooled to room temperature and added dropwise to diisopropyl ether (75 mL) followed by stirring at room temperature for 30 minutes. The precipitated product was filtered and dried under vacuum at 35 °C to 40°C to yield the title compound. All steps were carried out under nitrogen atmosphere and anhydrous conditions.

Yield: 4.1 g

10 Water (% w/w by KF): 0.05 %

XRD and FTIR as per Figure 1 and 2 respectively.

Example 7: Preparation of Substantially Amorphous Fluvastatin Sodium

Crude fluvastatin sodium (0.5 g) having a moisture content about 4.0 % w/w was suspended in tetrahydrofuran (50 mL) at room temperature. The mixture obtained was heated to 40 °C and stirred until the solids were completely dissolved. The solvent was evaporated from the mixture and an oil was obtained, which was dissolved in dichloromethane (1 mL). The solution obtained was then added dropwise to hexane (6 mL) at room temperature followed by stirring for 30 minutes. A precipitate thus formed was filtered and dried under vacuum at 35 °C to 40°C to yield the title compound. All steps were carried out under nitrogen atmosphere and anhydrous conditions

Yield: 0.17 g.

XRD and FTIR as per Figure 1 and 2 respectively.

Example 8: Preparation of Substantially Amorphous Fluvastatin Sodium By Spray Drying

Crystalline fluvastatin sodium (10 g; moisture content 4 % w/w by Karl Fischer analysis) was dissolved in methanol (100 mL) at 25 °C to 30 °C. A clear solution was obtained, which was then spray dried using LAB PLANT mini spray drier (Model SD05). Spray drier was set at a nozzle diameter of 0.5 mm, Inlet temperature: 75 °C, Liquid Flow

Rate: ~350 mL/hour, Compressor Air Pressure: 1.4 Bar, Air Flow Rate: ~45m³/hour.

The product obtained was dried at 40 °C to 45 °C under vacuum to yield the title compound having XRD similar to that depicted in Figure 3.

Yield: 3.2 g

- 5 Moisture content = 2.18 % w/w by Karl-Fischer method

XRD as per Figure 3.

Example 9: Preparation of Substantially Amorphous Fluvastatin Sodium

- Crystalline fluvastatin sodium (300 g; moisture content 4 % w/w by Karl Fischer analysis) was dissolved in methanol (3000 mL) at 25 °C to 30 °C. A clear solution was obtained, which was then spray dried using a 0.5 mm pressure nozzle having an inlet temperature of 90 °C and under nitrogen to yield the title compound having XRD similar to that depicted in Figure 3.
- 10

Yield: 220 g

- 15 Moisture content = 2.5 % w/w by Karl-Fischer method

XRD as per Figure 3.

Example 10 – Reference

- Fluvastatin sodium (25 g; moisture content 14.54 % w/w by Karl Fischer analysis) was dissolved in methanol (200 mL) and spray dried using the process provided in Example 9 above at 40 °C to 65 °C to yield a product that is a mixture of crystalline and amorphous fluvastatin sodium.
- 20

Yield: 11.5 g

XRD as per Figure 4.

Example 11: Preparation of Form R-1 Of Fluvastatin Sodium

Fluvastatin sodium (5 g) was dissolved in water (50 mL) and the solution was lyophilized/freeze-dried using following conditions to yield the title compound.

Freeze Dryer: Vertex.

5 A 10 % aqueous solution was taken in a loading tray and the following sequence of operations were carried out:

1. Freezing temperature: -40 °C
2. Condenser set point: -60 °C
3. Vacuum set point: 150 mTorr
- 10 4. Vacuum safety: 800 mTorr
5. Secondary temperature: 45 °C

The solution was maintained at -40 °C for 3 hours followed by -0 °C for 4 hours, 0°C for 6 hours then taken to 25°C over 2 hours and maintained at that temperature for 6 hours, then taken to 40°C over 2 hours and maintained at that temperature for 6 hours and
15 then finally cooled to 25°C and maintained at that temperature for 3 hours.

Lyophilized fluvastatin sodium (2 g) was added to a mixture of isopropyl alcohol (40 mL) and water (1 mL) at ambient temperature. The mixture was then stirred for 16 hours at ambient temperature. The product was then filtered and washed with isopropyl alcohol (4 mL) at ambient temperature, and dried at 35°C to 40°C under vacuum to yield
20 the title compound.

Yield: 1.5 g

Moisture content: 2.60 % w/w (by KF)

XRD and FTIR as per Figure 5 and 6 respectively.

25 Example 12: Preparation of Form R-2 Of Fluvastatin Sodium

Fluvastatin tert-butyl ester (20 g) was suspended in methanol (340 mL) at ambient temperature. The mixture was then warmed to 60 to 65°C and stirred to yield a clear solution. Slowly cooled the solution to 10-15°C and to this was added aqueous sodium

hydroxide solution (1.71 g, 1N) dropwise at 15 to 20°C and the mixture was stirred for 2 hours until the reaction was complete. Solvent methanol was removed under reduced pressure at 40°C and the residue thus obtained was stirred and dissolved in de-ionized water (250 mL). The aqueous phase was three times washed with methyl tert-butyl ether
5 (200 mL x 3). The aqueous layer was concentrated to dryness under reduced pressure at 40 °C. The residue was suspended in diethyl ether (200 mL) and stirred for 6 hours and filtered and dried. This solid material was re-dissolved in water (140 mL) and lyophilized/freeze dried using following conditions to yield the title compound:

Freeze Dryer: Vertex.

10 A 10 % aqueous solution was taken in a loading tray and the following sequence of operations were carried out:

1. Freezing temperature: -40 °C
2. Condenser set point: -60 °C
3. Vacuum set point: 150 mTorr
- 15 4. Vacuum safety: 800 mTorr
5. Secondary temperature: 45 °C

The solution was maintained at -40 °C for 3 hours followed by -0°C for 4 hours and maintained at 0°C for 6 hours, then taken to 25°C over 2 hours and maintained at that temperature for 6 hours, then brought to 40 °C over 2 hours and maintained at that
20 temperature for 6 hours, and then finally cooled to 25 °C and maintained at that temperature for 3 hours.

Yield: 10 g

Moisture content: 6.0 % w/w (by KF)

XRD and FTIR as per Figure 7 and 8 respectively.

25

Example 13: Preparation of Form R-3 Of Fluvastatin Sodium

Fluvastatin tert-butyl ester (50 g) was suspended in methanol (1000 mL) at ambient temperature. The mixture was then warmed to 40 to 45°C and stirred to yield a

clear solution. The solution was slowly cooled to 10 to 15 °C, aqueous sodium hydroxide solution (4.26 g, 1N) was dropwise to the solution at 15 to 20°C, and the mixture was stirred for 3 hours until the reaction was complete. Methanol was removed under reduced pressure at 40°C and the residue thus obtained was stirred and dissolved in de-ionized water (500 mL). The aqueous phase was extracted three times with methyl tert-butyl ether (400 mL x 3). The aqueous layer was concentrated under reduced pressure at 40 °C to dryness. A residue thus obtained was suspended in diethyl ether (250 mL) and stirred for 24 hours, filtered and dried. The solids were re-dissolved in methanol (400 mL) and spray dried using a parallel flow spray dryer, *i.e.*, the sprayed product and the drying gas flow in the same direction. The drying gas was nitrogen, the gas inlet temperature was maintained at 40 °C and outlet temperature was maintained at about 65 °C.

Yield: 40 g

Moisture content: 14.54 % w/w (by KF)

XRD and FTIR as per Figure 9 and 10 respectively.

15

Example 14: Preparation of Form R-4 Of Fluvastatin Sodium

Fluvastatin tert-butyl ester (100 g) was suspended in methanol (1500 mL) at ambient temperature. The mixture was then warmed to 50 to 60°C and stirred for 30 minutes to yield a clear solution. After cooling to 15 to 20°C, aqueous sodium hydroxide solution (8.56 g, 1N) was added dropwise to the mixture at 15 to 20°C and the mixture was stirred for 2 hours until the reaction was complete. Methanol was removed under reduced pressure at 40 °C and the residue thus obtained was stirred with de-ionized water (1000 mL). The aqueous layer was extracted three times with methyl tert-butyl ether (500 mL x 3). The resultant aqueous layer was concentrated to yield a residue and the residue was slurried in diisopropyl ether (600 mL). The solvent was removed under vacuum and the material was dissolved in water (1150 mL) to form a solution. The solution was lyophilized using following conditions to yield title compound.

25

Freeze Dryer: Vertex.

A 10 % aqueous solution was taken in a loading tray and the following sequence of operations were carried out:

30

1. Freezing temperature: -40 °C
2. Condenser set point: -60 °C
3. Vacuum set point: 150 mtorr
4. Vacuum safety: 800 mTorr
- 5 5. Secondary temperature: 45 °C

The solution was slowly cooled to -40 °C over 3 hours and maintained at -40 °C for 3 hours followed by -0 °C for 4 hours and maintained at 0 °C for 6 hours, then taken to 25 °C over 2 hours and maintained at that temperature for 6 hours, and then brought to 40 °C over 2 hours and maintained at that temperature for 6 hours, and
10 then finally cooled to 25 °C and maintained at that temperature for 3 hours.

Yield: 88 g

Moisture content: 6.0 % w/w (by KF)

XRD as per Figure 11.

15 Example 15: Preparation of Form R-5 Of Fluvastatin Sodium

Fluvastatin tert-butyl ester (50 g) was suspended in methanol (1000 mL) at ambient temperature. The mixture was then warmed to 40 to 45°C and stirred to yield a clear solution. Aqueous sodium hydroxide solution (4.26 g, 1N) was added dropwise to the solution at ambient temperature and the mixture was stirred for 3 hours until the
20 reaction was complete. Methanol was removed under reduced pressure at 40 °C and the residue thus obtained was stirred and dissolved in de-ionized water (500 mL). The aqueous phase was washed three times with methyl tert-butyl ether (400 mL x 3). The aqueous layer was concentrated to dryness under reduced pressure at 40 °C. The residue was suspended in diethyl ether (250 mL) and stirred for 24 hours and filtered and dried.
25 This solid material was re-dissolved in water (140 mL) and lyophilized/freeze dried using following conditions to yield the title compound.

Freeze Dryer: Vertex.

A 10 % aqueous solution was taken in a loading tray and the following sequence of operations were carried out:

1. Freezing temperature: -40 °C
2. Condenser set point: -60 °C
3. Vacuum set point: 150 mTorr
4. Vacuum safety: 800 mTorr
- 5 5. Secondary temperature: 45 °C

The solution was maintained at -40 °C for 3 hours followed by -0 °C for 4 hours, maintained at 0 °C for 6 hours, then taken to 25 °C over 2 hours and maintained at that temperature for 6 hours, then brought to 40 °C over 2 hours and maintained at that temperature for 6 hours, and then finally cooled to 25 °C and maintained at that
10 temperature for 3 hours.

Yield: 25 g

Moisture content: 12.64 % w/w (by KF)

XRD and FTIR as per Figure 12 and 13 respectively.

15 Example 16: Preparation of Form R-6 Of Fluvastatin Sodium

Fluvastatin tert-butyl ester (75 g) was dissolved in methanol (900 mL) by heating the solution to 50 to 60 °C. The solution was then cooled slowly to 20 to 25 °C and 1N sodium hydroxide solution (6.42 g) was added. The mixture was stirred for 2.5 hours and solvent was removed completely under vacuum at 40 °C. Addition of tetrahydrofuran
20 (1500 mL) to the residue gave a clear solution, which was then stirred for 16 hours. The material obtained was then filtered and dried under vacuum at 35 to 40 °C to yield the fluvastatin sodium.

Yield: 66 g

Tetrahydrofuran (200 mL) was added to the above-obtained fluvastatin sodium (10
25 g). The resultant mixture was seeded with Form R-6 of fluvastatin sodium seed (0.2 g) and the seeded mixture was stirred for 48 hours at ambient temperature. A precipitate thus formed was filtered under nitrogen atmosphere and dried under vacuum for 6 hours at 35 to 40 °C to yield the title compound.

Yield: 8.56 g

Water: 1.11 % w/w

XRD and FTIR as per Figure 14 and 15 respectively.

Example 17: Preparation of Form R-7 Of Fluvastatin Sodium

- 5 Amorphous fluvastatin sodium (2 g) was stirred in tetrahydrofuran (60 mL) for 48 hours at ambient temperature. The mixture was filtered under nitrogen atmosphere and dried under vacuum for 6 hours at 35 to 40°C to yield title compound.

Yield: 1.25 g

Moisture content: 0.92 % w/w (by KF)

- 10 XRD and FTIR as per Figure 16 and 17 respectively.

Example 18: Preparation of Form R-8 Of Fluvastatin Sodium

- Fluvastatin sodium (4 g) was dissolved in aqueous methanol (44 mL, 10 %) by stirring at ambient temperature for 15 to 20 minutes. The solvent was removed completely
15 under vacuum and tetrahydrofuran (100 mL) was added to the residue thus obtained. The resultant mixture was stirred at ambient temperature for 10 hours, filtered and the product was dried under high vacuum at 30 to 40 °C to yield title compound.

Yield: 3.5 g

Moisture content: 3.53 % w/w (by KF)

- 20 XRD and FTIR as per Figure 18 and 19 respectively.

Example 19: Preparation of Form R-9 Of Fluvastatin Sodium

- Fluvastatin sodium (1 g) was dissolved in methanol (10 mL) and water (2 mL) at ambient temperature. Dilute acetic acid was added to the reaction mass to adjust the pH to
25 7.6 to 7.7. To the resultant mass was added acetone (75 mL) and further stirred for 15 to 18 hours. The separated solids were filtered, dried at RT under vacuum for 6 hours to give the title compound.

Yield: 0.5 g

XRD and FTIR as per Figure 20 and 21 respectively.

Example 20: Preparation of Form R-10 Of Fluvastatin Sodium

5 Fluvastatin sodium (1 g) was dissolved in methanol (8 mL) and water (0.5 mL). Acetone (40 mL) was added to the mixture followed by a seed amount of Form R-10 of fluvastatin sodium (0.2 g). The resultant mixture was stirred for 15 to 18 hours. The separated solids thus obtained were filtered and dried under vacuum at ambient temperature to yield title compound.

10 Yield: 0.56 g

XRD and FTIR as per Figure 22 and 23 respectively.

Example 21: Preparation of Form R-11 Of Fluvastatin Sodium

15 Fluvastatin sodium (5 g) was suspended in water (25 mL). Acetone (2 mL) was added slowly to yield clear solution. A sodium chloride solution (10 mL, 20 % w/v) was added and stirred for 30 minutes at ambient temperature. The solid thus obtained was filtered and washed successively with water (2 x 5 mL) and diisopropyl ether (2 x 25 mL). The solid was further stirred with diisopropyl ether, filtered and dried at ambient temperature under vacuum to yield title compound.

20 Yield: 4 g

Moisture content: 9.76 % w/w (by KF)

XRD and FTIR as per Figure 24 and 25 respectively.

Example 22: Preparation of Form R-12 Of Fluvastatin Sodium

25 Fluvastatin sodium (1 g) was stirred with methyl tert-butyl ether (10 mL). Water (0.5 mL) was added to the solution, followed by addition of methyl tert-butyl ether (30 mL) and acetone (2 mL). The resultant mixture was stirred for 4 hours, and the solids thus

obtained were filtered and dried at ambient temperature under vacuum to yield title compound.

Yield: 0.8 g

Moisture content: 5 to 6.0 % w/w (by KF)

5 XRD as per Figure 26.

Example 23: Preparation of Form R-13 Of Fluvastatin Sodium

Fluvastatin sodium (1 g, Form R-5) was stirred in isopropanol (10 mL) and water (1 mL) for 15 minutes. Diisopropyl ether (10 mL) was added and the mixture was stirred for 1 hour. A solid obtained was filtered and dried at ambient temperature under vacuum
10 for 6 hours to yield the title compound.

Yield: 0.25 g

XRD as per Figure 27.

Example 24: Preparation of Form R-14 Of Fluvastatin Sodium

15 Fluvastatin sodium (1 g) was dissolved in dichloromethane (20 mL). Acetone (20 mL) was added and the mixture was stirred for 1 hour at ambient temperature. Water (0.5 mL) was added and the mixture was stirred for 18 hours at ambient temperature. The solid thus obtained was filtered and dried at ambient temperature under vacuum for 6 hours to yield the title compound.

20 Yield: 0.2 g

XRD as per Figure 28.

Example 25: Preparation of Form R-15 Of Fluvastatin Sodium

Fluvastatin sodium (1 g) was dissolved in methanol (10 mL). Water (0.5 mL) was
25 added to the mixture followed by acetone (30 mL) and a seed amount of Form R-15 of fluvastatin sodium (0.2 g). The resultant mixture was stirred for 1 hour at ambient temperature and the solids thus obtained were filtered and dried at ambient temperature under vacuum for 6 hours to yield title compound.

XRD as per Figure 29.

Example 26: Preparation of Form R-16 Of Fluvastatin Sodium

Fluvastatin tert-butyl ester (750 g) was dissolved in methanol (11.25 L) by heating
5 the solution to 50 to 60°C. The solution obtained was cooled slowly to about 20 to 25 °C
followed by the addition of 1N sodium hydroxide solution (64.2 g in 640 mL deionized
water). This mixture was stirred for 3 hours at room temperature and the solvent was
removed completely under vacuum at 40 °C. Tetrahydrofuran (3000 mL) was added to the
residue thus obtained to yield a clear solution. The solution was concentrated to one sixth
10 of the initial volume and a second lot of tetrahydrofuran (3000 mL) was added and
partially removed to yield one seventh of the initial volume. A third lot of tetrahydrofuran
(15.0 L) was added slowly at 40 °C followed by stirring for 20 hours. The product thus
obtained was filtered and dried under vacuum at 35 to 40°C to yield the title compound.

Yield: 600 g

15 Water (% w/w): 3.83 %

XRD, FTIR and DSC as per Figure 30, 31 and 32 respectively.

Example 27: Preparation of Anhydrous Crystalline Fluvastatin Sodium

a) Preparation of Fluvastatin Acid

20 Crude fluvastatin sodium salt (5 g) was suspended in a mixture of dichloromethane
(50 mL) and water (50 mL) at room temperature. The pH was adjusted to about 2.0 with
1N hydrochloric acid at room temperature followed by stirring for 15 to 20 minutes. The
organic portion of the mixture was separated and washed with a 10 % w/v sodium chloride
solution. The organic layer was separated and the solvent was removed completely to
25 yield the title compound.

Yield: 3.4 g

b) Preparation of Sodium Salt Of Fluvastatin Acid

Diethyl ether (50 mL) was added to the fluvastatin acid obtained in step a). Sodium ethylhexanoate (2.11 g) was added to the mixture and stirred for 10 hours, followed by filtration and washing with diethyl ether (5 mL). The product thus obtained was dried under high vacuum at 30 to 40 °C to yield the title compound.

5 Yield: 3.4 g

Water (% w/w by KF): 0.05 %

XRD, FTIR and DSC as per Figure 33, 34 and 35 respectively.

WE CLAIM:

- 1 1. Substantially amorphous fluvastatin sodium having about 15 % or less of
2 crystallinity.
- 1 2. Substantially amorphous fluvastatin sodium of claim 1 exhibiting an XRPD pattern
2 as depicted in Figure 1.
- 1 3. Substantially amorphous fluvastatin sodium of claim 1 exhibiting an FTIR
2 spectrum as depicted in Figure 2.
- 1 4. Substantially amorphous fluvastatin sodium of claim 1 having water content of less
2 than about 1.5 % w/w.
- 1 5. A process for preparing substantially amorphous fluvastatin sodium comprising the
2 steps of:
 - 3 a) contacting fluvastatin sodium with tetrahydrofuran to form a first mixture,
 - 4 b) optionally removing water from the first mixture obtained in step a) to form
5 a concentrated mixture and contacting the concentrated mixture with
6 tetrahydrofuran to form a second mixture,
 - 7 c) removing the solvent from the second mixture obtained in step c) to form a
8 resultant mass,
 - 9 d) contacting the resultant mass obtained in step c) with one or more organic
10 solvents selected from one or more C₅₋₈ alkanes, one or more C₅₋₇
11 cycloalkanes, one or more halogenated hydrocarbons, one or more aliphatic
12 ethers, one or more petroleum ethers, one or more ketones or mixtures
13 thereof to form a third mixture, and
 - 14 e) isolating substantially amorphous fluvastatin sodium from the third mixture
15 thereof,
- 1 6. The process of claim 5, wherein the water is removed azeotropically in step b).
- 1 7. A process for preparing substantially amorphous fluvastatin sodium comprising the
2 steps of:
 - 3 a) dissolving fluvastatin sodium having a moisture content of about 5 % w/w
4 or less in a one or more organic solvents, and

- 5 b) removing the one or more organic solvents from the solution thereof.
- 1 8. The process of claim 7, wherein the one or more organic solvents is removed by
2 spray drying in step b).
- 1 9. The process of claim 7, wherein the one or more organic solvents is one or more of
2 C₁₋₄ alcohols, C₃₋₈ ketones, C₃₋₆ esters, C₄₋₈ ethers, polar aprotic solvents, or
3 mixtures thereof.
- 1 10. Substantially amorphous fluvastatin sodium having 15 % or less of crystallinity
2 prepared by a process comprising the steps of:
- 3 a) dissolving fluvastatin sodium having a moisture content 5 % w/w or less in
4 a one or more organic solvents, and
- 5 b) removing the one or more organic solvents from the solution thereof.
- 1 11. Amorphous Form R-6 of fluvastatin sodium.
- 1 12. Form R-6 of fluvastatin sodium of claim 11 exhibiting an XRPD pattern as
2 depicted in Figure 14.
- 1 13. Form R-6 of fluvastatin sodium of claim 11 having water content of about 0.5 to
2 2.0 % as determined by Karl Fischer analysis.
- 1 14. Form R-6 of fluvastatin sodium of claim 11 exhibiting a FTIR spectrum in
2 potassium bromide as depicted in Figure 15.
- 1 15. A process for preparing polymorphic Form R-6 of fluvastatin sodium comprising
2 the steps of:
- 3 a) contacting fluvastatin sodium with tetrahydrofuran to form a mixture,
4 b) adding a seed amount of amorphous Form R-6 of fluvastatin sodium to the
5 mixture obtained in step a), and to form a seeded mixture
- 6 c) isolating Form R-6 of fluvastatin sodium from the seeded mixture thereof.
- 1 16. The process of claim 15, wherein the mixture of step a) is stirred for about 10 to 30
2 hours.
- 1 17. Anhydrous crystalline fluvastatin sodium.

- 1 18. Anhydrous crystalline fluvastatin sodium of claim 17 exhibiting an XRPD pattern
2 as depicted in Figure 33.
- 1 19. Anhydrous crystalline fluvastatin sodium of claim 17 exhibiting a FTIR spectrum
2 in potassium bromide as depicted in Figure 34.
- 1 20. Anhydrous crystalline fluvastatin sodium of claim 17 exhibiting a Differential
2 Scanning Calorimetric thermogram as depicted in Figure 35.
- 1 21. Anhydrous crystalline fluvastatin sodium of claim 17 having water content of less
2 than about 0.1 % w/w.
- 1 22. Anhydrous crystalline fluvastatin sodium of claim 17 exhibiting a XRPD pattern
2 having 2θ values at about 4.2, 10.4, 18.6, 21.3 and 24.5.
- 1 23. A process for preparing anhydrous crystalline fluvastatin sodium comprising the
2 steps of:
- 3 a) contacting fluvastatin sodium with one or more organic solvents and
4 optionally water to form a first mixture, and acidifying the first mixture
5 with an acid to form an acidified first mixture, wherein the one or more
6 organic solvents is selected from one or more C₅₋₈ alkanes, one or more C₅₋₇
7 cycloalkanes, one or more halogenated hydrocarbons, one or more aliphatic
8 ethers, one or more petroleum ethers, one or more ketones or mixtures
9 thereof,
- 10 b) isolating a solid residue from the acidified first mixture obtained in step a),
- 11 c) forming a second mixture by contacting the solid residue of step b) with
12 one or more sodium-containing alkali compounds in the presence of one or
13 more ethers,
- 14 d) isolating anhydrous crystalline fluvastatin sodium from the second mixture
15 thereof.
- 1 24. The process of claim 23, wherein the one or more sodium-containing alkali
2 compounds are selected from sodium hydroxide, sodium carbonate, sodium
3 bicarbonate, sodium alkoxide, sodium alkanoate or mixtures thereof.

- 1 25. A pharmaceutical composition comprising a therapeutically effective amount of
2 substantially amorphous fluvastatin sodium and optionally one or more
3 pharmaceutically acceptable diluents or excipients.
- 1 26. A pharmaceutical composition comprising a therapeutically effective amount of
2 Form R-6 of fluvastatin sodium and optionally one or more pharmaceutically
3 acceptable diluents or excipients.
- 1 27. A pharmaceutical composition comprising a therapeutically effective amount of
2 anhydrous crystalline fluvastatin sodium and optionally one or more
3 pharmaceutically acceptable diluents or excipients.
- 1 28. A method of antagonizing HMG-CoA in mammal comprising administering to the
2 mammal a therapeutically effective amount of one or more of anhydrous
3 crystalline fluvastatin sodium, substantially amorphous fluvastatin sodium, Form
4 R-6 of fluvastatin sodium or mixtures thereof.

FIGURE 1

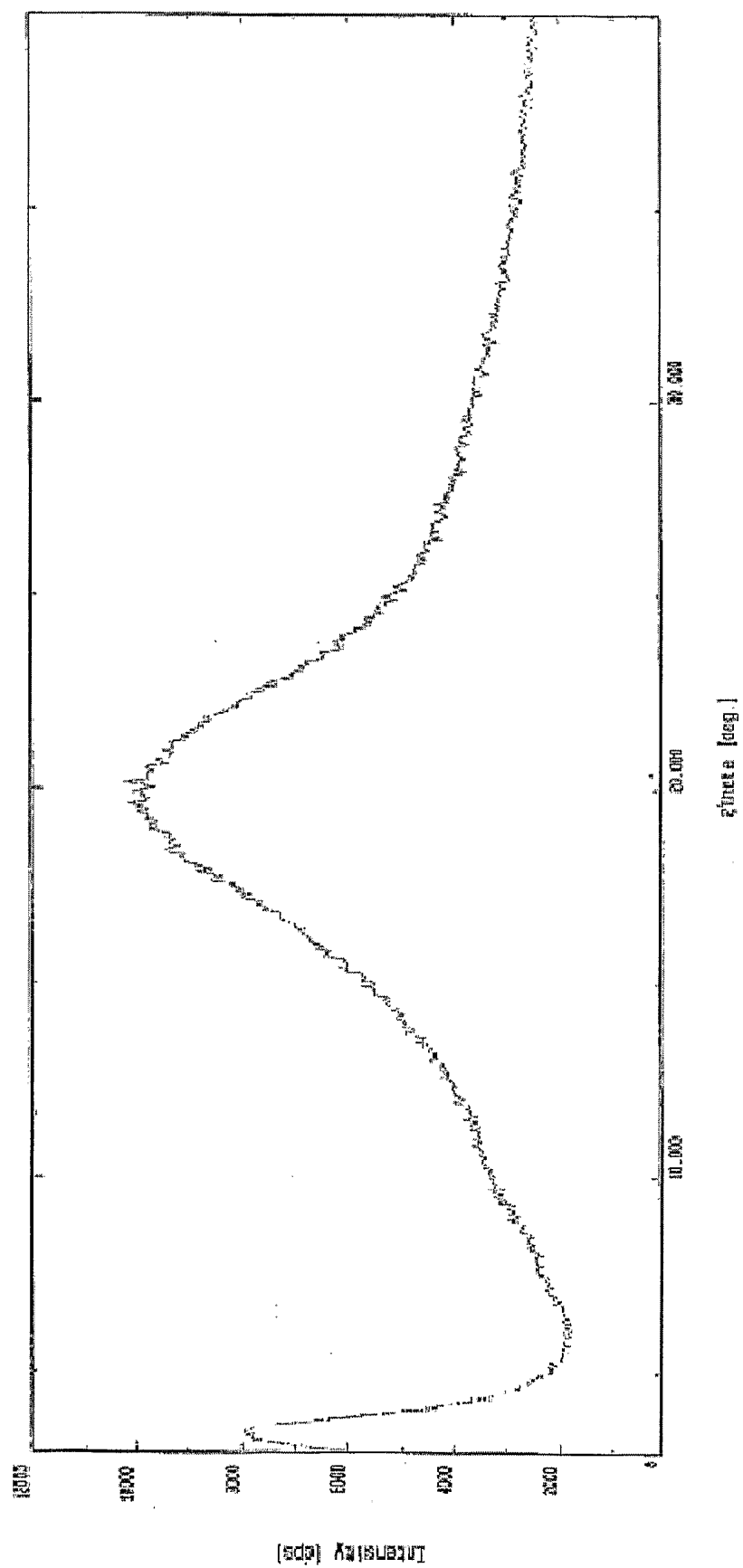


FIGURE 2

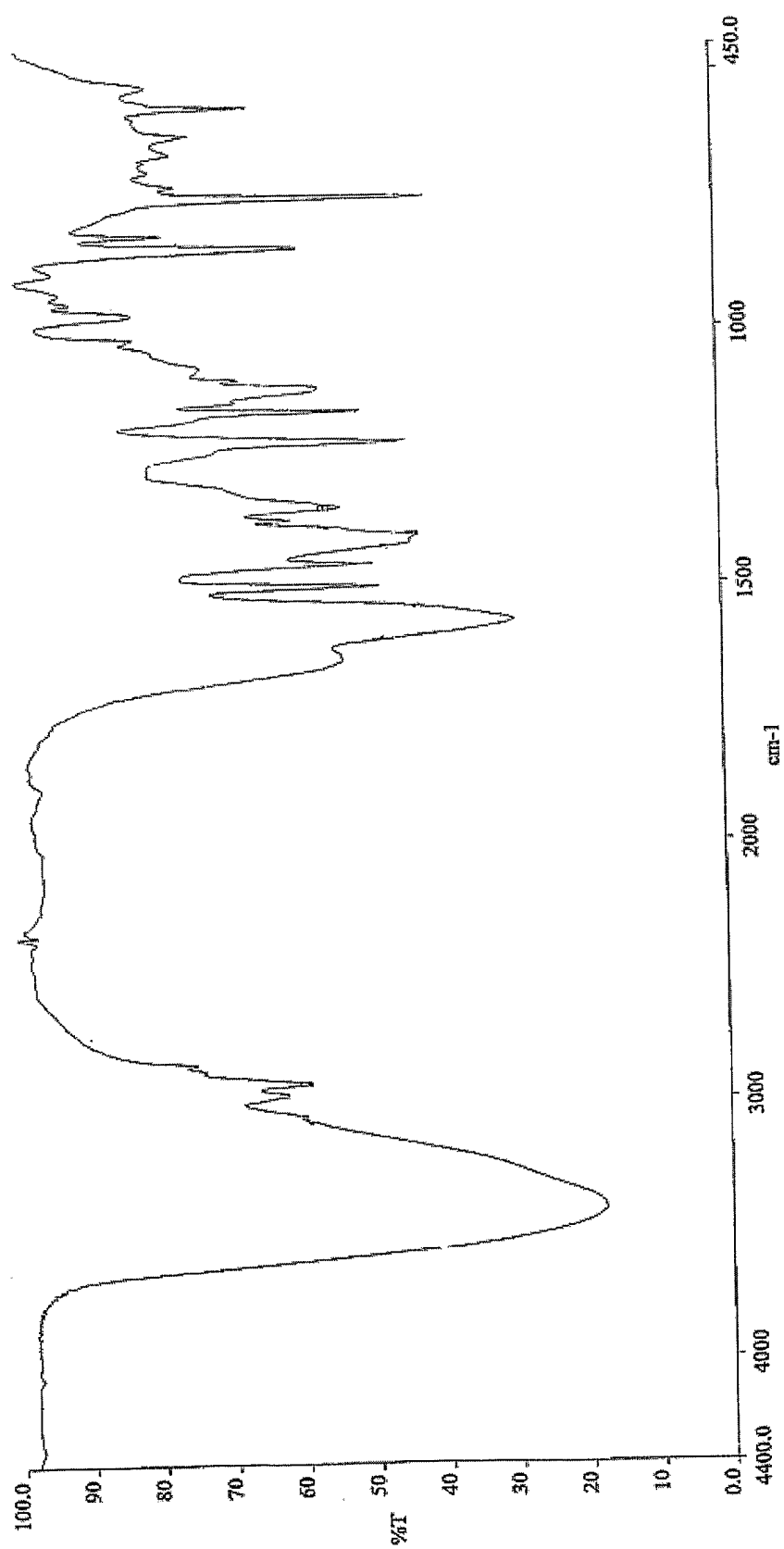


FIGURE 3

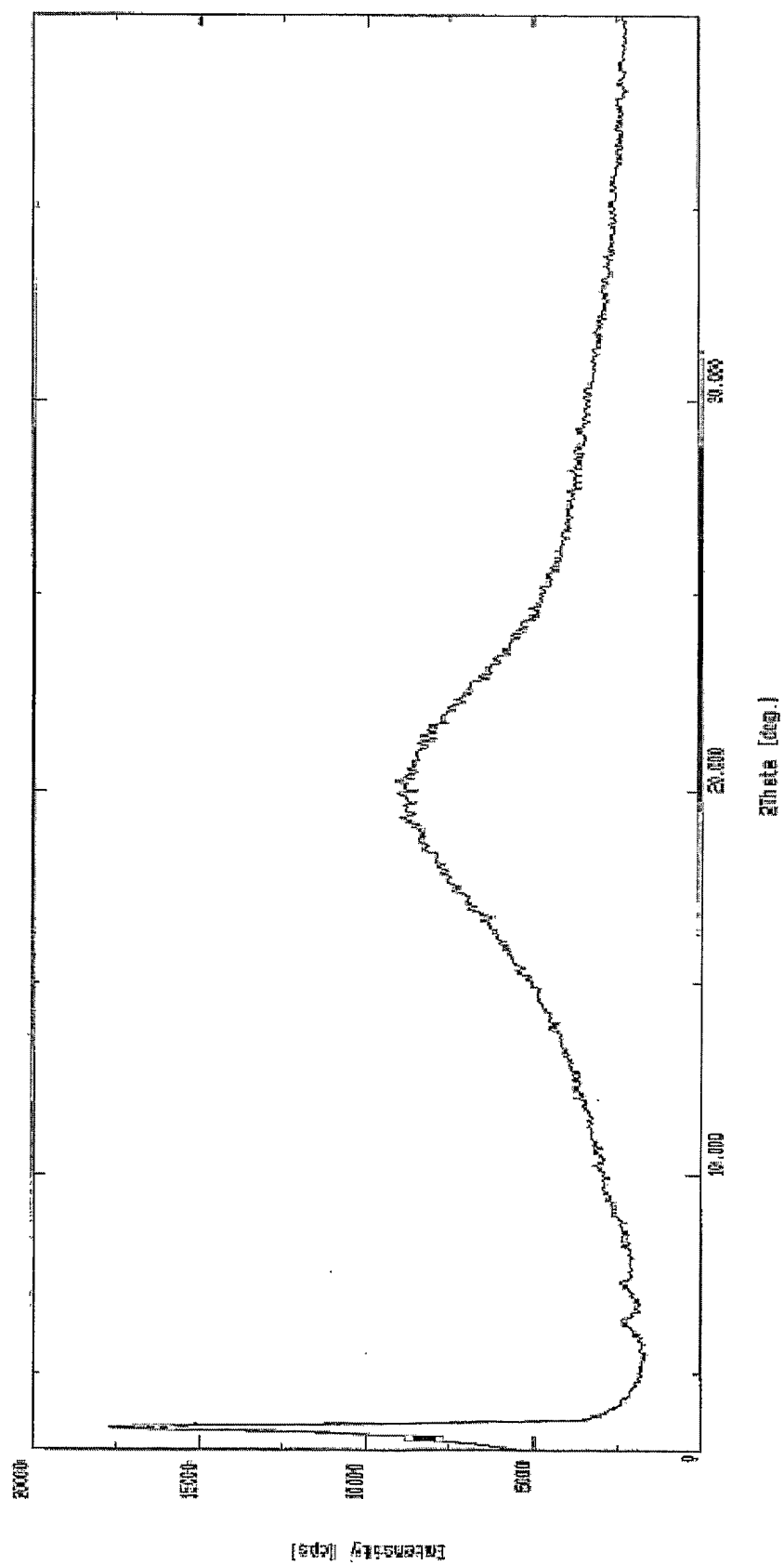


FIGURE 4

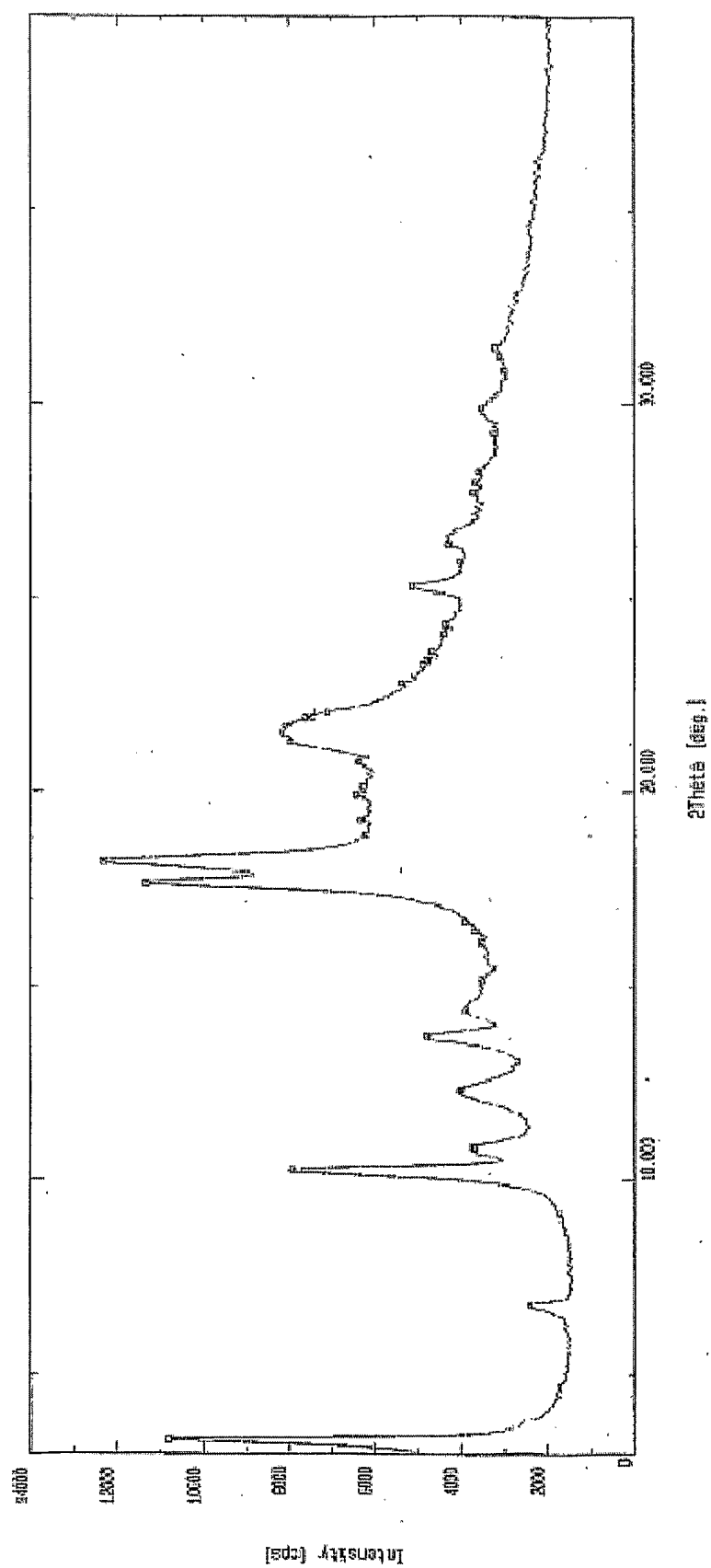


FIGURE 5

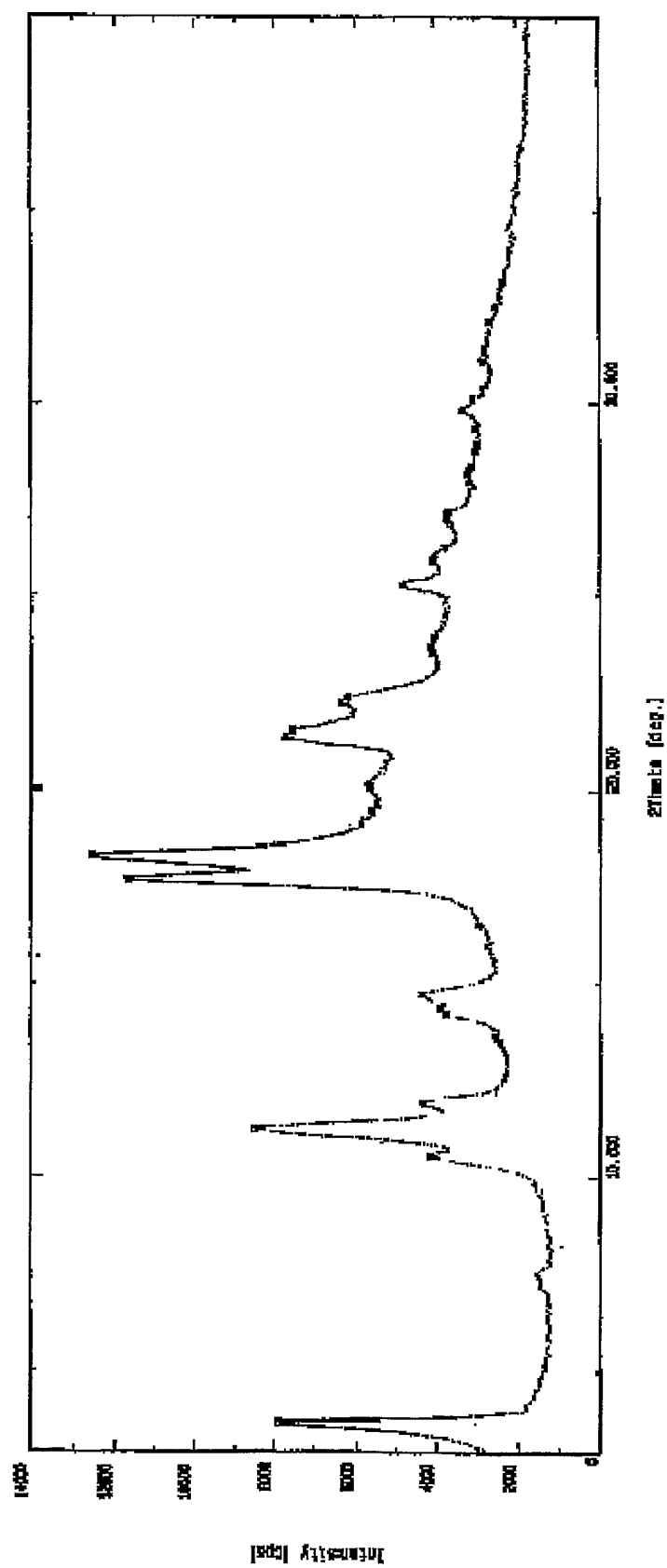


FIGURE 6

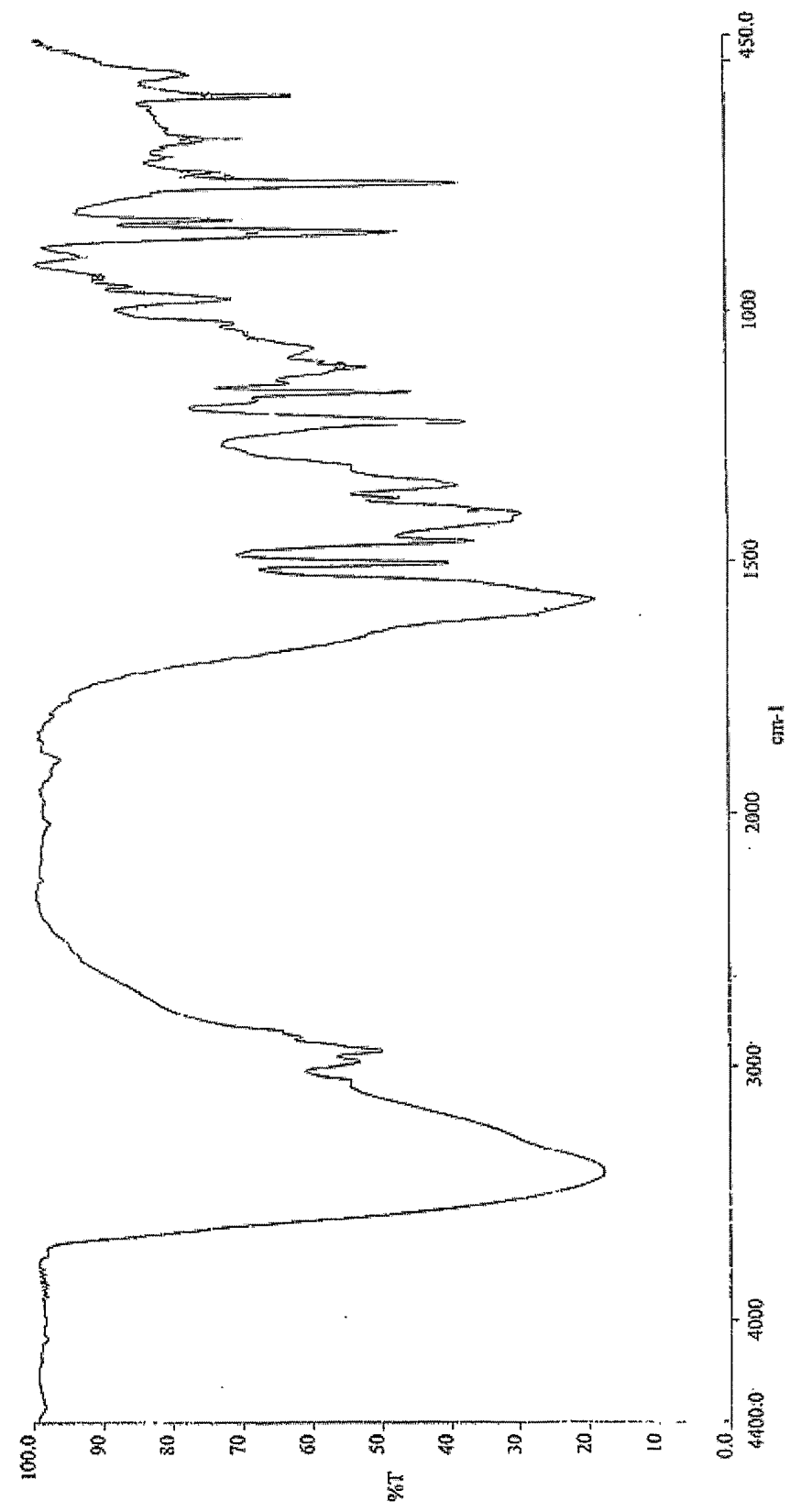


FIGURE 7

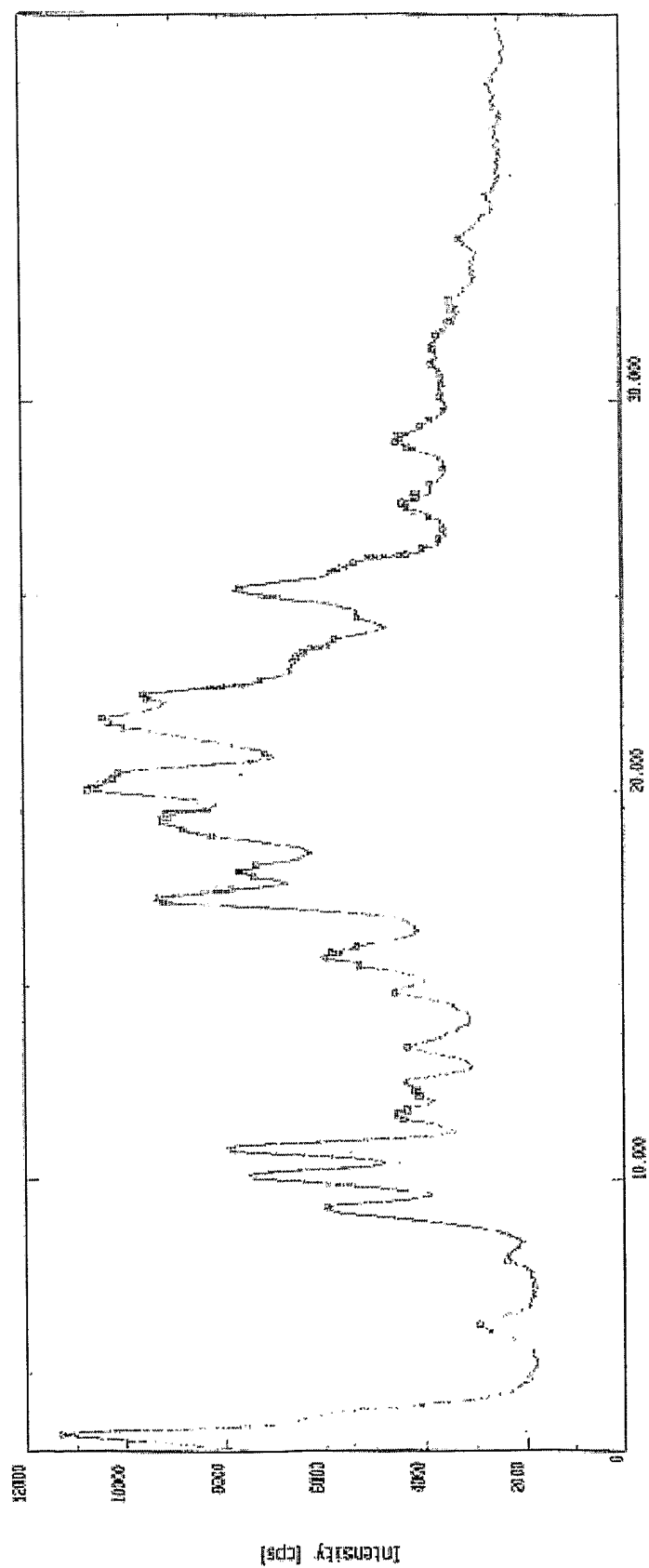


FIGURE 8

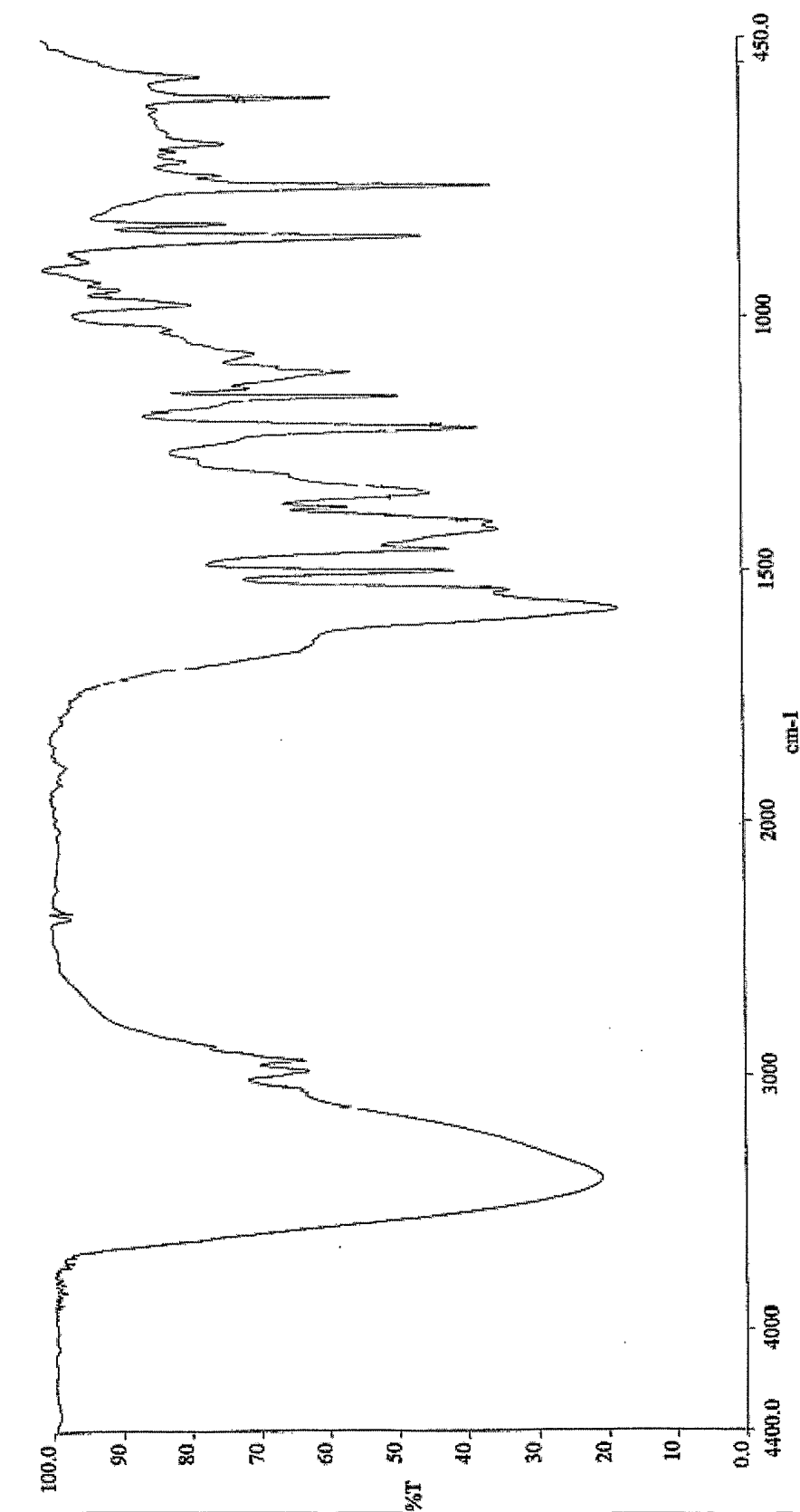


FIGURE 9

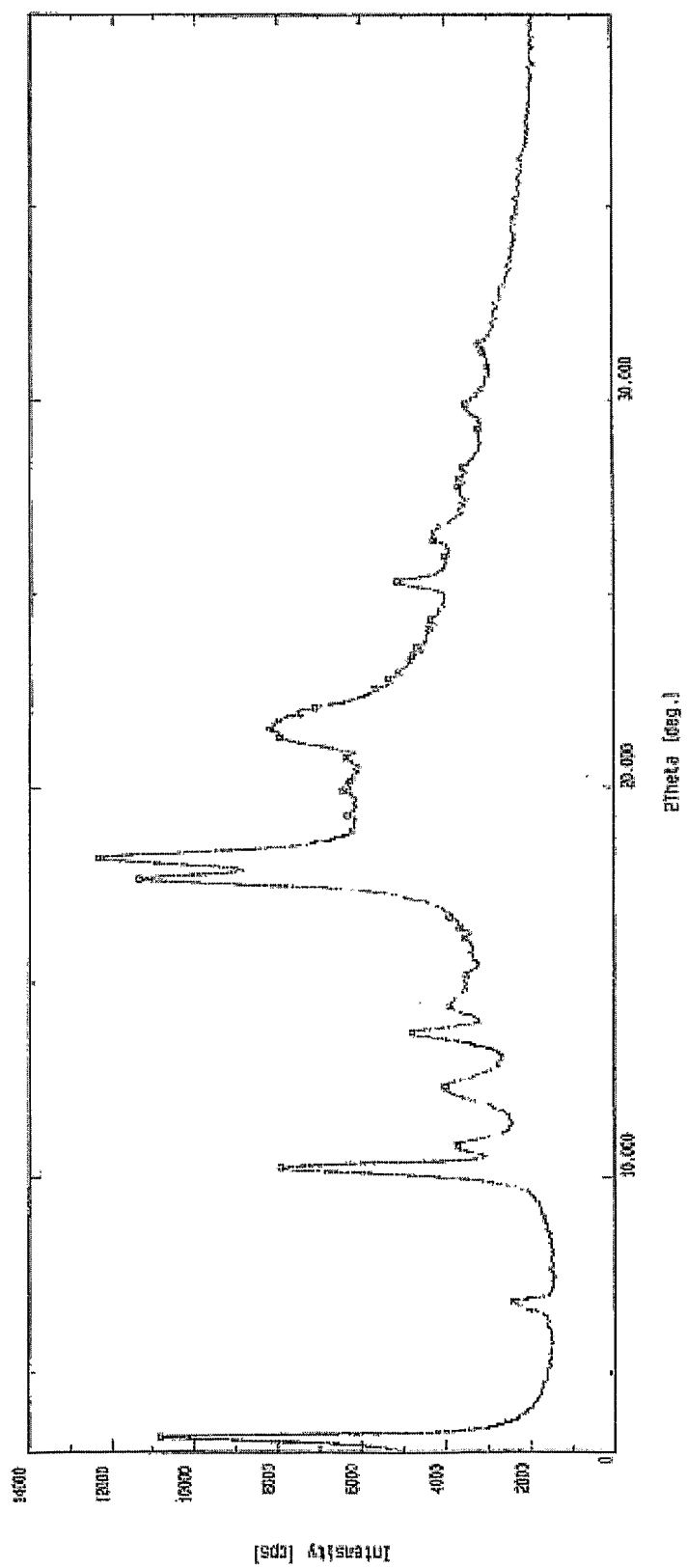


FIGURE 10

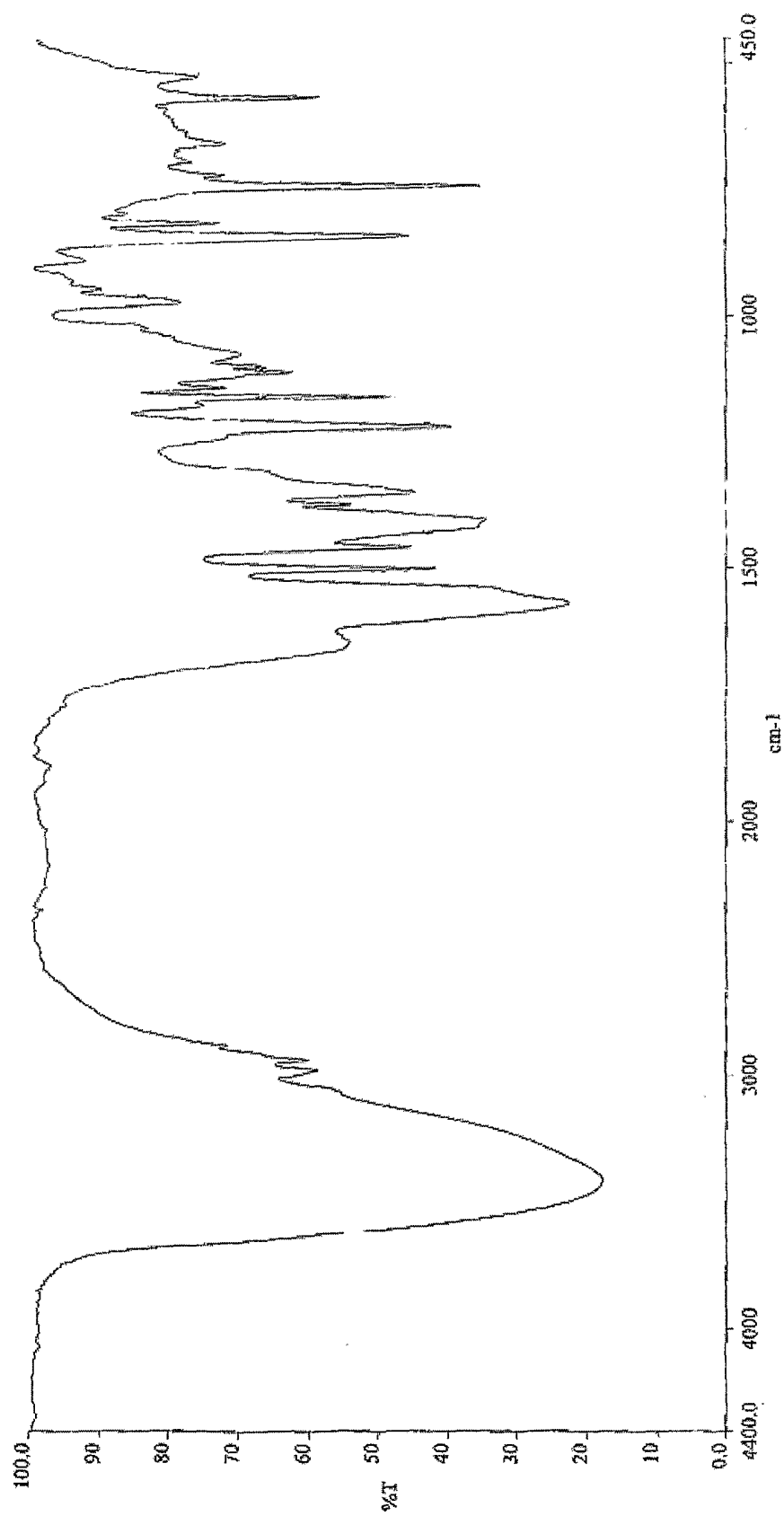


FIGURE 11

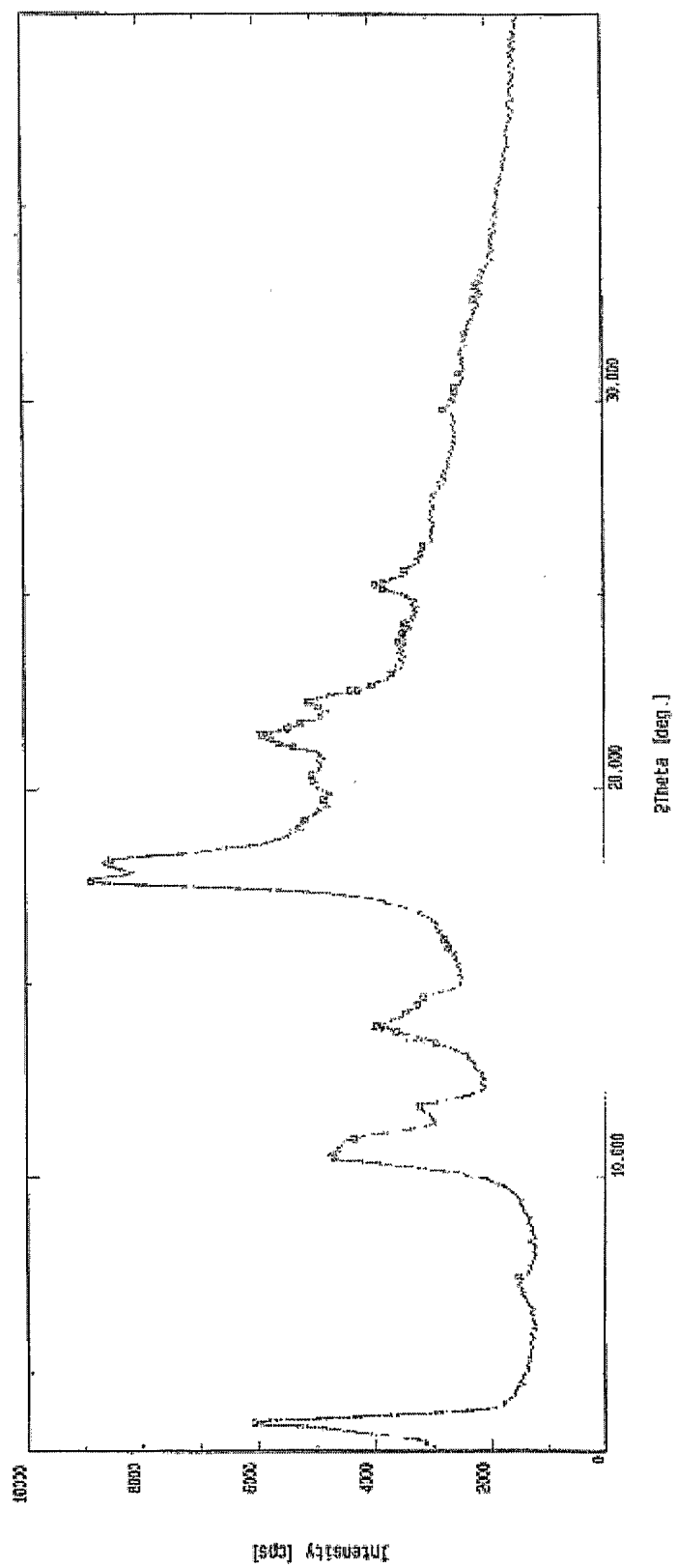


FIGURE 12

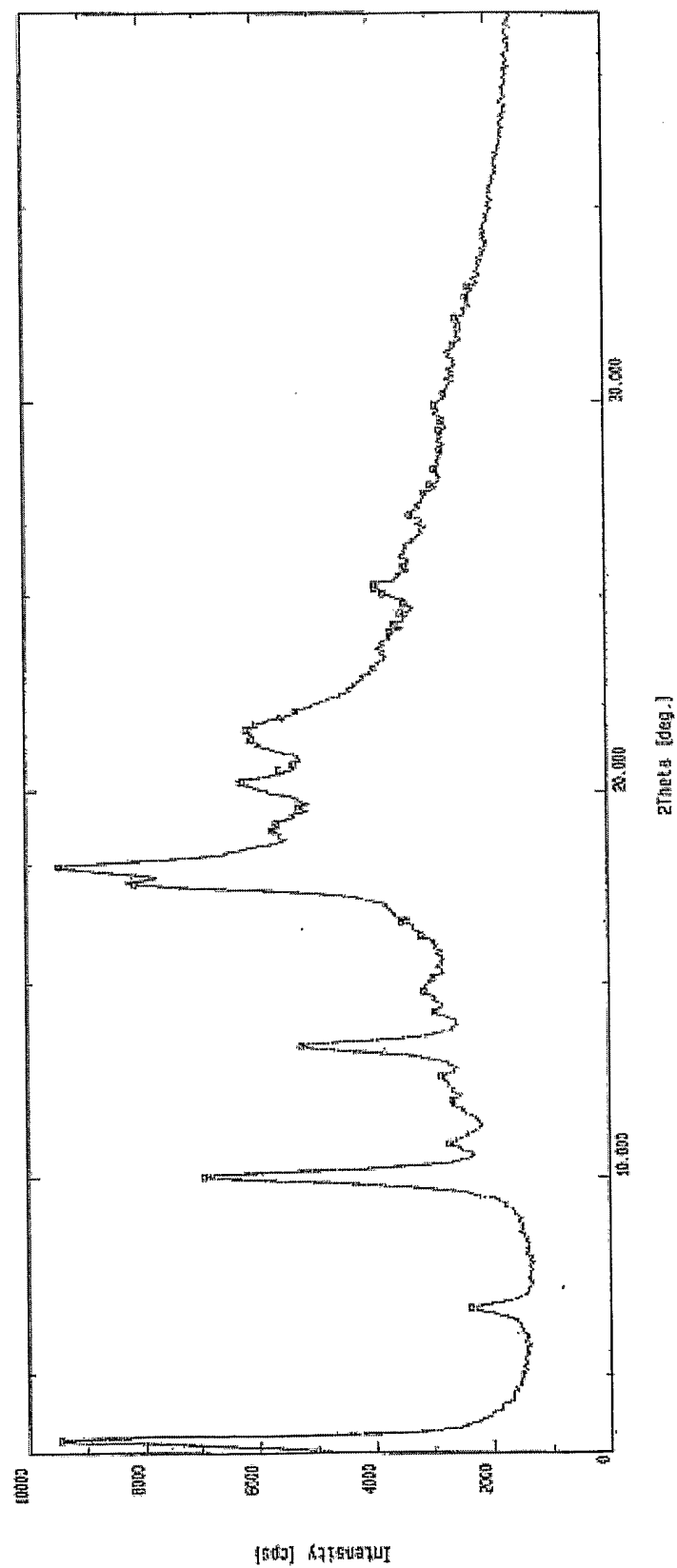


FIGURE 13

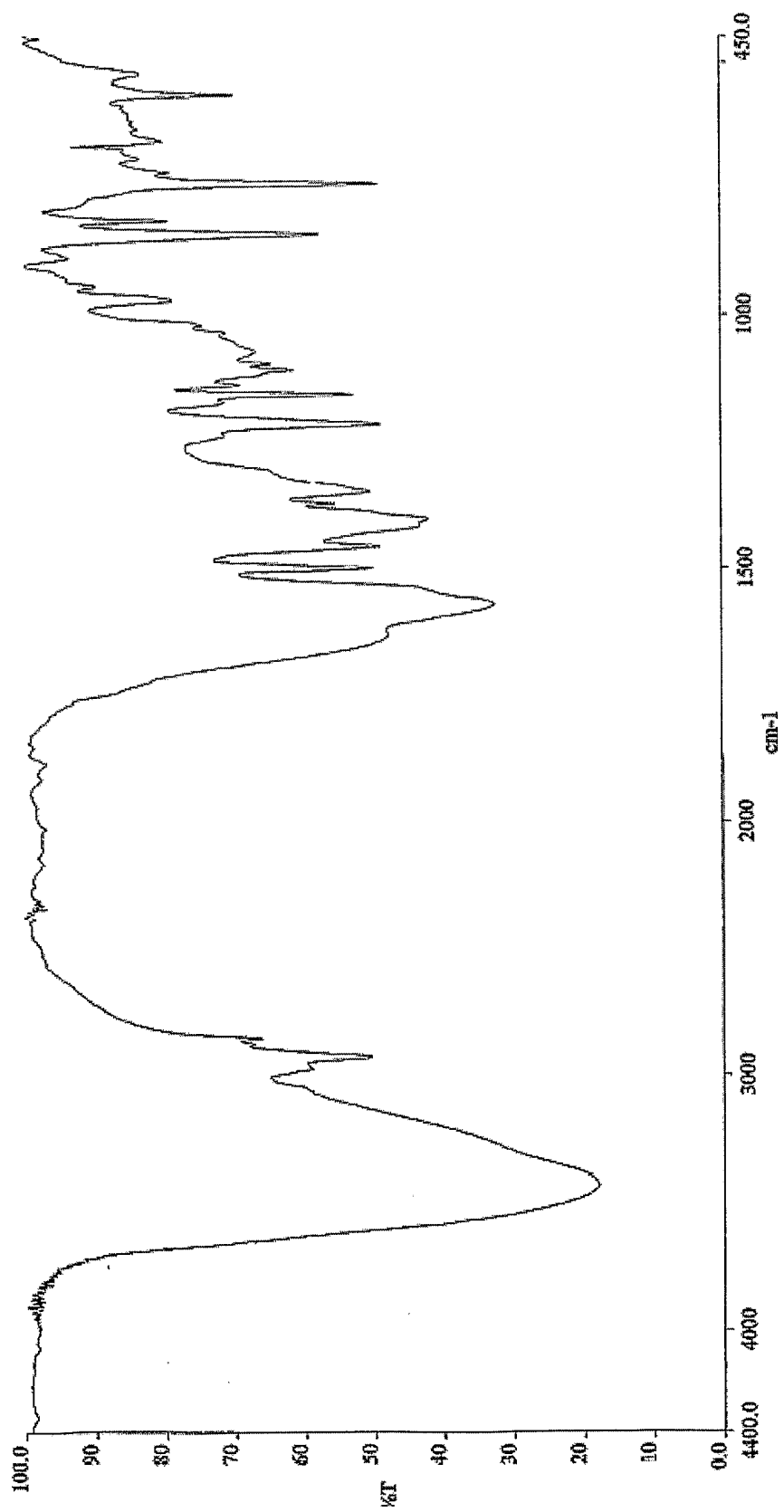


FIGURE 14

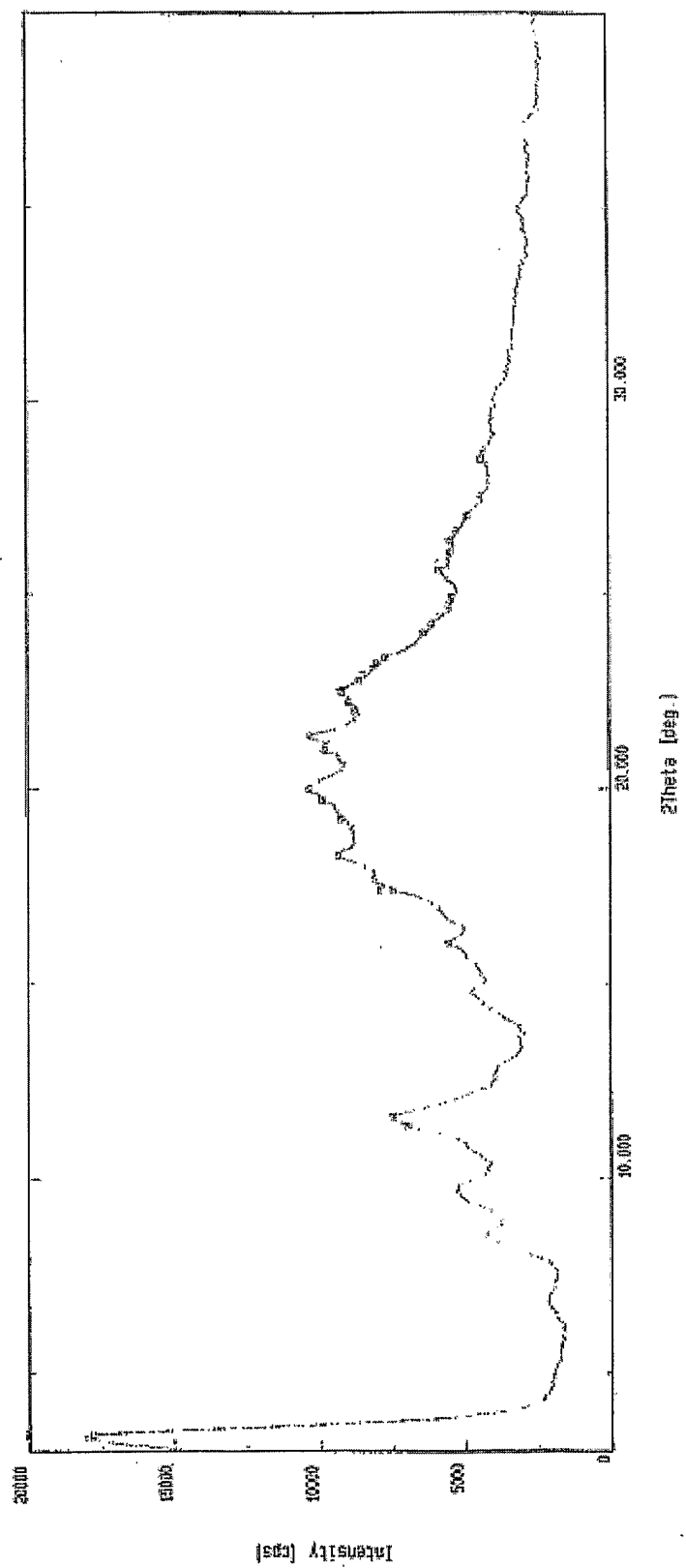


FIGURE 15

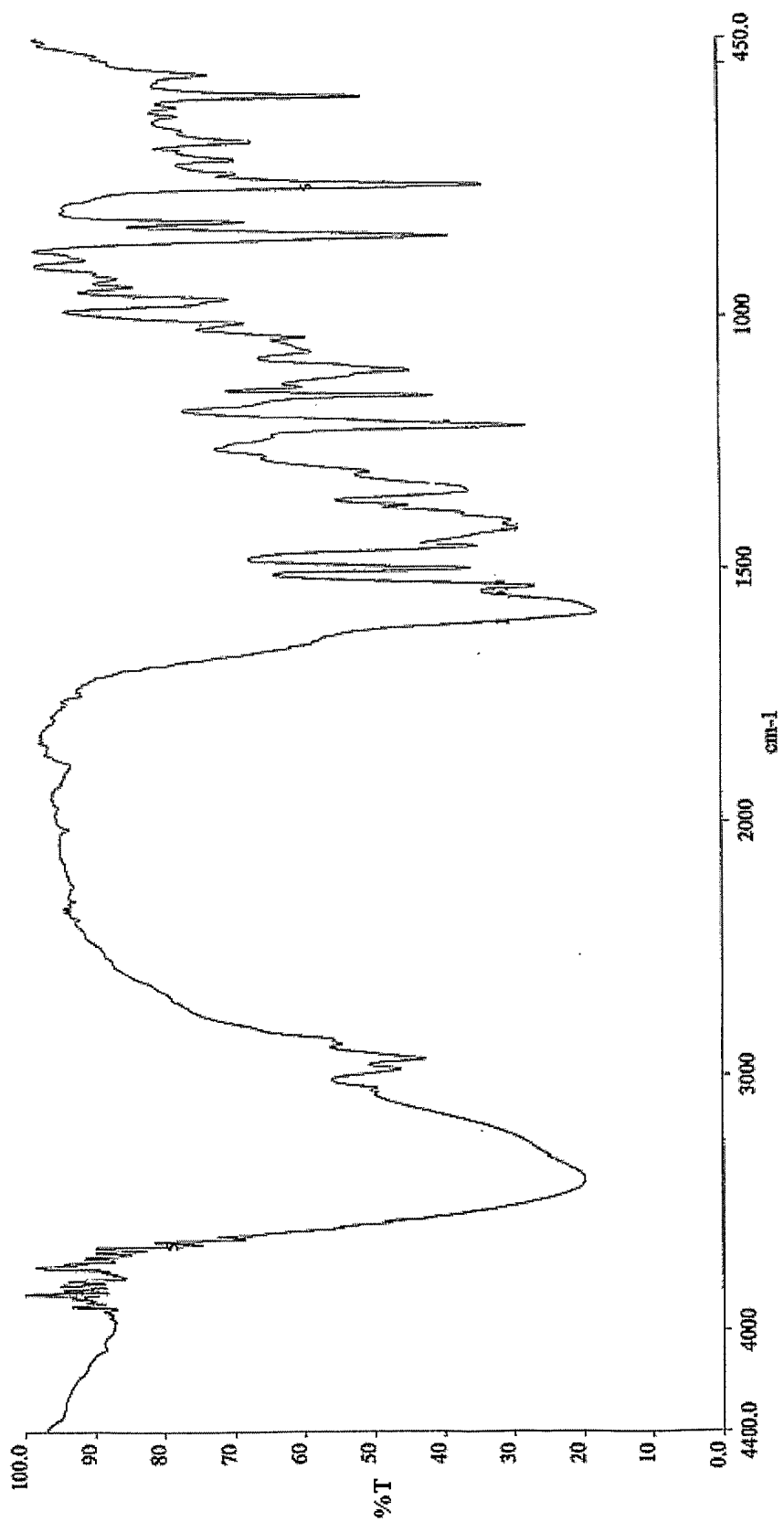


FIGURE 16

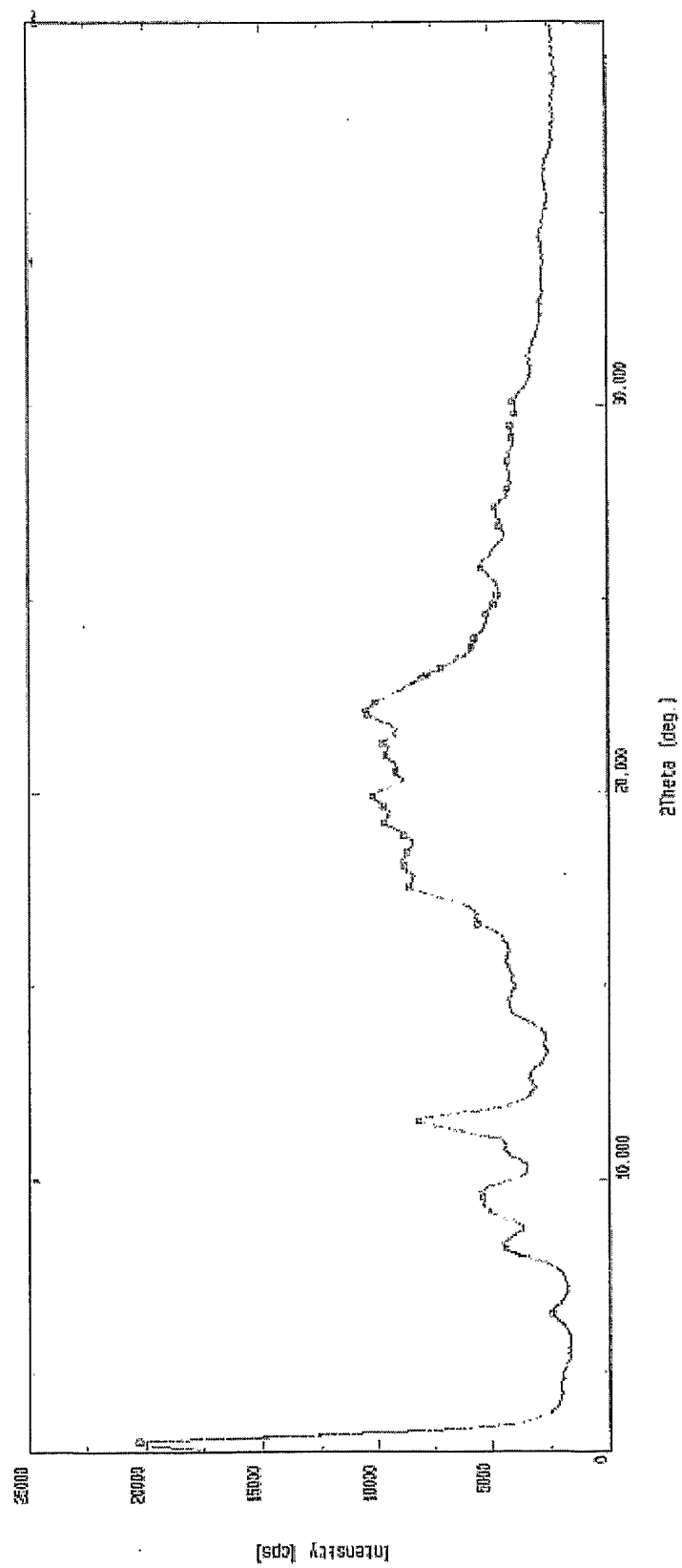


FIGURE 17

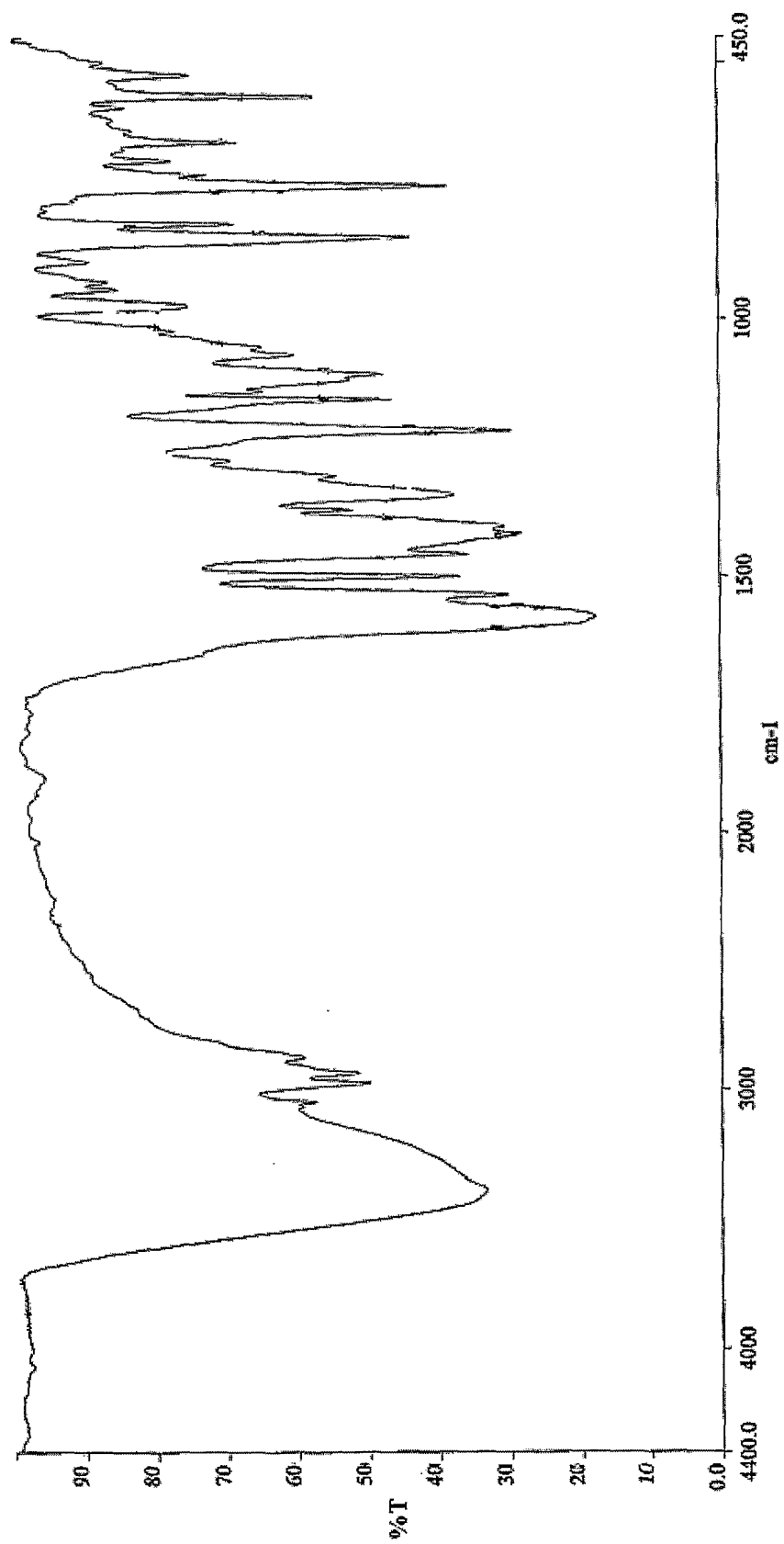


FIGURE 18

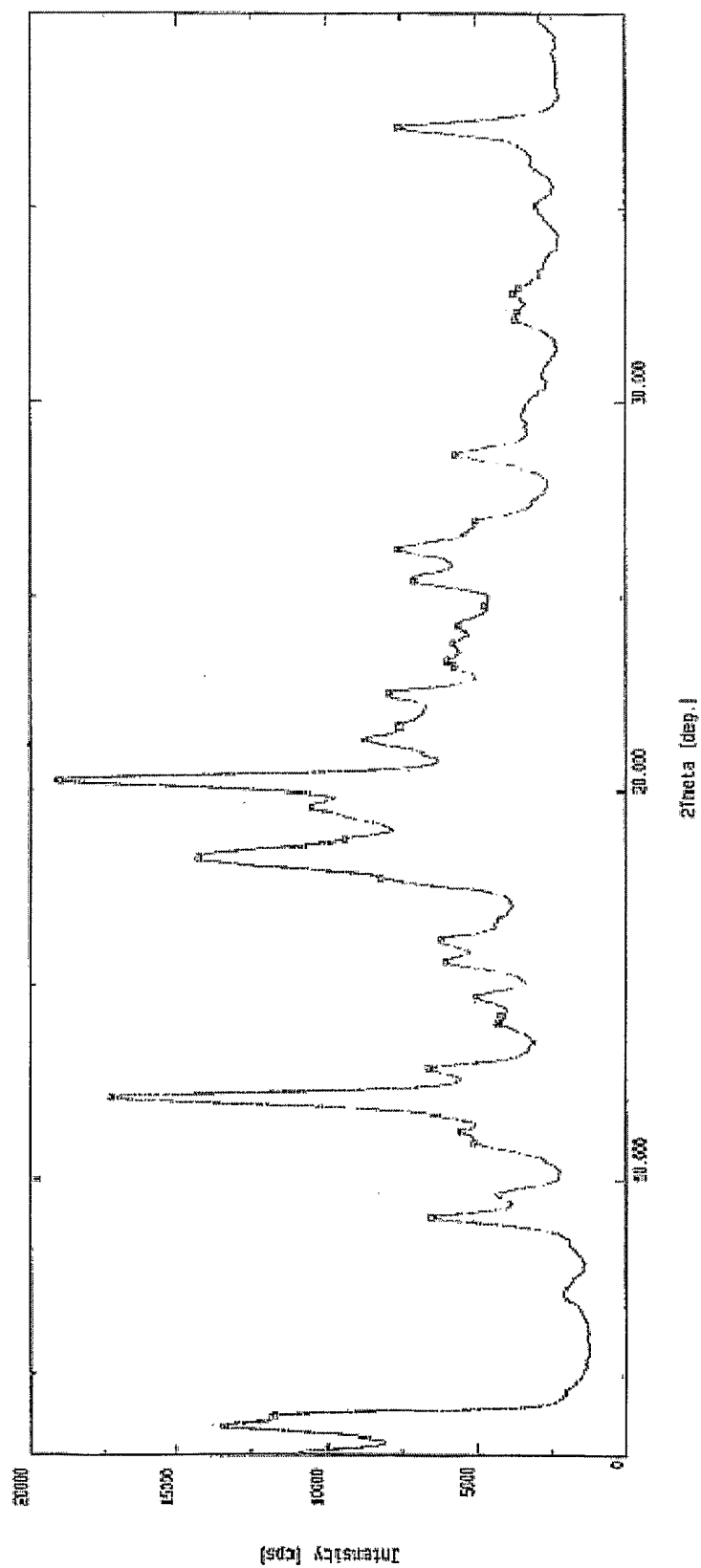


FIGURE 19

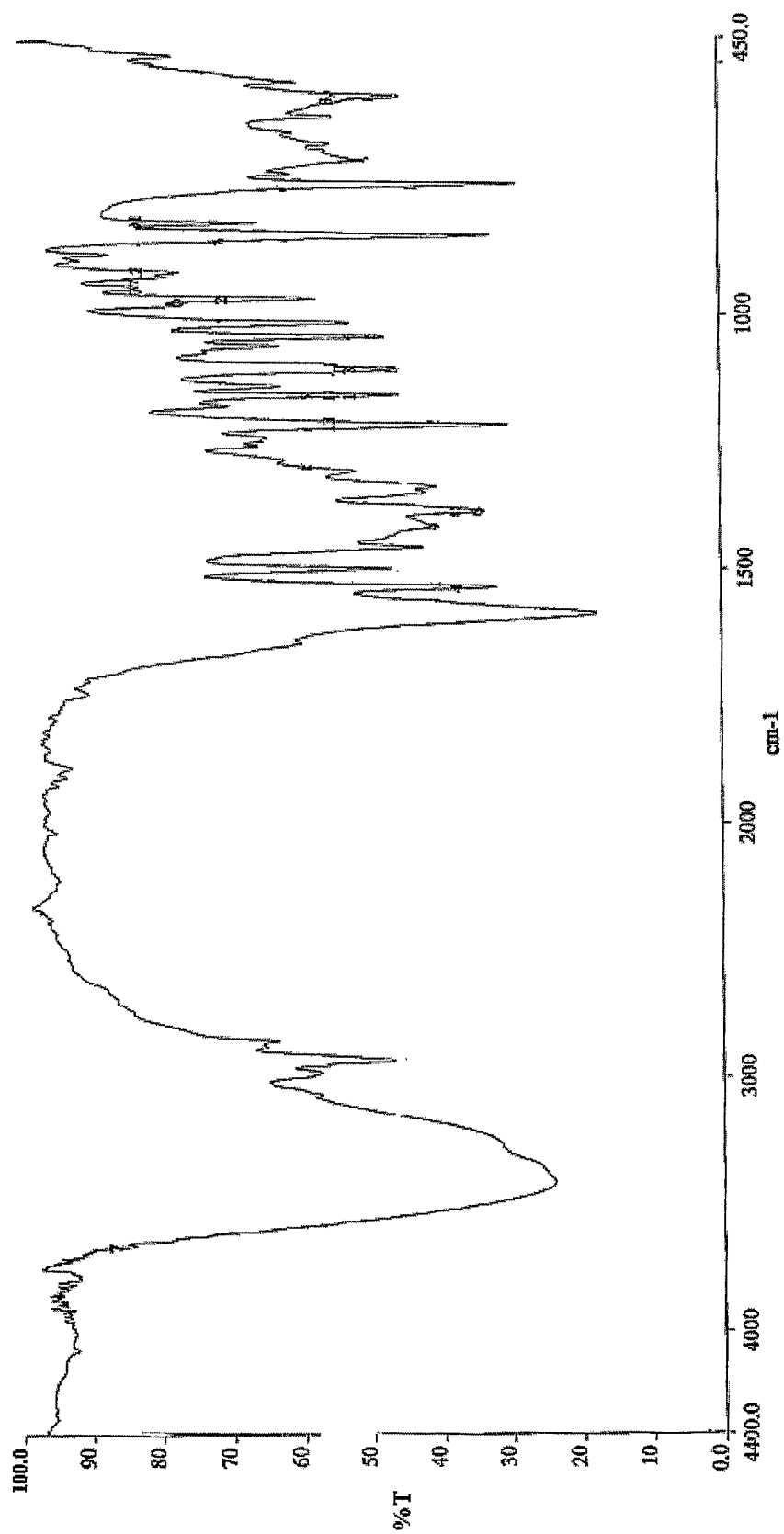


FIGURE 20

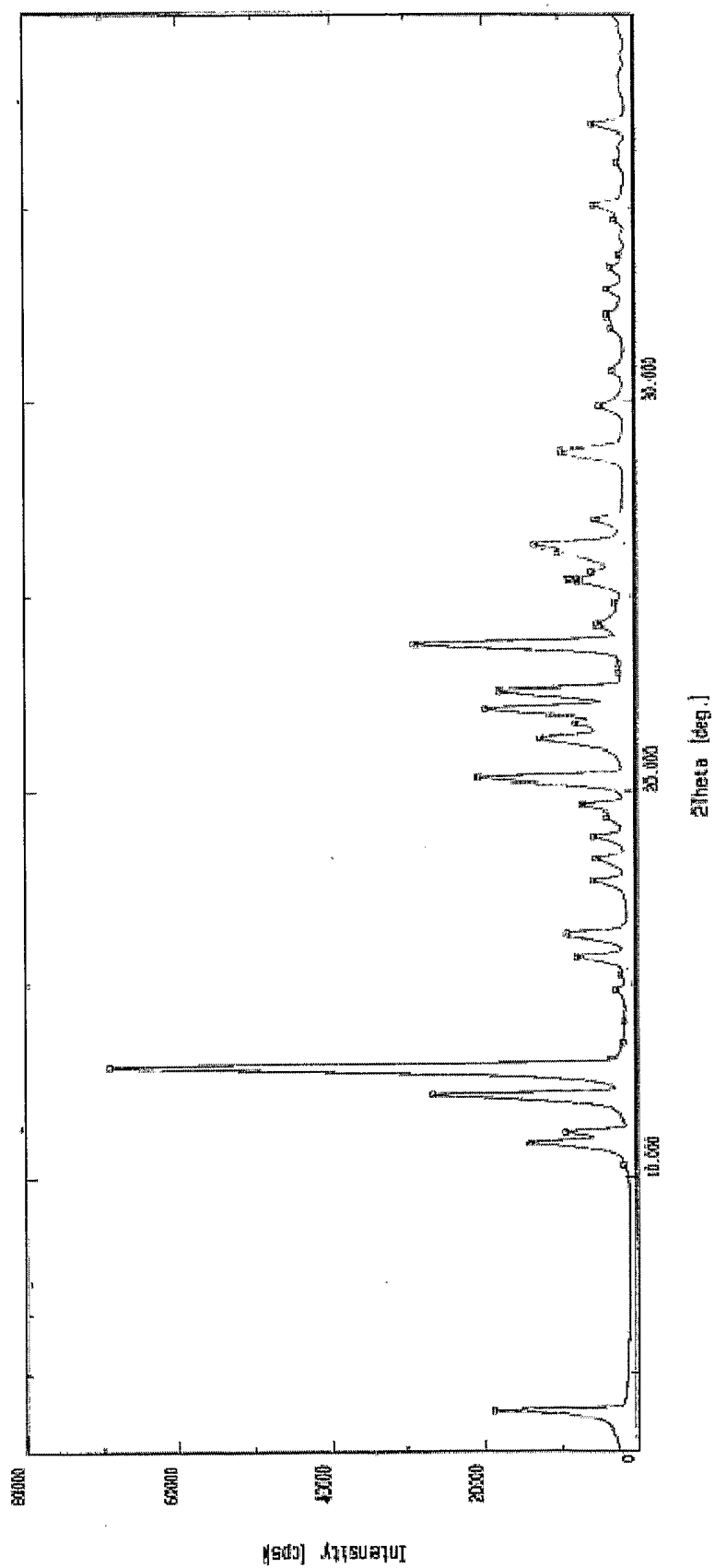


FIGURE 21

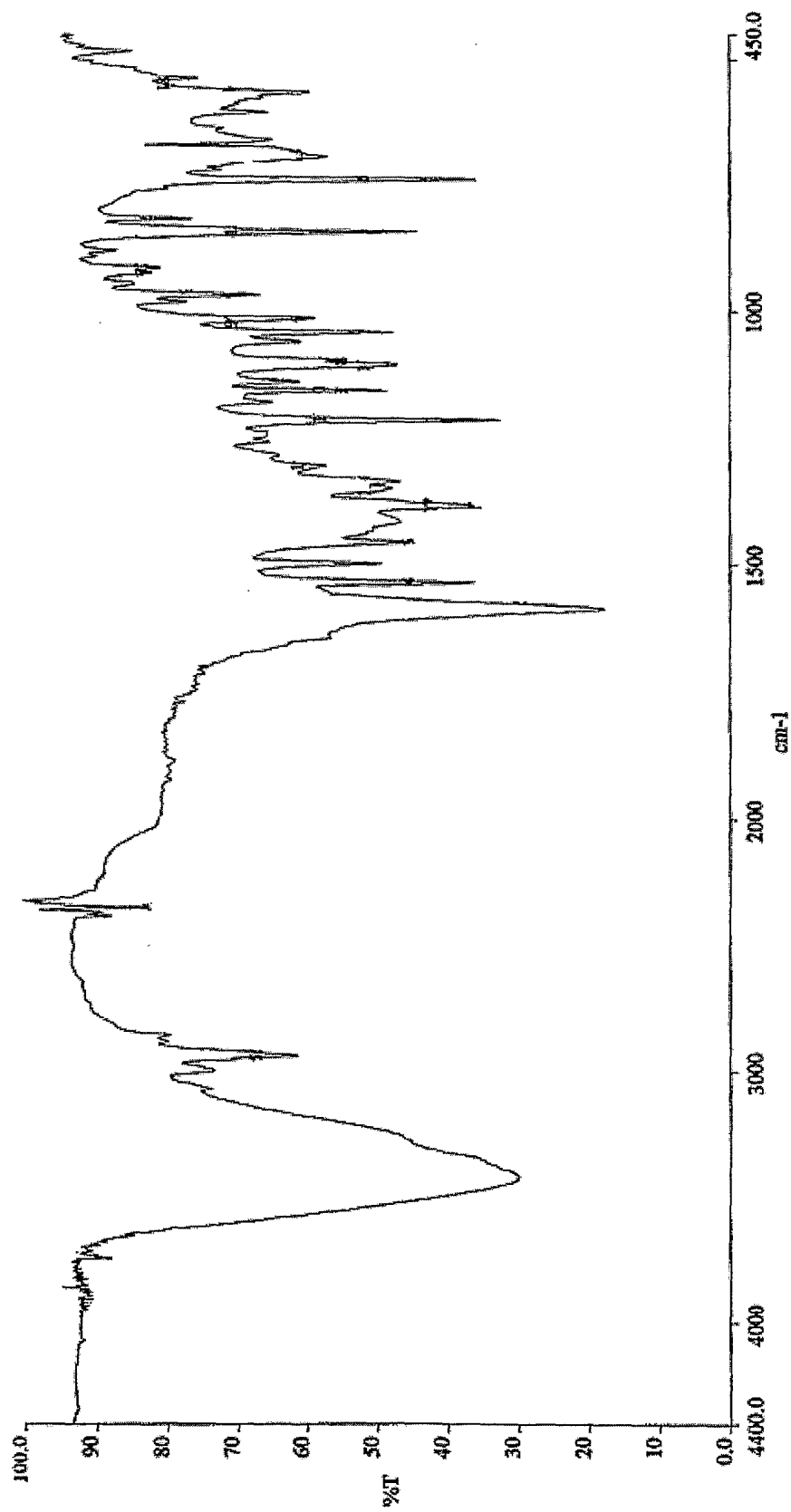


FIGURE 22

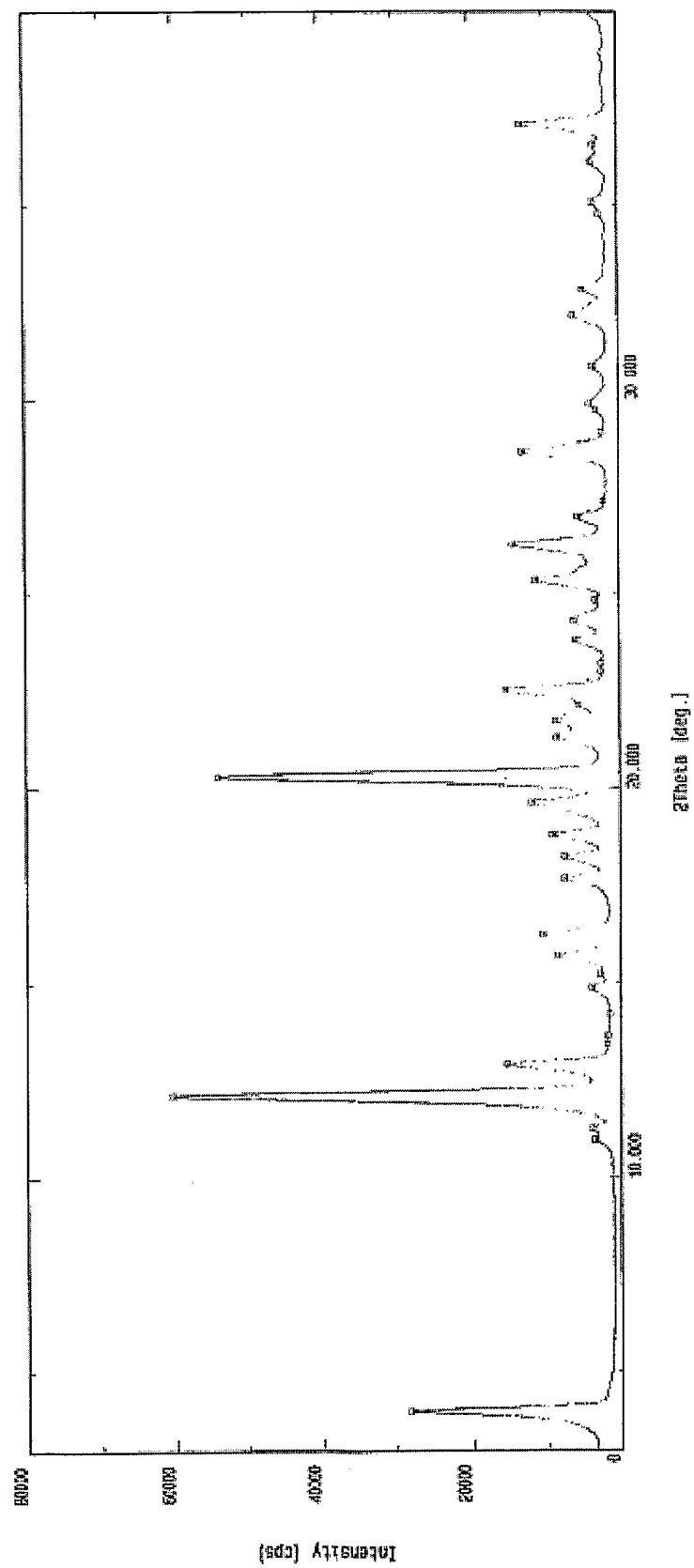


FIGURE 23

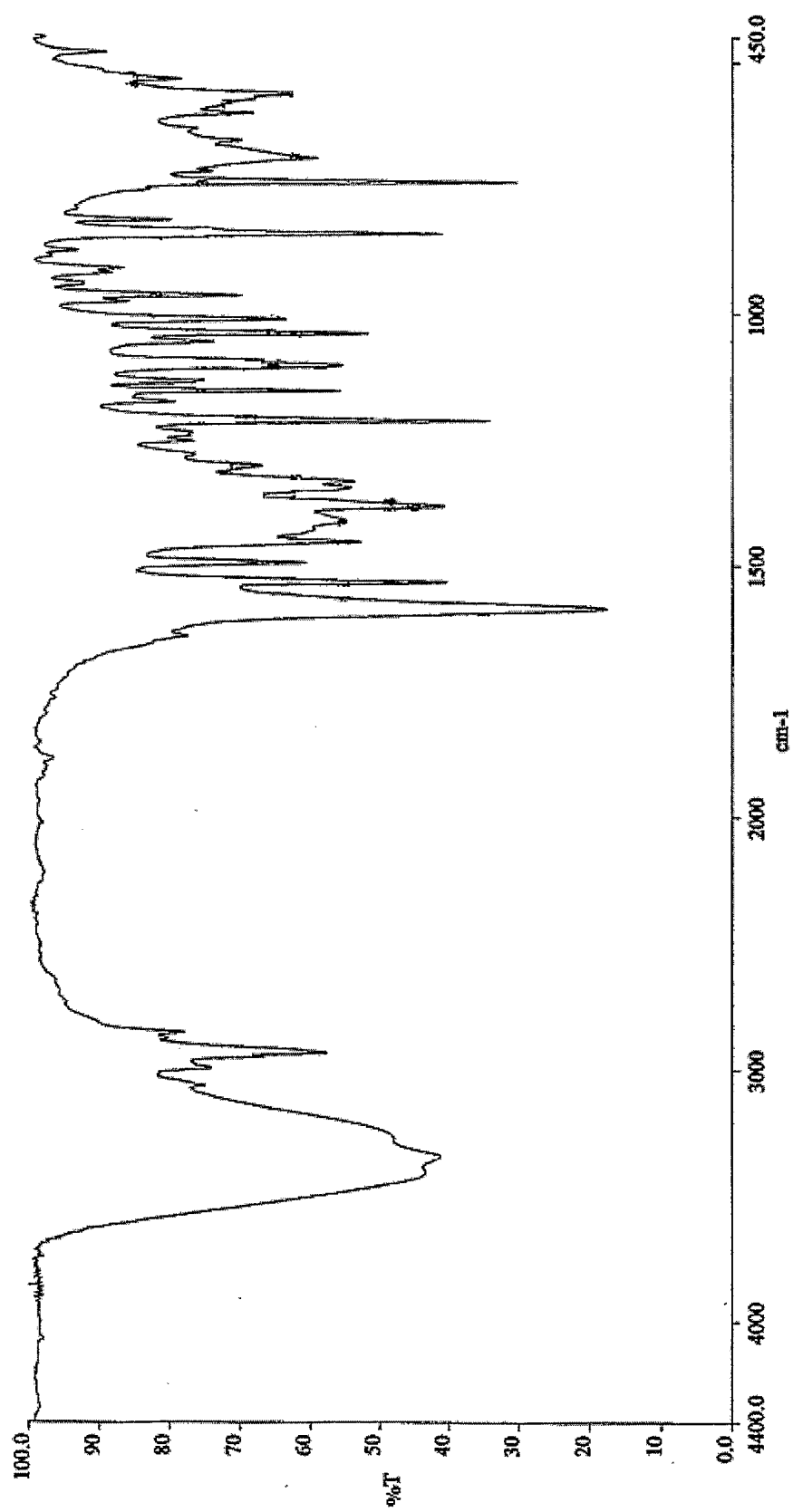


FIGURE 24

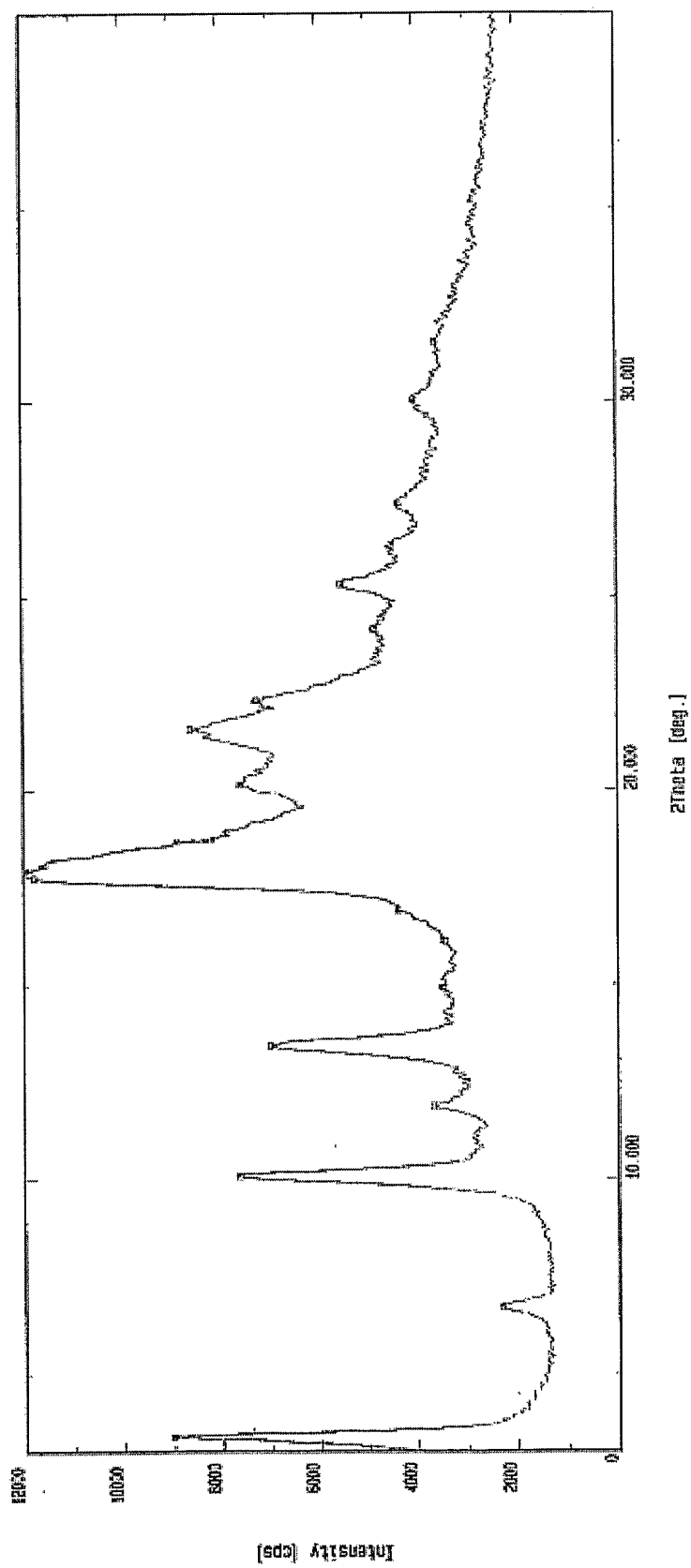


FIGURE 25

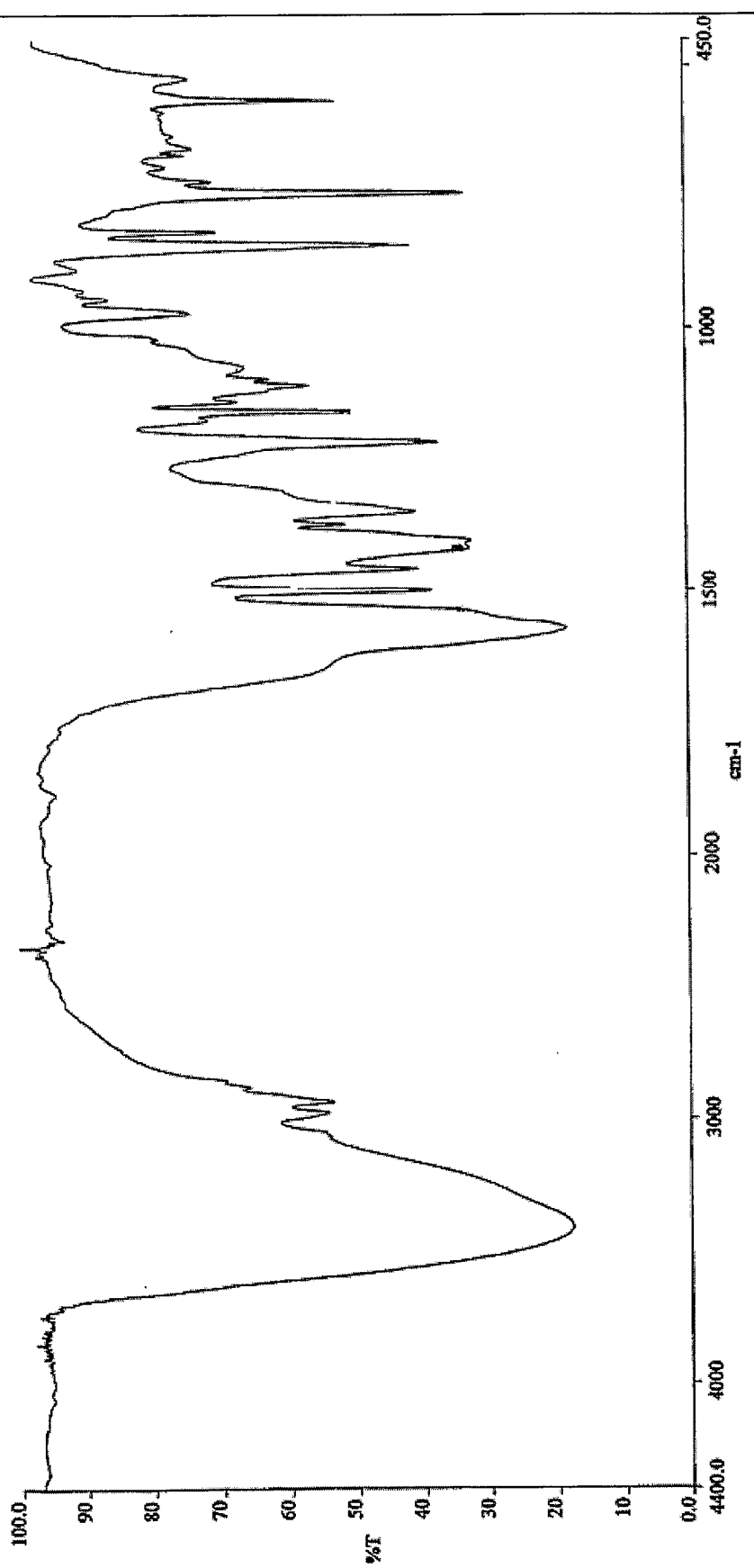


FIGURE 26

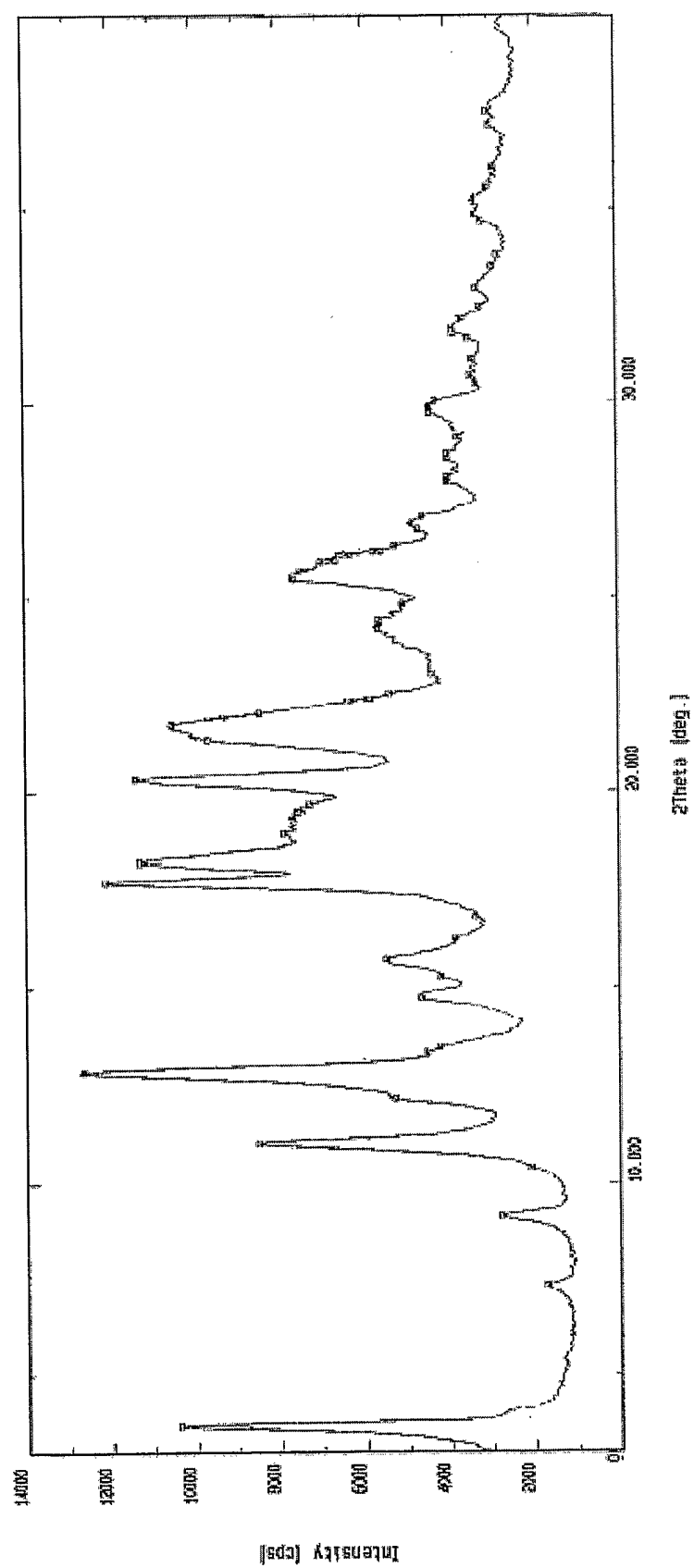


FIGURE 27

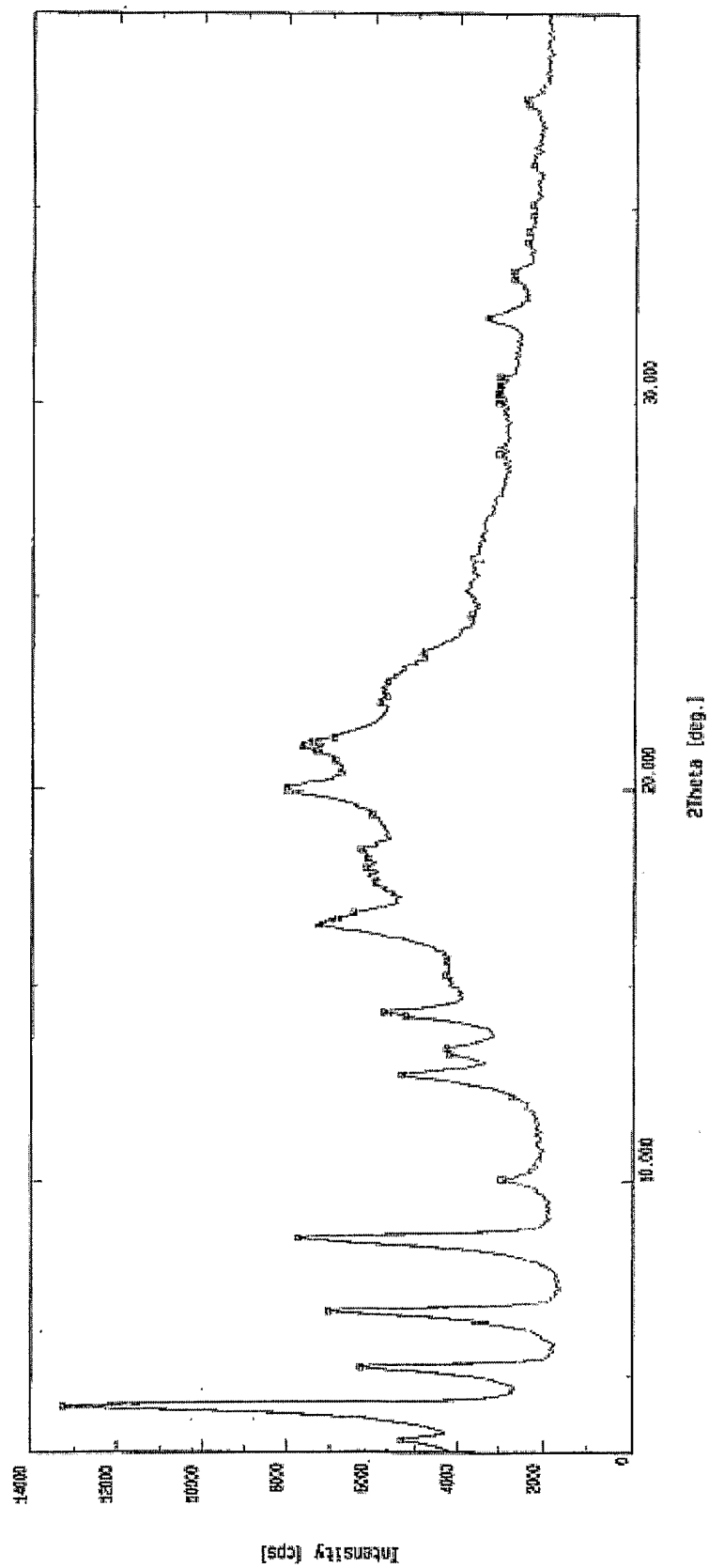


FIGURE 28

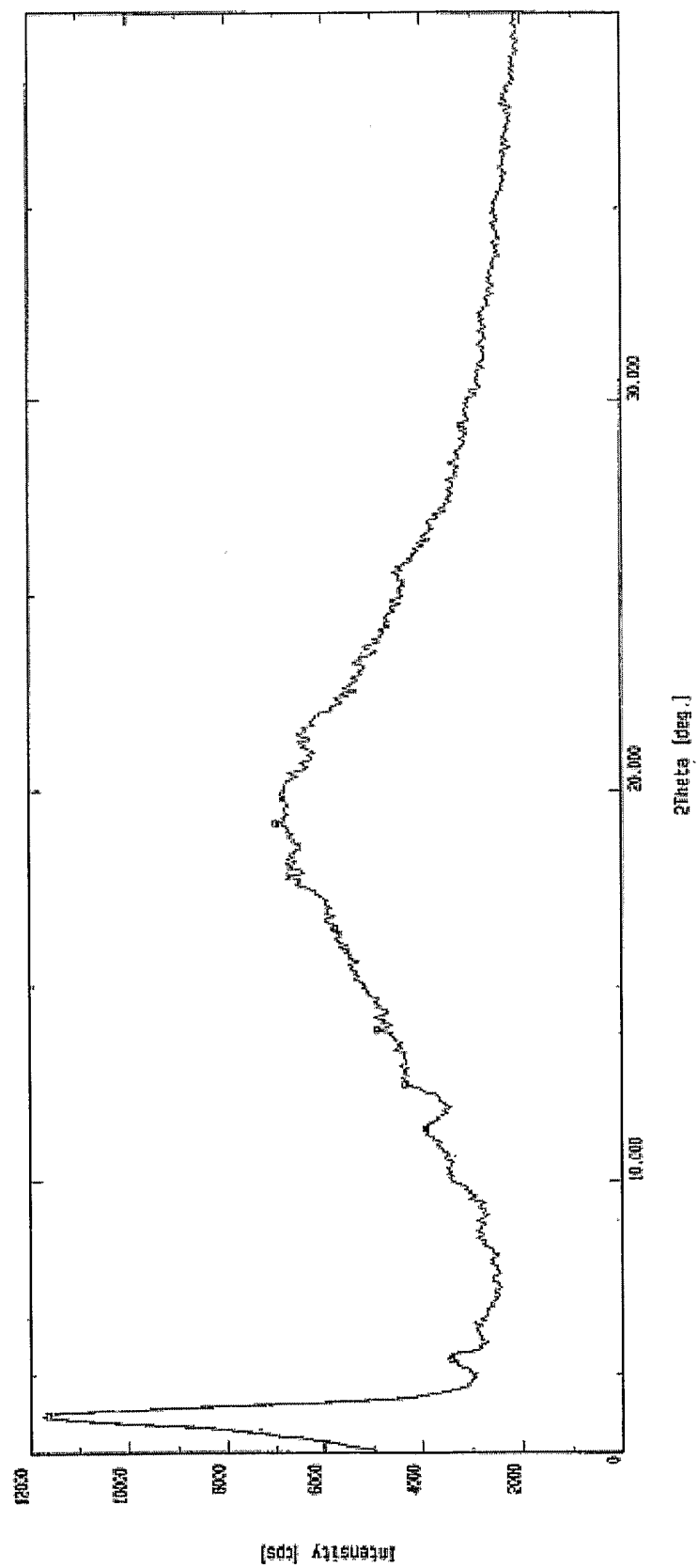


FIGURE 29

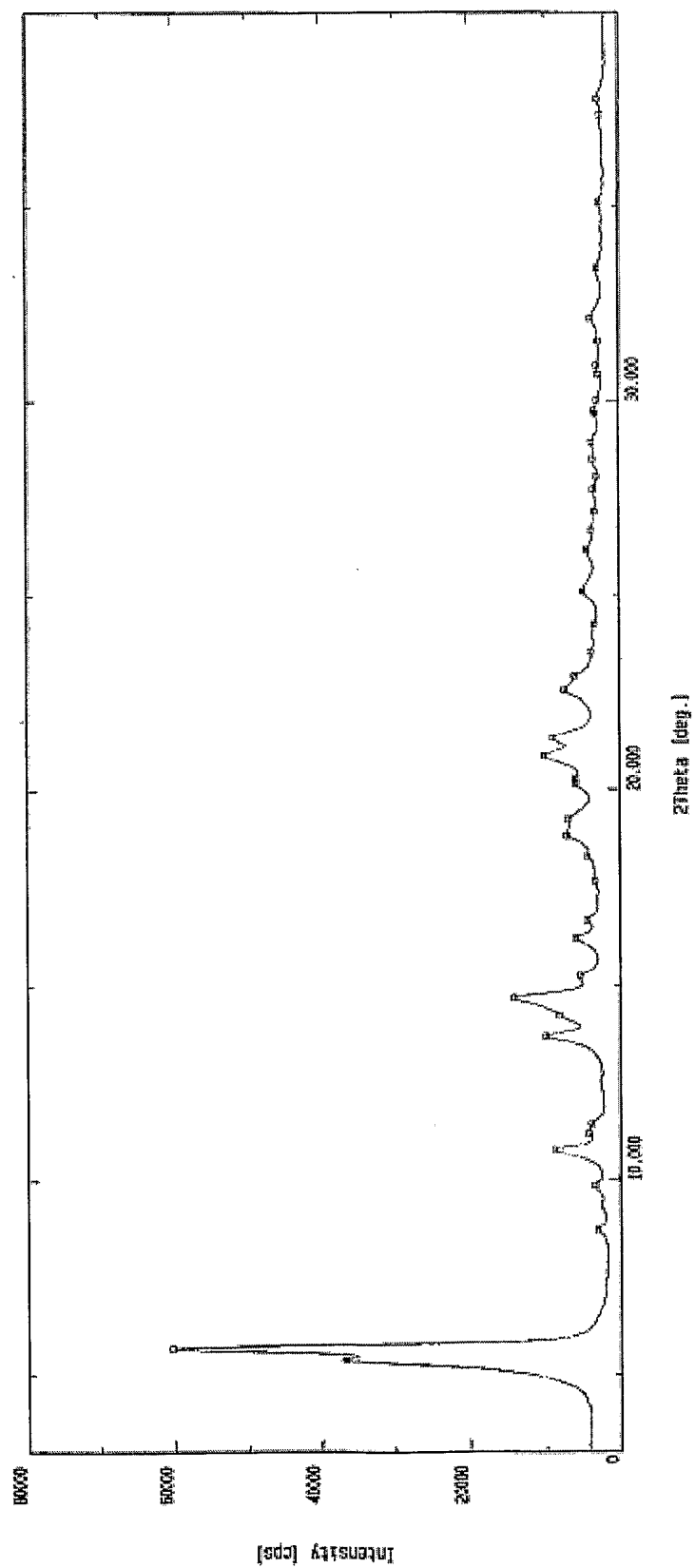
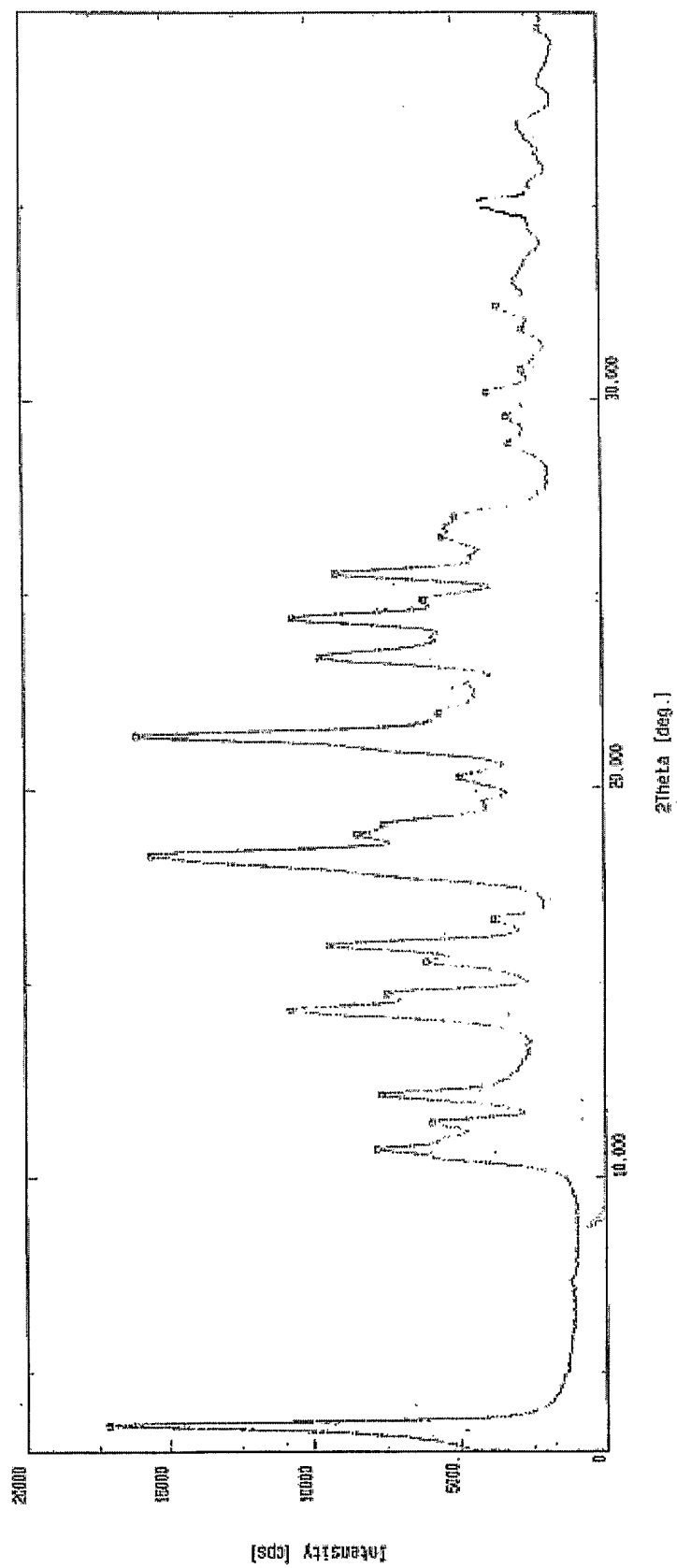


FIGURE 30



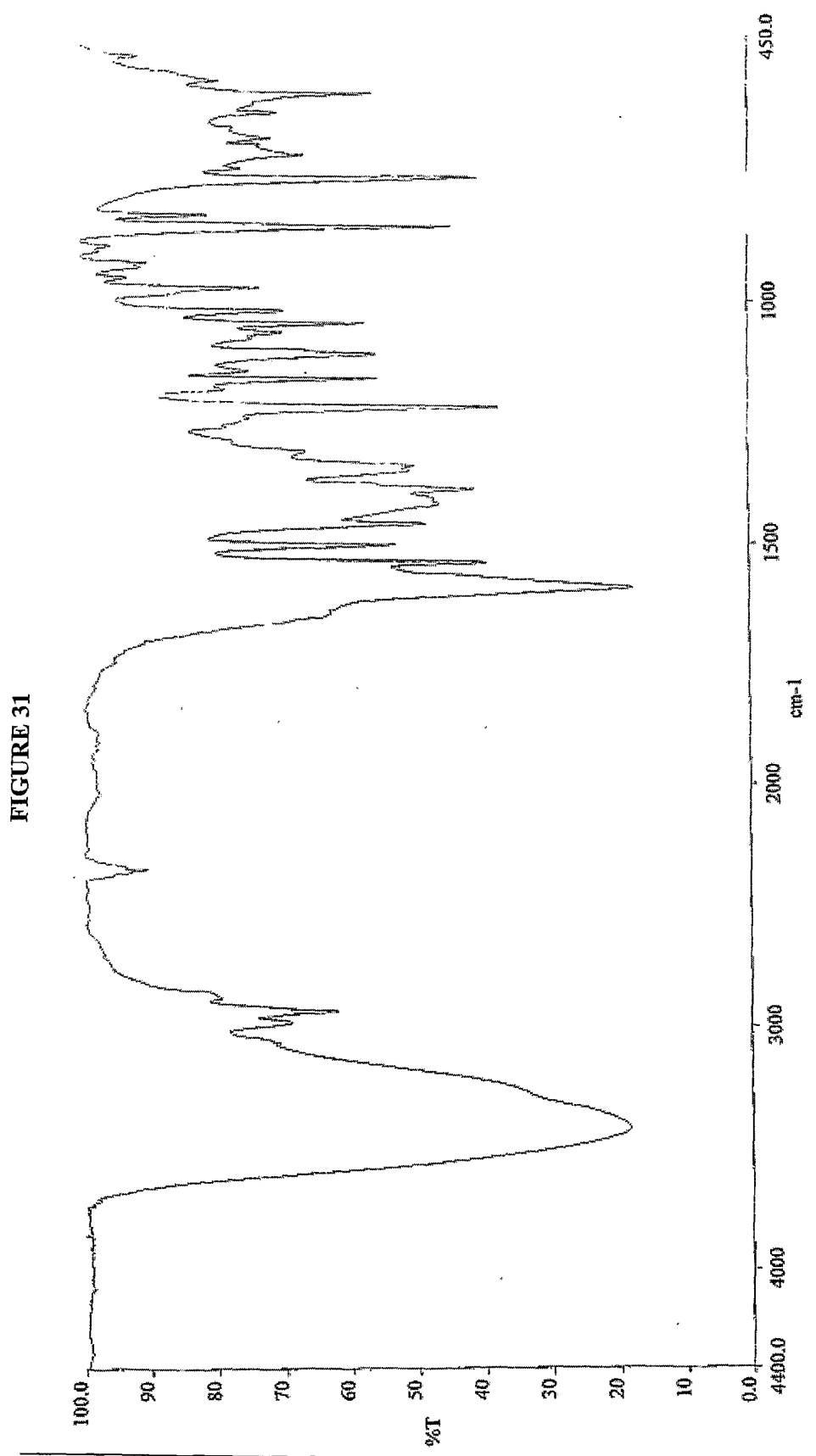


FIGURE 32

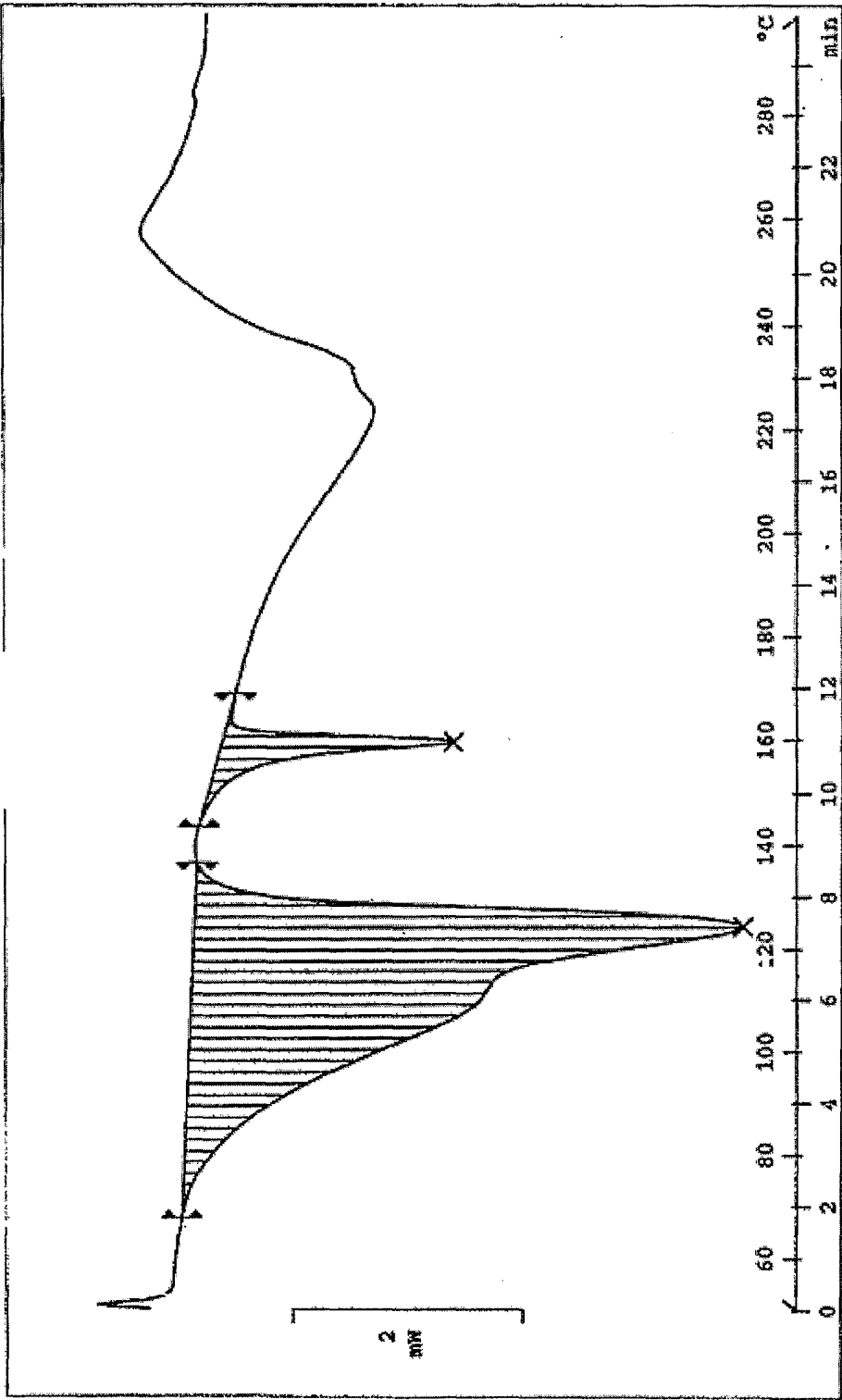


FIGURE 33

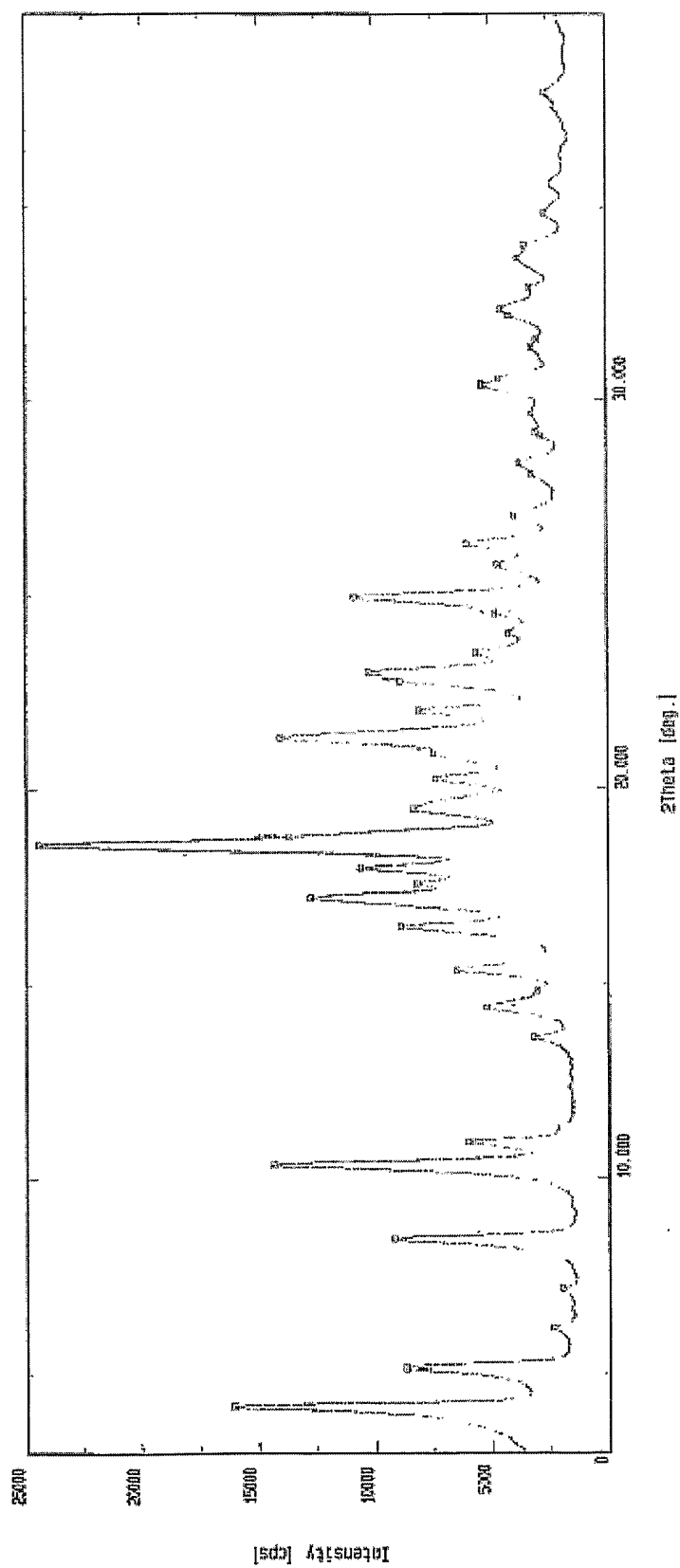


FIGURE 34

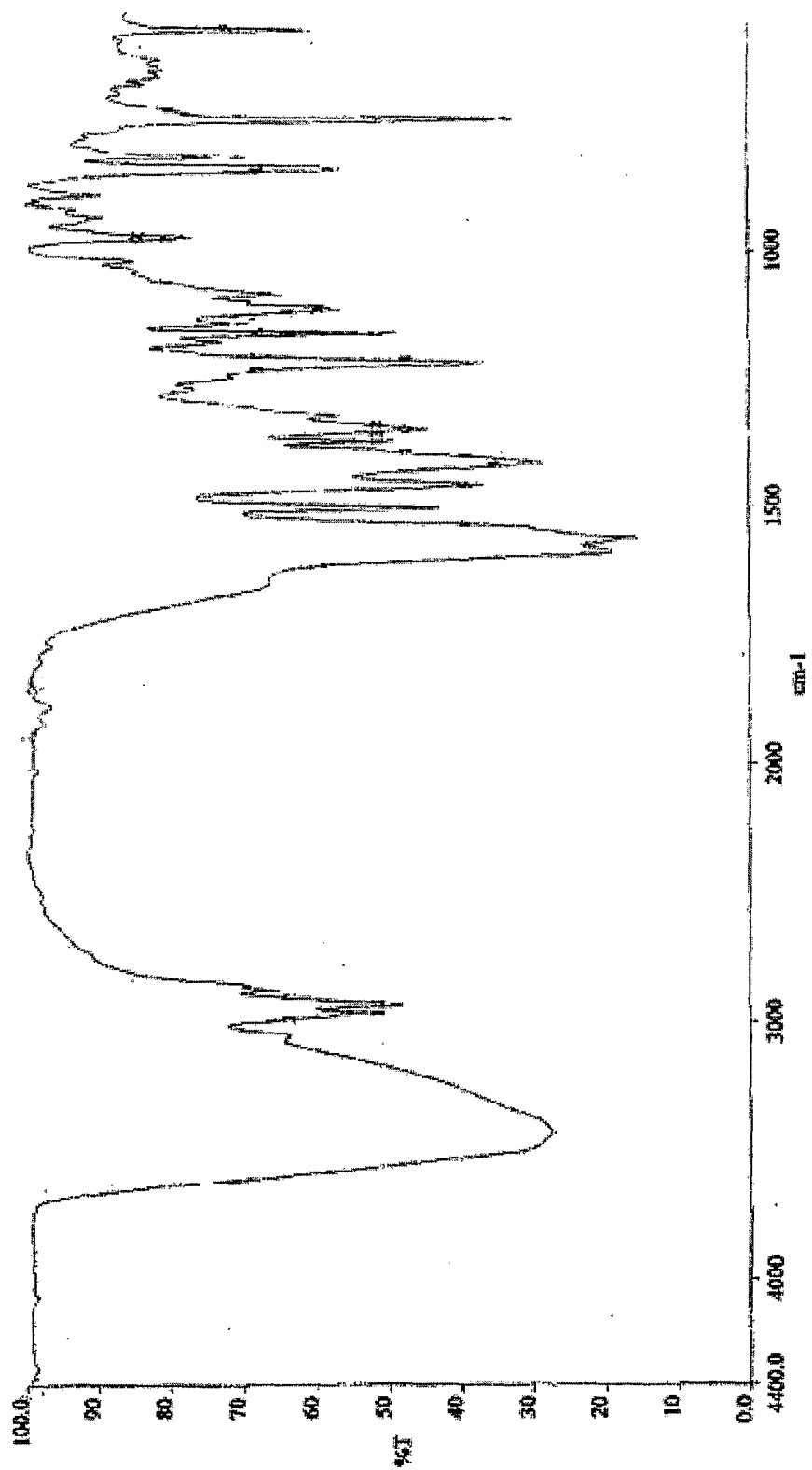


FIGURE 35

