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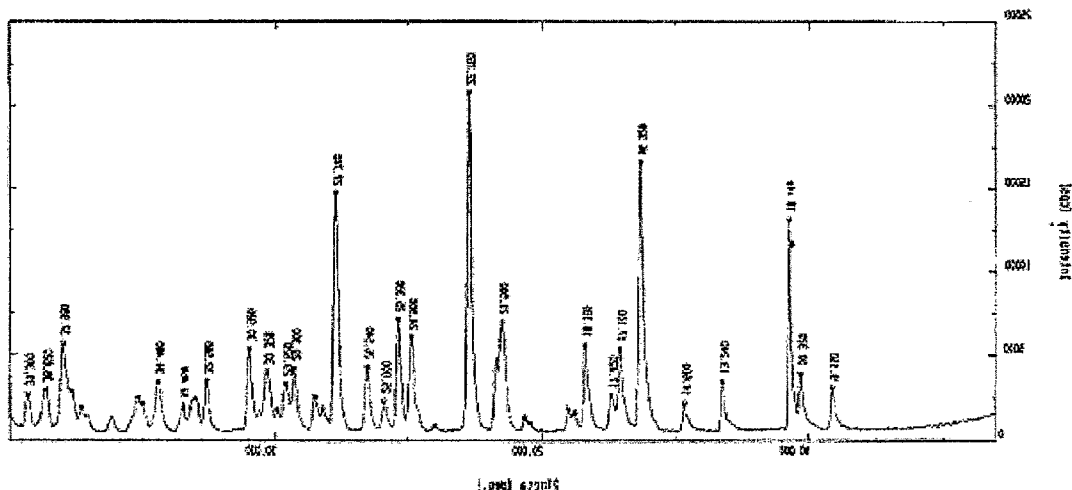
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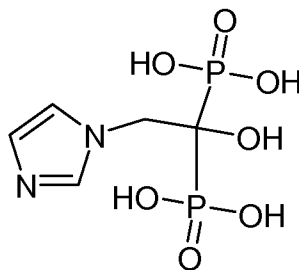
POLYMORPHIC FORM OF ZOLEDRONIC ACID AND PROCESSES FOR THEIR PREPARATION

Field of the Invention

The present invention provides a polymorphic form (Form A) of zoledronic acid and amorphous zoledronic acid. The present invention further provides processes for preparation of said Form A and amorphous zoledronic acid. In addition, the present invention provides pharmaceutical compositions comprising Form A or amorphous zoledronic acid.

Background of the Invention

Zoledronic acid is chemically, (1-hydroxy-2-imidazol-1-yl-phosphonoethyl) phosphonic acid of the Formula I,



Formula I

Bisphosphonates are a class of drugs developed for use in various metabolic diseases of bone, the target being excessive bone resorption and inappropriate calcification and ossification. Zoledronic acid belongs to the therapeutics class of geminal bisphosphonates. The principle pharmacologic action of zoledronic acid is inhibition of osteoclastic bone resorption of mineralized bone and cartilage through its binding to bone. It inhibits the increased osteoclastic activity and skeletal calcium release induced by various stimulatory factors released by tumors. It is used in the treatment of hypercalcemia (high levels of blood calcium) that may occur in patients with some types of cancer and a type of cancer called multiple myeloma (tumors formed by the cells of the bone marrow) or certain types of bone metastases (the spread of cancer).

U.S. Patent No 4,939,130 discloses a method for preparing zoledronic acid by reacting imidazol-1-yl-acetic acid with phosphoric acid and phosphorous trichloride and recrystallizing the product from water.

PCT application No WO 2005/05447 (herein after the '447 application) discloses crystalline forms of zoledronic acid and zoledronate sodium and amorphous form of zoledronate sodium. Of the crystal forms of zoledronic acid disclosed in the '447 application, the crystal

form characterized by powder X-ray diffraction pattern having peaks at 2θ values ($^{\circ}$) of 12.1, 12.8, 15.7 and 18.9 is designated as Form I. Amorphous form of the sodium salt of zoledronic acid is also reported which is obtained by treating zoledronic acid with sodium hydroxide in water followed by precipitating amorphous zoledronate sodium by concentration of the solution thereof under vacuum.

Summary of the Invention

The present inventors have developed a hitherto unknown polymorphic form of zoledronic acid, designated Form A, and the amorphous form of zoledronic acid. The present invention also provides processes for preparation of Form A of zoledronic acid, amorphous zoledronic acid and of Form I of zoledronic acid disclosed in the '447 Application.

Detailed Description of the Invention

A first aspect of the present invention provides crystalline Form A of zoledronic acid having characteristic X-ray diffraction with the following characteristic peak values (2θ): 9.2, 13.2, 14.6, 17.4, 18.4, and 25.4 ± 0.2 . The crystalline Form A exhibits characteristic Differential Scanning Calorimetric Thermogram as depicted in Figure 2 and Thermogravimetric Analysis profile as depicted in Figure 3.

A second aspect of the present invention provides a process for the preparation of crystalline Form A of zoledronic acid wherein the said process comprises of,

- a) heating an aqueous solution zoledronic acid to about 60°C to 100°C ,
- b) cooling the solution of step a) to about 30°C to -10°C ,
- c) isolating crystalline Form A of zoledronic acid from the reaction mass.

A third aspect of the present invention provides a process for the preparation of crystalline Form A of zoledronic acid wherein the said process comprises of,

- a) stirring a suspension of zoledronic acid in an organic solvent and optionally water,
- b) isolating crystalline Form A of zoledronic acid from the reaction mass thereof.

Suitable organic solvent may contain water or water may be added additionally to the reaction mixture. Suitable organic solvent consists one or more of linear or branched chain carboxylic acid esters containing 3 to 8 carbon atoms, halogenated hydrocarbons, or aromatic hydrocarbons.

The ester is preferably selected from among ethyl acetate, propyl acetate, isopropyl acetate, butyl acetate, or isobutyl acetate. The aromatic hydrocarbon is preferably selected from

among benzene, toluene, o-, m-, p-xylene or mixtures thereof. The halogenated hydrocarbon is preferably selected from among dichloromethane, 1,2-dichloroethane, or chloroform.

A fourth aspect of the present invention provides a process for the preparation of crystalline Form A of zoledronic acid wherein the said process comprises of subjecting an aqueous solution of zoledronic acid to agitated thin film drying at a temperature of about 50°C to about 90°C.

Zoledronic acid is dissolved in water and the solution is fed to agitated thin film drier at a rate of 1 to 10 ml/minute under reduced pressure of 5 to 300 mm Hg and temperature of about 50 to about 90°C to obtain crystalline Form A of zoledronic acid.

A fifth aspect of the present invention provides amorphous zoledronic acid, having characteristic X-ray diffraction pattern as depicted in Figure 5 of the accompanying drawings.

A sixth aspect of the present invention provides a process for the preparation of amorphous zoledronic acid wherein the said process comprises of subjecting an aqueous solution of zoledronic acid to spray drying.

Zoledronic acid is dissolved in water and the solution is fed to a spray drier having inlet temperature of about 50 to about 100°C, outlet temperature of about 40 to about 95°C at a rate of about 1 mL/min to about 10 mL/min to obtain amorphous zoledronic acid by using two fluid pressure nozzles and rotary atomizer.

A seventh aspect of the present invention provides a process for the preparation of Form I of zoledronic acid wherein the said process comprises of subjecting an aqueous solution of zoledronic acid to agitated thin film drying at a temperature of 90°C to about 100°C.

Zoledronic acid is dissolved in water and the solution is fed to agitated thin film drier at a rate of about 1 mL/min to about 10 mL/min under reduced pressure of about 5 to about 300 mmHg and temperature of about 90°C to about 100°C to obtain crystalline Form I of zoledronic acid.

An eighth aspect of the present invention provides a process for the preparation of Form I of zoledronic acid wherein the said process comprises of lyophilizing an aqueous solution of zoledronic acid.

Zoledronic acid is dissolved in water, the solution is frozen from about -20 to about -60°C and a pressure of about 10 to about 80 mTorr is applied. The temperature of the frozen mass is increased to about 0°C in 1 to 10 hours and then maintained at about 0°C for 1 to 24

hours. Then the temperature is increased to about 10°C in 1 to 12 hours and maintained at about 10°C for 1 to 24 hours. The mass is heated to about 20 to about 50°C and unloaded to obtain Form I of zoledronic acid.

5 A ninth aspect of the present invention provides a pharmaceutical composition comprising crystalline Form A of zoledronic acid.

A tenth aspect of the present invention provides a pharmaceutical composition comprising amorphous zoledronic acid.

10 The crystalline Form A or amorphous zoledronic acid of the present invention can be used to prepare pharmaceutical compositions by methods known in the art, for example that disclosed in U.S. 4,939,130.

Zoledronic acid can be prepared by methods known in the art, for example, using the process described in U.S. Patent No 4,939,130, which is incorporated by reference herein.

Brief Description of Figures

Figure 1 depicts powder X-ray diffractogram of crystalline Form A of zoledronic acid.

15 Figure 2 depicts Differential Scanning Calorimetric Thermogram of crystalline Form A of zoledronic acid.

Figure 3 depicts and Thermogravimetric Analysis profile of crystalline Form A of zoledronic acid.

Figure 4 depicts powder X-ray diffractogram of amorphous zoledronic acid.

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

Powder XRD of the samples were determined by using a Rigaku RU-H3R X-Ray Diffractometer X-Ray tube with Cu target anode, Power: 40 KV, scanning speed: 2 deg/min
25 step: 0.02 deg, Wave length: 1.5406 Å.

DSC thermograms were recorded using a Mettler Toledo DSC821e Differential Scanning Calorimeter, sample weight: 3-5 mg, temperature range: 50-350° C, heating rate: 20° C/min, and Nitrogen flow set at 80.0 mL/min

The percentage weight loss was recorded using a Perkin Elmer, Model Pyris 1 thermogravimetric analyzer (TGA), Temperature range: 20-350°C, Heating rate: 10° C/min, purged with Nitrogen.

EXAMPLE 1

5 **Preparation of crystalline Form A of zoledronic acid**

Zoledronic acid (175 g) was dissolved in deionized water (3.8 L) at 80 to 85°C. The solution was filtered through hyflo bed and cooled to 25°C in about 4 hours. The cooled solution was stirred at 25 to 15°C for 20 hours. The product obtained was dried at 40 to 45°C under vacuum for 4-5 hours to afford the title compound.

10 Yield: 63 g

XRD matches Figure 1.

EXAMPLE 2

Preparation of crystalline Form A of zoledronic acid

A suspension of zoledronic acid (5 g) in ethyl acetate (47.5 mL) and water (2.5 mL) was stirred at 15 to 20°C for about 36 hours. The product obtained was dried at 40 to 45°C for 4 hours to afford the title compound.

Yield: 3.3 g

XRD matches Figure 1.

EXAMPLE 3

20 **Preparation of crystalline Form A of zoledronic acid**

Zoledronic acid (5 g) was dissolved in water (100 mL) at 95 to 97°C. The solution was filtered through hyflo bed and cooled to 5 to 10°C in 10 to 15 minutes. The cooled solution was stirred for 1 hour and filtered and the product obtained was dried to afford the title compound.

Yield: 4.5 g

25 XRD matches Figure 1.

EXAMPLE 4

Preparation of crystalline Form A of zoledronic acid

Zoledronic acid (5 g) was dissolved in water (250 mL) at 60°C. The solution was maintained at 60°C and fed to agitated thin film drier at the rate of 5 ml/min under reduced pressure of 10 mm Hg. The temperature was kept at 75°C and the title compound was obtained.

30 Yield: 4.0 g

XRD matches Figure 1.

EXAMPLE 5**Preparation of amorphous zoledronic acid**

Zoledronic acid (5 g) was dissolved in water (250 mL) at 60°C. The solution was maintained at 60°C and fed to spray drier at a rate of 5 ml/min (inlet temperature: 75°C, outlet temperature 55°C) to afford the title compound.

Yield: 3.5 g

XRD matches Figure 4.

EXAMPLE 6**Preparation of amorphous zoledronic acid**

Zoledronic acid (5 g) was dissolved in water (250 mL) at 60°C. The solution was maintained at 60°C and fed to spray drier at a rate of 5 ml/min (inlet temperature: 75°C, outlet temperature at 55°C) to afford the title compound.

Yield: 3.3 g

XRD matches Figure 4.

EXAMPLE 7**Preparation of crystalline Form I of zoledronic acid**

Zoledronic acid (5 g) was dissolved in water (125 mL) at 90°C. The solution was maintained at 90°C and fed to agitated thin film drier at the rate of 5 ml/min under reduced pressure of 10 mm Hg. The temperature was kept at 95°C and the title compound was obtained.

Yield: 3.9 g

EXAMPLE 8**Preparation of crystalline Form I of zoledronic acid**

Zoledronic acid (5 g) was dissolved in water (250 mL). The solution was frozen at -40°C and maintained at -40°C for 2 hours and a pressure of 40-100 mtorr was applied. The temperature of the frozen mass was increased to 0°C in 2 hours and the mass was maintained at 0°C for 12 hours. The temperature of the mass was increased to 10°C in 2 hours and the mass maintained at 10°C for 12 hours. The mass was heated to 25°C and unloaded to obtain the title compound.

Yield: 4.1 g

We Claim:

- 1 1. Crystalline Form A of zoledronic acid having an X-ray diffraction pattern wherein
2 characteristic 2θ values are obtained at the following characteristic peak values (2θ): 9.2, 13.2,
3 14.6, 17.4, 18.4, and 25.4 ± 0.2
- 1 2. The crystalline form of claim 1, further characterized by a Differential Scanning Calorimetric
2 Thermogram as depicted in Figure 2.
- 1 3. The crystalline form of claim 1, further characterized by a Thermogravimetric Analysis
2 profile as depicted in Figure 3.
- 1 4. A process for the preparation of a crystalline form of zoledronic acid which has characteristic
2 peak values (2θ): 9.2, 13.2, 14.6, 17.4, 18.4, and 25.4 ± 0.2 , wherein said process comprises the
3 use of an aqueous solution medium for dissolving or dispersing zoledronic acid.
- 1 5. The process for claim 4 which further comprises of
2 a) heating an aqueous solution zoledronic acid to about 60°C to 100°C , and
3 b) cooling the solution of step a) to about 30°C to -10°C .
- 1 6. The process for claim 4 which further comprises of stirring a suspension of zoledronic acid in
2 a mixture of water and an organic solvent
- 1 7. The process according to claim 6 wherein the organic solvent at least one of comprising of
2 C_{3-8} esters, halogenated hydrocarbons, aromatic hydrocarbons or mixtures thereof.
- 1 8. The process according to claim 7 wherein the organic solvent comprises one or more of a
2 linear or branched chain carboxylic acid ester containing 3 to 8 carbon atoms, a halogenated
3 hydrocarbon, or an aromatic hydrocarbon.
- 1 9. The process according to claim 7 wherein the organic solvent is ethyl acetate.
- 1 10. A process of claim 4 wherein said process further comprises subjecting an aqueous solution
2 of zoledronic acid to agitated thin film drying at a temperature of about 50°C to about 90°C .
- 1 11. The process according to claim 10 wherein the temperature is about 60°C .
- 1 12. Amorphous zoledronic acid.
- 1 13. A process for the preparation of amorphous zoledronic acid wherein the said process
2 comprises of subjecting an aqueous solution of zoledronic acid to spray drying.
- 1 14. A process for the preparation of Form I of zoledronic acid wherein the said process
2 comprises of subjecting an aqueous solution of zoledronic acid to agitated thin film drying at a
3 temperature of about 90°C to about 100°C .
- 1 15. The process according to claim 14 wherein the temperature is about 90°C .
- 1 16. A process for the preparation of Form I of zoledronic acid wherein said process comprises of
2 lyophilizing an aqueous solution of zoledronic acid.

FIGURE 1

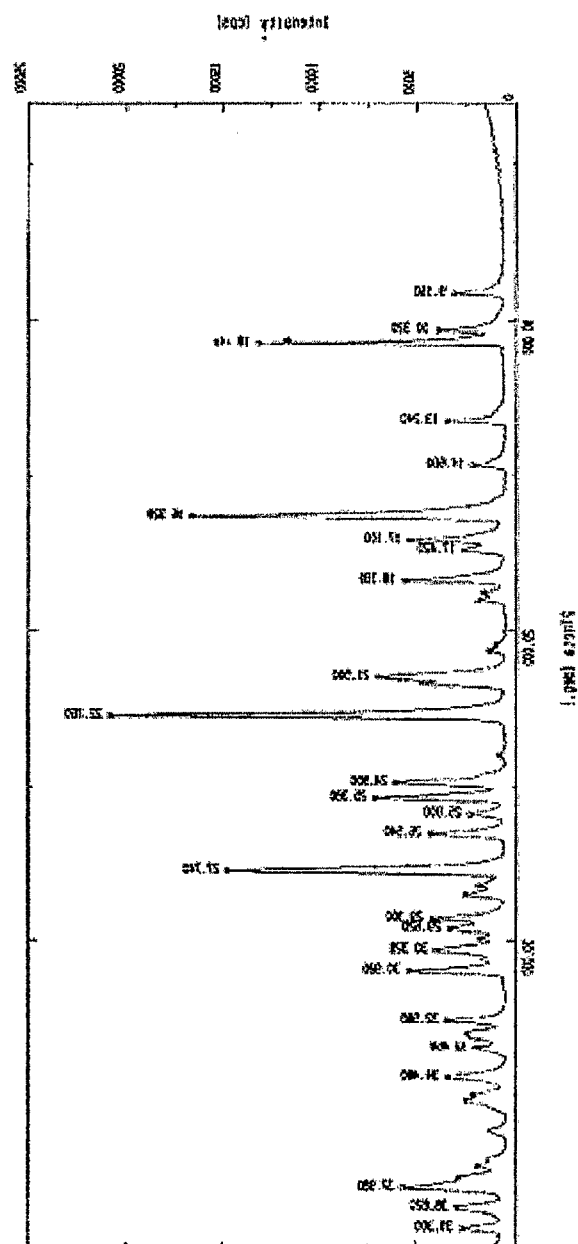


FIGURE 2

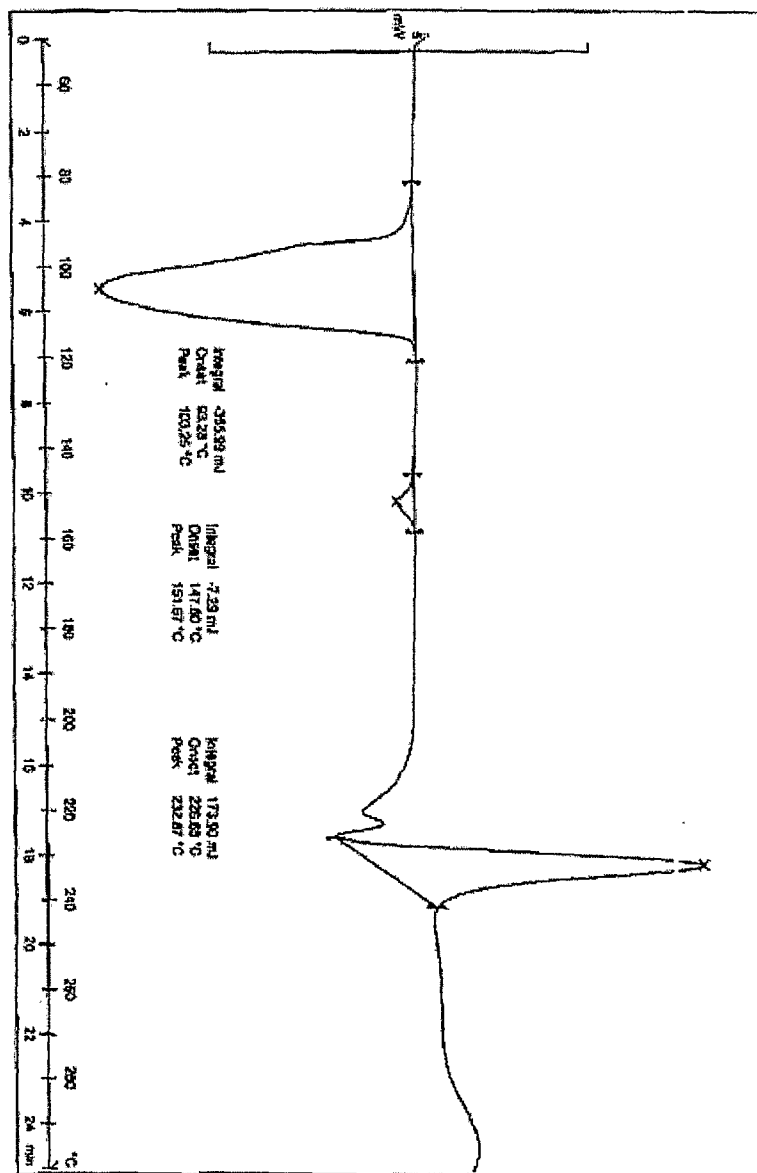


FIGURE 3

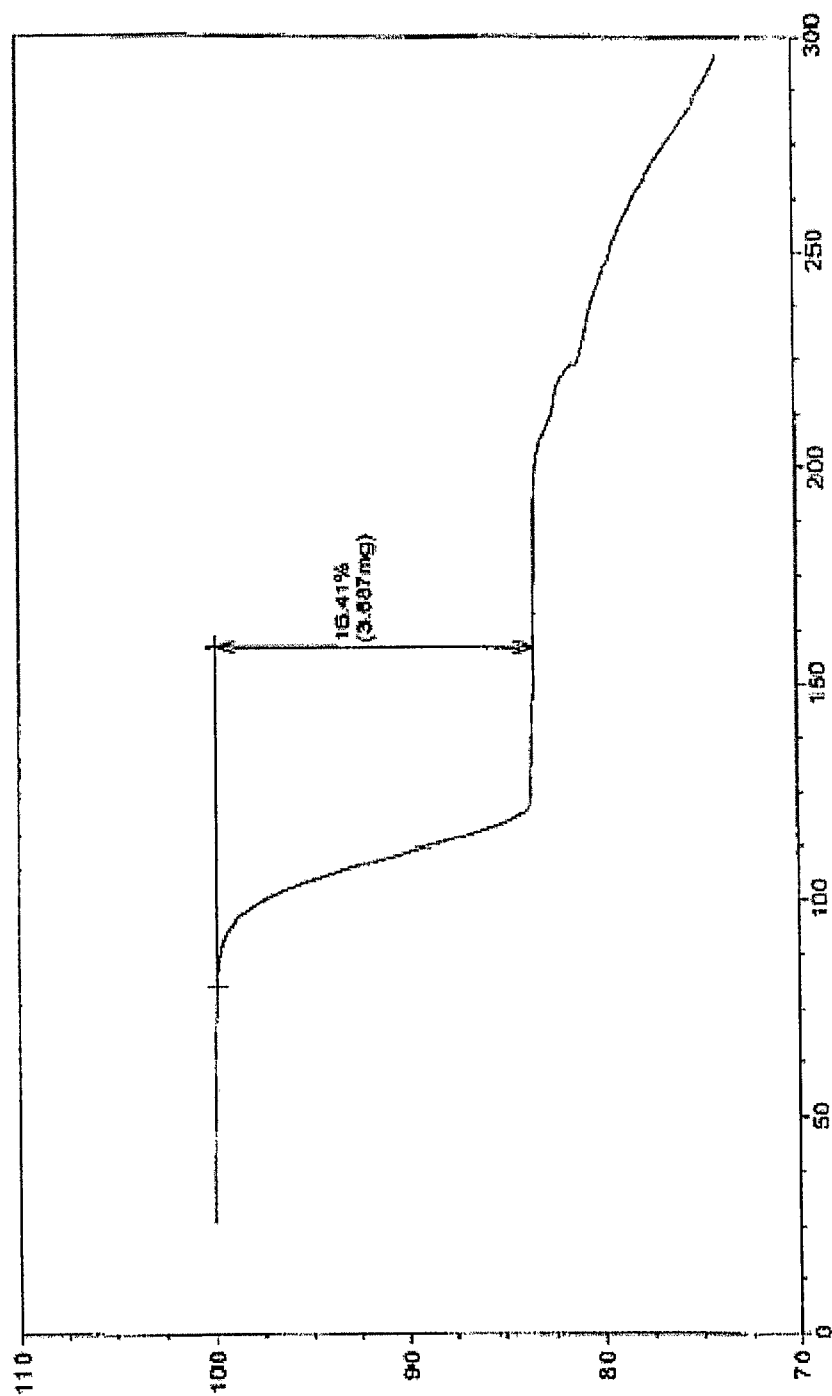


FIGURE 4