

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
13 October 2005 (13.10.2005)

PCT

(10) International Publication Number  
**WO 2005/094800 A2**

- (51) International Patent Classification<sup>7</sup>: **A61K 31/00**
- (21) International Application Number: PCT/IN2005/000095
- (22) International Filing Date: 30 March 2005 (30.03.2005)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:  
393/MUM/2004 31 March 2004 (31.03.2004) IN
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- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**  
— without international search report and to be republished upon receipt of that report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: A CO-PRECIPIATED CEFEPIME COMPOSITION AND PROCESS FOR PREPARATION THEREOF

(57) Abstract: The present invention provides a stable and sterile composition of Cefepime with a pharmaceutically acceptable non-toxic organic and inorganic base in high purity which exhibits good thermal stability which is obtained by co precipitation of composition containing non-sterile Cefepime and non-sterile pharmaceutically acceptable base. The method of preparing the co-precipitated composition of Cefepime with pharmaceutically acceptable non-toxic base comprises of, i) dissolving a composition containing mixture of non sterile Cefepime and a non sterile pharmaceutically acceptable non-toxic organic or inorganic base in water to obtain a clear aqueous solution having a pH in the range of 3.5-7 and ii) filtration of aqueous solution through 0.2 micron membrane filter and then adding the clear aqueous solution to a suitable an organic solvent followed by stirring, filtration and drying.



WO 2005/094800 A2

**A CO-PRECIPIATED CEFEPIME COMPOSITION AND PROCESS FOR PREPARATION THEREOF**

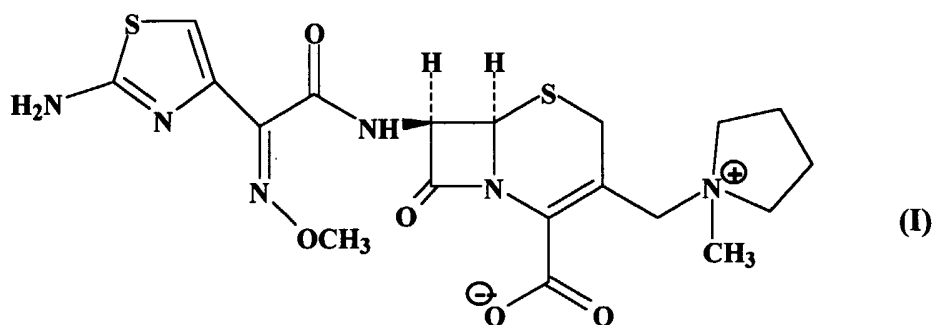
**FIELD OF THE INVENTION**

The present invention provides a sterile composition of Cefepime with a pharmaceutically acceptable non-toxic organic and inorganic base in high purity which exhibits good thermal stability which is obtained by co precipitation of non-sterile composition containing non-sterile Cefepime and non-sterile pharmaceutically acceptable base.

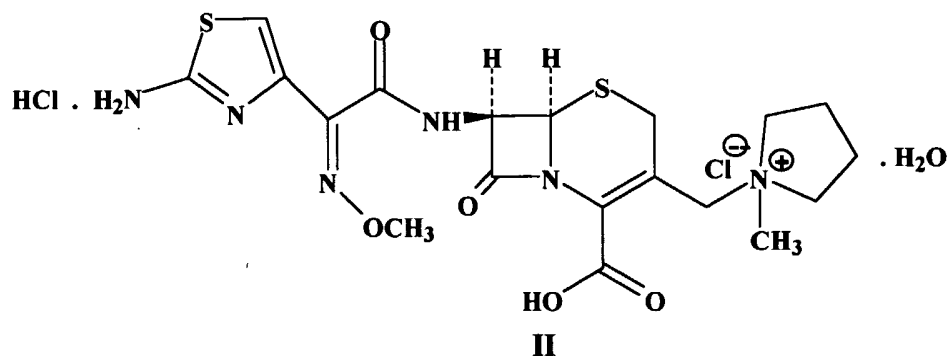
The invention further relates to provide a simple, cost-effective co precipitation method for preparation of the same.

**BACKGROUND OF THE INVENTION**

The chemical entity, 7-[ $\alpha$ -(2-aminothiazol-4-yl)- $\alpha$ -(Z)-methoxyiminoacetamido]-3-[(1-methyl-1-pyrrolidinio) methyl]-3-cephem-4-carboxylate, generically known as Cefepime, is a semi synthetic, fourth generation injectable cephalosporin antibiotic effective against infections caused by both Gram-positive and Gram-negative organisms. The compound, which exists in the zwitterion form, is represented by formula (I).



Cefepime, either because of its poor solubility in water or its inherent instability in zwitterionic form, is administered in the form of acid addition salts. The marketed MAXIPIME<sup>®</sup> formulation of Cefepime contains Cefepime dihydrochloride monohydrate salt of formula II as the active ingredient.



- 5 U.S. Pat. No. 4,406,899 discloses Cefepime in the zwitterion form and the corresponding acid addition salts. However, there is neither any enabling disclosure for preparation of the acid addition salts nor any mention of the solid-state nature of the product in the specification.
- 10 Crystalline acid addition salts of Cefepime such as the  $H_2SO_4$ , di- $HNO_3$ , HCl, di-HCl, and sesqui- $H_3PO_4$  salts and their solvates are disclosed in U.S. Pat. No. 4,910,301. The patent mentions that the zwitterion form disclosed in US '899 is unstable both as a dry powder and as an injectable composition and requires special packaging and storage conditions. The US patent '301 further discloses that when Cefepime is in zwitterionic
- 15 form it loses 30% activity at 45°C in one week. In contrast, US '301 patent claims that the crystalline material obtained therein exhibits excellent thermal stability and is hence more suited for formulation into an injectable dosage form. This implies that the zwitterion form of US '899 is probably an amorphous like crystalline material which exhibits very poor stability on storage.
- 20 Further, US '301 patent discloses selective process for preparation of the crystalline acid addition salts which comprises of dissolving the zwitterion in a mineral acid and causing crystallization by addition of a solvent such as acetone or isopropanol, followed by filtration, washing and drying to obtain the acid addition salt. This process is usually
- 25 conducted in sterile conditions and in an aqueous medium resulting in an acidic solution

thereby leading to extensive corrosion of the reactor vessel, which calls for the use of special corrosion-resistant reactors.

However, the above mentioned acid addition salts of Cefepime cannot be administered  
5 directly after reconstitution with sterile water as they provide acidic solutions which  
provoke unacceptable irritation on intravenous administration and unacceptably painful  
sensation on intramuscular administration. Also some of the acid addition salts have  
reduced solubility's which are insufficient for typical injectable compositions. To  
overcome these limitations, the acid addition salt compositions are mixed with buffering  
10 agents during reconstitution to provide a pH of about 3.5 to about 7.

Another alternative to overcome the limitations associated with acidic solutions is  
utilizing the acid addition salts in physical admixture with a pharmaceutically acceptable  
base. Such a composition is disclosed in U.S. Pat. No. 4,994,451 and U.S. Pat. 5,244,891  
15 wherein, injectable compositions of temperature stable acid addition salts of Cefepime in  
physical admixture with a pharmaceutically acceptable non-toxic organic or inorganic  
base, specifically, arginine in proportions to provide a pH of about 3.5 to about 7 on  
dilution with water to injectable concentration, are described. The physical admixture is  
prepared by blending the sterile salt and the base into a uniform blend, e.g. utilizing a  
20 standard blender in a dry atmosphere, and is then preferably filled into a vial or other  
container, all under aseptic conditions.

The admixtures mentioned hereinabove require the use of sterile raw materials and  
totally aseptic and dry conditions, thus rendering the process expensive. Moreover, the  
25 physical admixtures of the crystalline, stable Cefepime acid addition salts and L(+)  
arginine are known to exhibit poor solid state stability at elevated temperatures. Also,  
anhydrous L(+) arginine is extremely hygroscopic and it can accept two moles of water  
of crystallization. The physical admixtures need to be vacuum-dried under a variety of  
conditions, preferably, using the lyophilization technique, to remove free extraneous  
30 water.

U.S. Pat. No. 4,808,617 claims a stable antibiotic composition consisting of amorphous Cefepime zwitterion formed by lyophilization or co solvent precipitation of an aqueous solution of Cefepime zwitterion and a salt or mixture of salts. Solvent such as acetone or isopropanol is used to precipitate the zwitterion-salt complex. The salt is one wherein the  
5 cation is selected from the group consisting of sodium, lithium, calcium and magnesium and the anion is selected from chloride, bromide and iodide. This patent further claims a stable solvates of antibiotic composition as mentioned above.

U.S. Pat. No. 5,095,011 claims a stable, amorphous, lyophilized dihydrochloride salt of  
10 Cefepime and a reconstituted, injectable composition which comprises an effective amount of the amorphous salt in an aqueous solution having a suitable organic or inorganic base wherein the pH of the resulting solution is between 3 and 7.0.

Although the patent claims that the amorphous form of Cefepime is stable, it requires  
15 lyophilization or freeze-drying. Lyophilization is not cost-effective and universal since it involves the utilization of an expensive lyophilizer and moreover, the method is exclusive to only those manufacturers who have such a facility. Also the composition requires external addition of suitable base during reconstitution.

20 From the foregoing, it would be apparent that the prior art methods for manufacture of a sterile powder composition of injectable Cefepime suffer from the following limitations, viz.

- 25 i) use of mineral acid under aqueous conditions which results in extensive corrosion of the reactor vessel by the acidic solution and calls for the use of special corrosion-resistant reactors.
- ii) requires dry, sterile conditions for blending, thus adding to the cost of the process.
- iii) requires sterile raw materials which render the method expensive.
- iv) not cost-effective since such methods involve lyophilization, requiring capital  
30 expenditure for installation of a lyophilizer.
- v) the methods do not have universal applicability since they are exclusive only to those manufacturers who have an in-house lyophilizer.

We have surprisingly found that by co-precipitating the composition containing mixture of non-sterile Cefepime with a pharmaceutically acceptable non-sterile non-toxic organic or inorganic base, a stable co precipitated sterile composition of Cefepime and non-toxic base is obtained. This co precipitation method does not have stringent requirements of prior art processes as described above. More over, the co precipitated sterile composition can be administered as an injectable directly after reconstitution with water.

### **SUMMARY OF THE INVENTION**

10 The present invention relates to a sterile co-precipitated blend of a Cefepime salt with a pharmaceutically acceptable non toxic base in high purity and having good thermal stability, and a simple, cost-effective, selective solvent precipitation method for its preparation.

15 The process does not require separate facilities for the preparation of sterile acid addition salt of Cefepime and of sterile pharmaceutically acceptable non-toxic base, and a sterile blender to prepare their admixture.

Depending on the selection of solvents and control of the process parameters, the resulting co precipitated composition of cefepime and non-toxic base can be obtained in substantially amorphous, semi crystalline or crystalline form.

The term "co precipitation" utilised herein to mean adding aqueous solution of composition containing non sterile cefepime and a non sterile non-toxic base to a suitable organic solvent to co precipitate both cefepime as well as non toxic base or adding a suitable organic solvent to aqueous solution of composition containing non sterile cefepime and a non sterile non-toxic base to co precipitate both cefepime as well as non toxic base. The composition thus obtained is termed as "co precipitated composition"

30 Thus, in one aspect of the present invention, there is provided a sterile co-precipitated injectable Cefepime composition, which exhibits good stability before and after reconstitution with water.

In another aspect, the present invention provides a simple, cost-effective method for preparation of sterile Cefepime dihydrochloride-L(+)-arginine mixture useful in the pharmaceutical composition.

5

In yet another aspect, the present invention provides a stable, co precipitated blend of Cefepime with a pharmaceutically acceptable organic or inorganic base which can be administered directly after reconstitution with sterile water without further pH adjustment.

10

According to a preferred aspect there is provided a process to obtain pharmaceutical composition by co precipitation of cefepime and a pharmaceutically acceptable non-toxic base comprising of:

- 15 (i) dissolving an admixture of cefepime acid addition salt and solvates thereof with pharmaceutically acceptable non toxic organic and inorganic base in water to obtain a clear aqueous solution having a pH in the range of 3.5-7, and
- (ii) filtering the aqueous solution through 0.2 micron membrane filter and then adding the clear aqueous solution to a suitable organic solvent  
20 followed by stirring, filtration and drying.

The experimental conditions are simple and applicable to large-scale production.

### **DETAILED DESCRIPTION OF THE INVENTION**

25 The present invention provides a stable co-precipitated composition of Cefepime with a pharmaceutically acceptable non-toxic organic or inorganic base.

In another aspect of the present invention, there is provided a process for manufacture of injectable Cefepime composition by a selective co-precipitation process comprising:

- 30 (i) dissolving a composition containing mixture of non sterile Cefepime and a non sterile pharmaceutically acceptable non-toxic organic or inorganic base in water to obtain a clear aqueous solution having a pH in the range of 3.5-7, and

- (ii) filtration of aqueous solution through 0.2 micron membrane filter and then adding the clear aqueous solution drop wise to an organic solvent followed by stirring, filtration and drying.

5 The sterile dry powder can then be filled into a vial or other container.

In the above-mentioned process, alternatively, an organic solvent can be added drop wise to the clear aqueous solution of composition containing non-sterile Cefepime and a non-sterile pharmaceutically acceptable non-toxic organic or inorganic base.

10

Since the aqueous solution of Cefepime acid addition salt and arginine has a pH of 4-6, it does not lead to corrosion of the reactor vessel unlike in prior-art methods.

Suitable organic or inorganic bases in the composition according to the invention include  
15 sodium citrate, potassium citrate, N-methylglucosamine, N-methylglucamine, L(+)-lysine, L(+)-arginine tris(hydroxymethyl) aminomethane,  $\text{NaHCO}_3$ ,  $\text{Na}_2\text{CO}_3$ ,  $\text{NaH}_2\text{PO}_4$ ,  $\text{Na}_2\text{HPO}_4$ ,  $\text{Na}_3\text{PO}_4$ ,  $\text{KHCO}_3$ ,  $\text{K}_2\text{CO}_3$ ,  $\text{KH}_2\text{PO}_4$ ,  $\text{K}_2\text{HPO}_4$  and  $\text{K}_3\text{PO}_4$ . Most preferred bases in the composition are L(+)-lysine and L(+)-arginine.

20 A non-sterile composition containing various crystalline acid addition salts of Cefepime sulfuric, di-nitric, monohydrochloric, dihydrochloric, and di- and sesquiorthophosphoric acid addition salts or solvates thereof can be used for the process of present invention.

The molar ratio of Cefepime acid addition salt or solvates thereof to the pharmaceutically  
25 acceptable base in the composition can be in the range of 1:1 to 1:5, preferably in the range of 1:2 to 1:3.

Suitable solvents for co-precipitation is water miscible solvent such as acetone, methanol, ethanol, acetonitrile, tetrahydrofuran, dimethylformamide and isopropanol or mixtures  
30 thereof. Isopropanol is the preferred solvent.



Such a sterile co precipitated composition on reconstitution with a suitable solvent, such as sterile water, gives an injectable solution having pH in the range of 3-7 which is amenable for I.M. or I.V. administration directly without further pH adjustment.

- 5 The sterile composition of Cefepime-L(+) arginine obtained by co-precipitation as per method of present invention exhibits comparable stability with that of the marketed sample of Maxipime<sup>®</sup> as indicated by the formation of impurities up to 1.78% in the marketed sample at 25±2°C (60±5RH) in one month. The stability of amorphous composition of Cefepime-L(+) arginine obtained by co-precipitation as per method of  
10 present invention is shown in Table 1

**Table 1 Stability data at 25±2°C (60±5RH)**

Time	Total impurity (% by HPLC)		Powder XRD of samples of present invention
	Marketed sample of Maxipime <sup>®</sup>	Sample from present invention	
Initial	0.41	0.42	Figure 1
After 1 month	1.78	1.25	Figure 2

- 15 The sterile composition of cefepime and non-toxic base obtained by co-precipitation can be present in substantially amorphous, semi crystalline or crystalline form depending on the selection of solvents and control of the process parameters. The substantially amorphous composition of cefepime and L(+)arginine obtained by co-precipitation as per method of the present invention is shown in Figure 1.

- 20 The invention is illustrated in the following examples.

- The starting material i. e. composition containing admixture of crystalline cefepime dihydrochloride monohydrate and L-arginine available from the market was used. The powder XRD of the starting material used is shown in Figure 3. Solvents were filtered  
25 through 0.2 micron membrane filter before use.

### Example 1

Composition containing crystalline cefepime dihydrochloride monohydrate and L-arginine (50 gm) was dissolved in demineralized water (50 ml) at 25-30°C. The pH of clear solution was 5.4. The clear solution was filtered through 0.2 micron membrane filter and then added to isopropyl alcohol (1500 ml) with stirring at 25-30°C. After complete addition stirring was continued for 1 hour at 25-30°C. Solid was filtered, washed with isopropyl alcohol (500 ml) and dried under vacuum at 25-30°C for 14 hours. Yield of co-precipitated composition was 49.8 gm. HPLC purity 99.4%.

### 10 Example 2

Composition containing crystalline cefepime dihydrochloride monohydrate and L-arginine (5 gm) was dissolved in demineralized water (5 ml) at 25-30°C. The clear solution was filtered through 0.2 micron membrane filter and then added to isopropyl alcohol (150 ml) with stirring at 25-30°C. After complete addition stirring was continued for 1 hour at 25-30°C. Solid was filtered, washed with diisopropyl ether (25 ml) and dried under vacuum at 25-30°C for 6 hours. Yield of co-precipitated composition was 4.6 gm. HPLC purity 96.58%.

### Example 3

20 Composition containing crystalline cefepime dihydrochloride monohydrate and L-arginine (5 gm) was dissolved in demineralized water (5 ml) at 25-30°C. The clear solution was filtered through 0.2 micron membrane filter and then added to isopropyl alcohol (150 ml) with stirring at 25-30°C. After complete addition stirring was continued for 1 hour at 25-30°C. Solid was filtered, washed with 25 ml of ethyl acetate and dried under vacuum at 25-30°C for 10 hours. Yield of co-precipitated composition was 3.3 gm. Purity by HPLC 95.17%.

**CLAIMS**

1. A process to obtain pharmaceutical composition by co precipitation of cefepime and a pharmaceutically acceptable non-toxic base comprising of:
  - 5 (i) dissolving an admixture of cefepime acid addition salt and solvates thereof with pharmaceutically acceptable non toxic organic and inorganic base in water to obtain a clear aqueous solution having a pH in the range of 3.5-7, and
  - 10 (ii) filtering the aqueous solution through 0.2 micron membrane filter and then adding the clear aqueous solution to a suitable organic solvent followed by stirring, filtration and drying.
2. A process according to claim 1 wherein the clear aqueous solution is dropwise added to the organic solvent or the organic solvent is added dropwise to the clear aqueous  
15 solution.
3. A process according to claim 1 wherein the cefepime used is zwitterion or its acid addition salt or solvates thereof which are in amorphous or crystalline form.
- 20 4. A process according to claim 1 wherein the cefepime used in the admixture is sterile or non sterile.
5. A process according to claim 1 wherein a pharmaceutically acceptable non-toxic organic or inorganic base in the admixture is sterile or non sterile.  
25
6. A process according to claim 1 wherein a pharmaceutically acceptable non-toxic organic or inorganic base in the admixture is selected from alkali metal carbonates, ammonium carbonate, guanidine carbonate, alkali metal bicarbonates, alkali metal phosphates or ammonium phosphates, sodium citrate and potassium citrate.  
30
7. A process according to claims 1 and 6 wherein the alkali metal carbonate is selected from sodium carbonate and potassium carbonate.

8. A process according to claims 1 and 6 wherein the alkali metal bicarbonate is selected from sodium bicarbonate and potassium bicarbonate.
- 5 9. A process according to claims 1 and 6 wherein the alkali metal phosphate is selected from sodium dihydrogen phosphate, disodium hydrogen phosphate, trisodium phosphate, potassium dihydrogen phosphate, potassium hydrogen phosphate or potassium phosphate.
- 10 10. A process according to claim 1 wherein the molar ratio of cefepime to base is in the range 1:1 to 1:5.
11. A process according to claims 1 and 10 wherein the molar ratio of cefepime to base is in the range 1:2 to 1:3.
- 15 12. A process according to claim 1 wherein the pH of aqueous solution is in the range 4-6.
13. A process according to claim 1 wherein the co precipitation is performed at - 20 to  
20 50°C.
14. A process according to claims 1 and 13 wherein the co precipitation is performed preferably at 20-40°C.
- 25 15. A process according to claim 1 wherein the suitable organic solvent is water miscible solvent selected from but are not limited to alcohols, ketones, nitriles, cyclic ethers and amides.
- 30 16. A process according to claims 1 and 15 wherein the alcoholic solvent is methanol, ethanol and isopropanol, most preferably isopropanol.

17. A process according to claims 1 and 15 wherein the ketonic solvent is acetone, methyl ethyl ketone.
18. A process according to claims 1 and 15 wherein the nitrile solvent is acetonitrile.
- 5 19. A process according to claims 1 and 15 wherein the cyclic ether solvent is, tetrahydrofuran and 1,4-dioxane.
20. A process according to claims 1 and 15 wherein the amide solvent is  
10 dimethylformamide and dimethyl acetamide.
21. A sterile pharmaceutical composition of cefepime and a pharmaceutically acceptable non-toxic organic or inorganic base obtained by the process according to claim 1.
- 15 22. A pharmaceutical composition obtained by co precipitation according to claim 1 in the form of injectable solution.

Figure 1

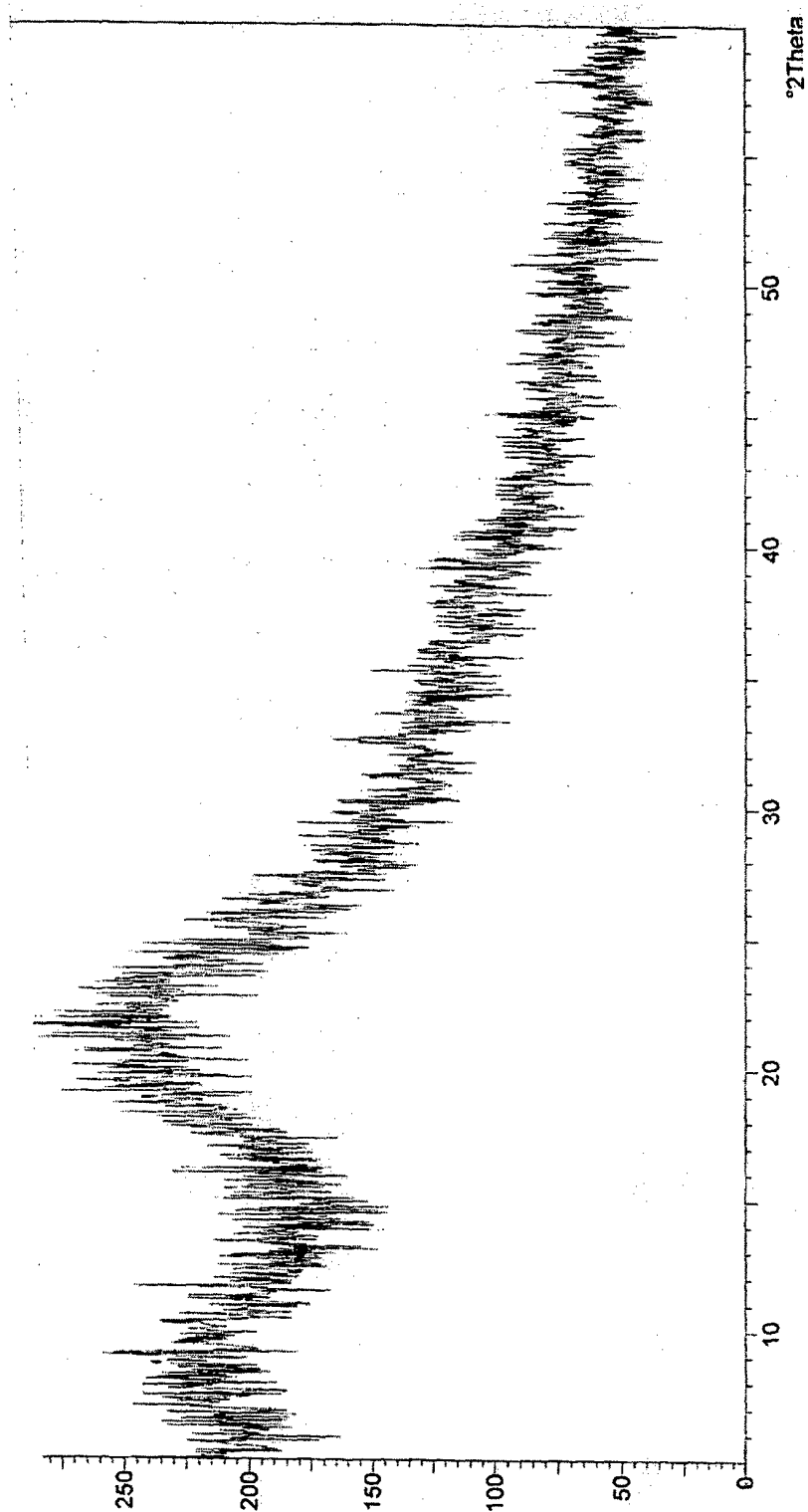


Figure 2

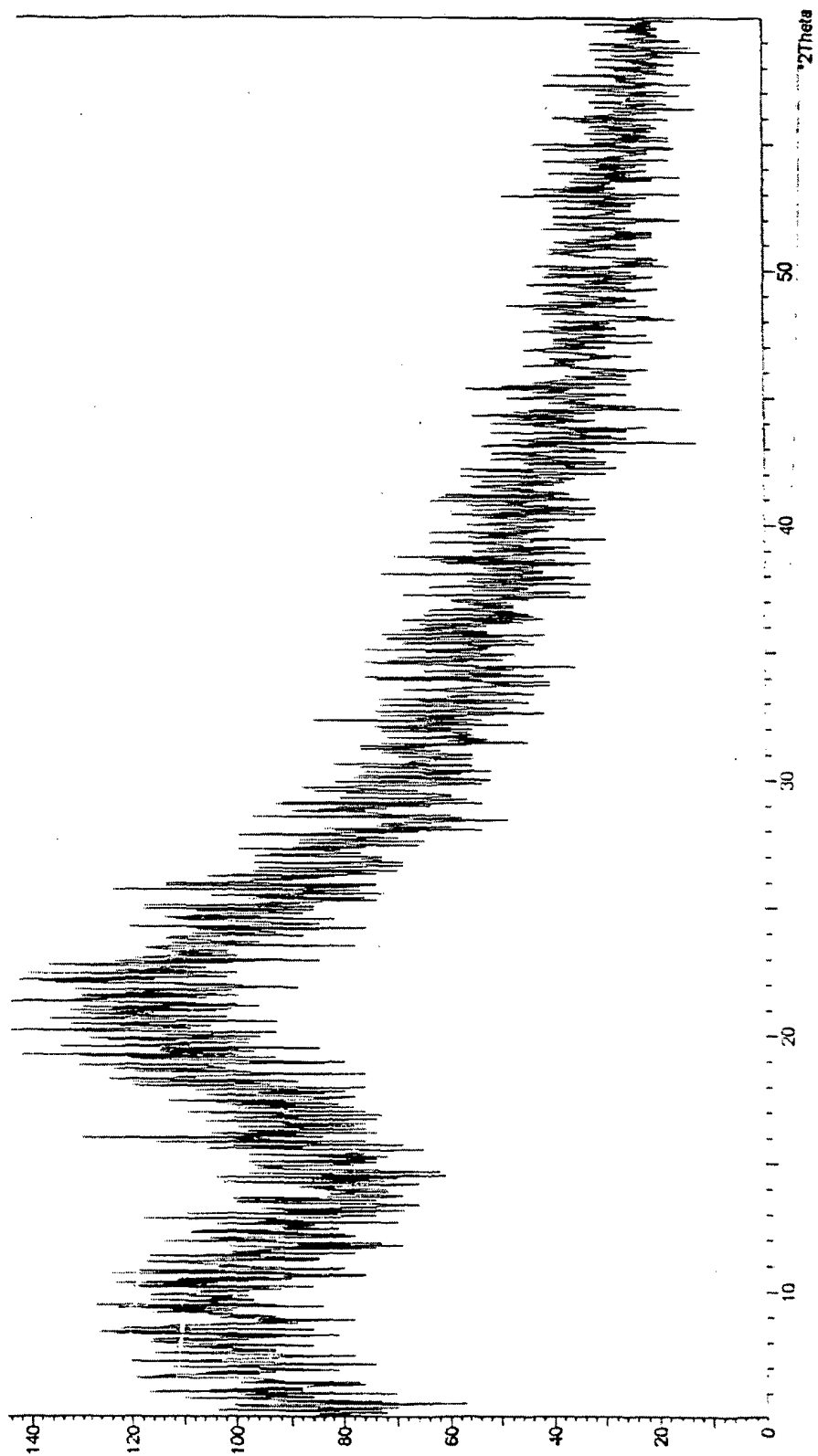


Figure 3

