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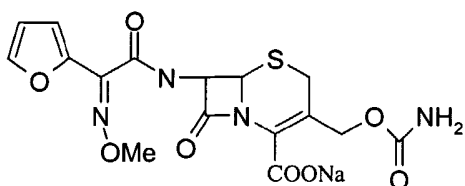
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**(54) Title:** AN IMPROVED PROCESS FOR THE PREPARATION OF CEFUROXIME SODIUM



(I)

**(57) Abstract:** The present invention relates to an improved process for the preparation of the sterile cefuroxime sodium of formula (I).

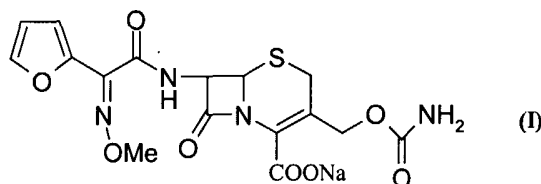
**WO 2004/050663 A2**

## AN IMPROVED PROCESS FOR THE PREPARATION OF CEFUROXIME SODIUM

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### Field of the invention

The present invention relates to an improved process for the preparation of active cephalosporin antibiotic derivative. The present invention more particularly relates to an improved process for the preparation of cefuroxime sodium of the  
10 formula (I).



### Description of the prior art

Cefuroxime is a valuable broad spectrum antibiotic and having activity against wide range of gram-positive and gram-negative microorganisms.  
15 Cefuroxime sodium is physiologically acceptable non-toxic salt of cefuroxime and may be administered to human or used as a veterinary medicine. The preparation involves the condensation of 3-hydroxymethyl-7-amino cephalosporanic acid with (fur-2-yl)-2-methoxyimino acetic acid to produce (6R,7R)-7-[(Z)-2-(fur-2-yl)-2-methoxyiminoacetamido]-3-hydroxymethylceph-3-em-4-carboxylic acid.  
20 Carbamoylation of resulting acid with isocyanate of formula RNCO wherein R is a labile substituent to get (6R,7R)-3-carbamoyloxymethyl-7-[Z-2-(fur-2-yl)-2-methoxyiminoacetamido]-ceph-3-em-4-carboxylic acid (cefuroxime), followed by converting the cefuroxime into its sodium salt using mixture of water soluble sodium salt.

25 US patent 4,775,750 discloses the process for the preparation of the compound of formula (I), which involves carbamoylation of (6R,7R)-7-[Z-2-(fur-

2-yl)-2-methoxyiminoacetamido]-3-hydroxymethylceph-3-em-4-carboxylic acid, and *in situ* preparation of cefuroxime sodium using sodium-2-ethylhexanoate. The product obtained from this patent suffers in non-acceptable color and low purity. Reprocessing is needed to get sterile cefuroxime sodium.

5 US patent 4,277,601 describes the process for the preparation of cefuroxime sodium as its THF solvate *in situ* manner. The process described in this patent involves the usage of multiple organic solvent systems and thereby making the process complicated. Moreover, recrystallisation is needed to get the sterile cefuroxime sodium.

10 The synthesis of cefuroxime disclosed in US 3,966,717 and US 3,974,513 comprises 8 synthetic steps starting from 7-ACA. Such high number of steps, which causes low overall yield, is due to the introduction of two protective groups.

A process for the preparation of cefuroxime starting from 7-ACA has been described in Chemistry and Industry 1984, 217, which do not involve any protective groups.

15 WO 00/71547 describes a process for the preparation of cefuroxime, which involves enzymatic hydrolysis of 7-glutaryl ACA, which is not industrially viable.

With our continued search and intense investigation, we finally achieved a process for the preparation cefuroxime sodium, which overcomes all difficulties and makes the process industrially viable and yield the title compound in required quantity and quality.

### Objectives of the invention

25 The main objective of the present invention is to provide a process for the preparation of cefuroxime sodium of the formula (I), which has better quality such as color and solubility.

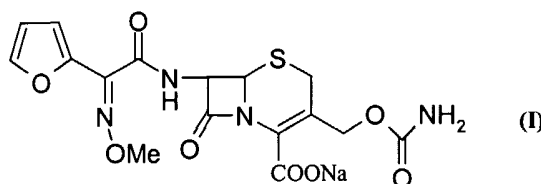
Another objective of the present invention is to provide direct manufacturing process for the preparation of sterile crystalline cefuroxime sodium of the formula (I) from cefuroxime acid.

Still another objective of the present invention is to provide a process for the preparation of cefuroxime sodium of the formula (I) in good yield, high purity and with desirable particle size.

Yet another objective of the present invention is to provide a simple method for the preparation of cefuroxime of the formula (II) in pure form.

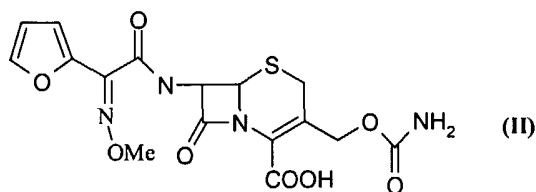
## 10 Summary of the invention

Accordingly, the present invention provides an improved process for the preparation of cefuroxime sodium of the formula (I),



which comprises the steps of:

- 15 (i) dissolving the cefuroxime of the formula (II)



in a water miscible solvent /water at a temperature in the range of 10°C to 50°C,

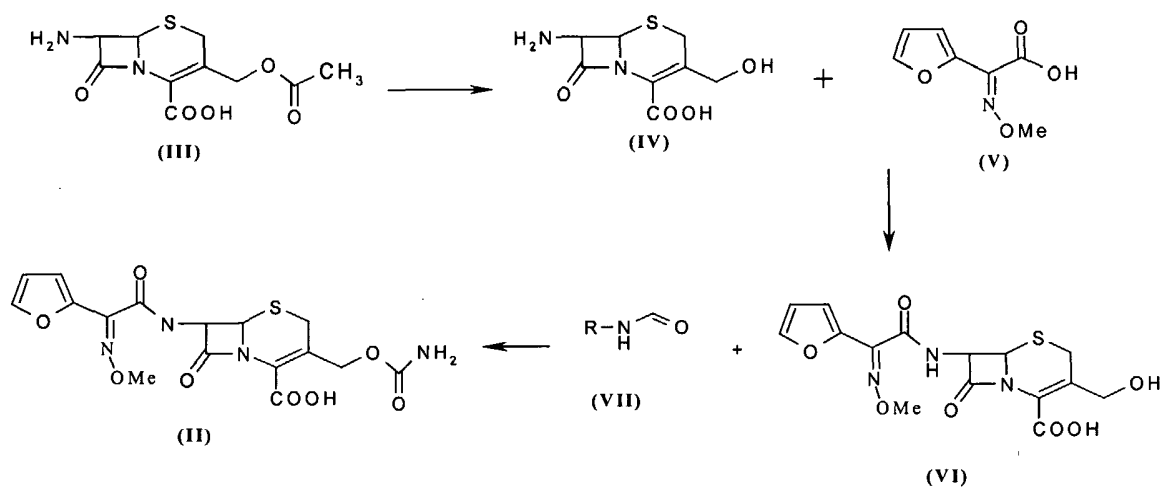
- (ii) charcoalising the solution followed by micron filtration,

- (iii) treating the solution with mixture of water soluble sodium salts of two weak acids in suitable alcoholic solvent at a temperature in the range of 10°C to 50°C and
- (iv) isolating the precipitated cefuroxime sodium of the formula (I) in pure form.

5 Another embodiment of the present invention is to provide a process for the preparation of cefuroxime of the formula (II), which comprises the steps of:

- (i) condensing 3-hydroxymethyl-7-amino cephalosporanic acid of formula (IV) with activated (fur-2-yl)-2-methoxyimino acetic acid of formula (V) in the presence of an inorganic base in a solvent at a temperature in the range of -  
10 40°C to 10°C and isolating the product by adjusting the pH to 1.5 to 2.5 using an acid to produce (6R,7R)-7-[(Z)-2-(fur-2-yl)-2-methoxyiminoacetamido]-3-hydroxymethylceph-3-em-4-carboxylic acid of formula (VI) and
- (ii) carbamoylating the compound of formula (VI) with isocyanate of formula  
15 (VII) wherein R is a labile group in the presence of a solvent at a temperature in the range of -60°C to 0°C to get cefuroxime of the formula (II).

The process is shown in scheme-I as given below:



### Detailed description of the invention

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In an embodiment of the present invention, cefuroxime of formula (II) was dissolved in water miscible solvent /water such as acetone, THF, acetonitrile, alcohols like methanol, ethanol at a temperature in the range of 10°C to 50°C.

In still another embodiment of the present invention, the mixture of water  
 10 soluble sodium salt of weak acid is selected from sodium lactate/sodium acetate, sodium 2-ethyl hexonate/sodium acetate and the like. The reaction may be carried out in an alcoholic solvent selected from methanol, ethanol, isopropyl alcohol or mixtures thereof, at a temperature in the range of 10°C to 50°C.

In still another embodiment of the present invention, the compound of  
 15 formula (I) was isolated from reaction mass by adding suitable water miscible solvent such as acetone, methanol, ethanol, isopropyl alcohol or mixtures thereof.

In another embodiment of the present invention, the isolated mass was washed with solvents such as acetone, methanol, ethyl acetate, isopropyl ether, hexane, diethyl ether, toluene and the like or mixtures thereof.

In yet another embodiment of the present invention, 7-amino cephalosporanic acid of formula (III) was dissolved in solvents such as methanol, acetone, dichloromethane, THF, water or mixtures thereof, to that sodium hydroxide solution was added at a temperature in the range of -90°C to 0°C, to  
5 produce compound of formula (IV).

In still another embodiment of the present invention, the activation of fur-2-yl methoxyimino acetic acid of formula (V) is carried out using  $\text{PCl}_5$ ,  $\text{DMF/POCl}_3$ , oxalyl chloride,  $\text{SOCl}_2/\text{DMF}$ , diphenylchlorophosphoridate, dialkyl chlorophosphoridate, in the presence of a solvent selected from halogenated  
10 alkanes, ethyl acetate, tetrahydrofuran, aromatic hydrocarbons, acetone, acetonitrile, dialkylethers or mixtures thereof at a temperature in the range of -40°C to 10°C.

In still another embodiment of present invention the compound of formula (IV) was reacted with the active derivative of fur-2-yl methoxyimino acetic acid ammonium salt of formula (V), in the presence of inorganic base such as sodium  
15 bicarbonate, sodium hydroxide, potassium carbonate and sodium carbonate in the presence of solvents such as methanol, acetone, dichloromethane, THF, water or mixtures thereof to produce the compound of formula (VI).

In yet another embodiment of the present invention, the acid used for adjusting pH in step (i) is selected from hydrochloric acid, sulphuric acid or ortho  
20 phosphoric acid.

In yet another embodiment of the present invention, the labile group represented by R is selected from chlorosulphonyl, mono, di or trichloroacetyl, bromosulphonyl, trichloroethoxycarbonyl, trimethylsilyl or chlorobenzene sulphonyl group.

25 In still another embodiment of the present invention the compound of formula (VI) was reacted with the compound of formula (VII) to produce the

compound of formula (II), in the presence of a solvent selected from THF, methanol dichloromethane, acetone, water or mixtures thereof.

In one more embodiment of the present invention the cefuroxime sodium of the formula (I) obtained is sterile crystalline syn isomer.

5       The present invention is exemplified by the following examples, which is provided for illustration only and should not be construed to limit the scope of the invention.

**Example (1):**

10       **Step       (i):       Preparation       of       (6R,7R)-7-[(Z)-2-(fur-2-yl)-2-methoxyiminoacetamido]-3-hydroxymethylceph-3-em-4-carboxylic acid.**

(i)       To a mixture of dimethyl acetamide (145 ml), dichloromethane (22 ml) and dimethylformamide (28 ml) in a dry flask, (fur-2-yl)-2-methoxyimino acetic acid ammonium salt (73 gm) was added and cooled the reaction mass to -  
15       40°C. To the reaction mass POCl<sub>3</sub> (60 gm) was added at -40°C and stirred the reaction mass at -20±2°C for 45 minutes. The mass was cooled to -30°C and kept at that temperature for condensation.

(ii)       To a mixture of water (400 ml) and methanol (400 ml) in another  
20       flask, 7-amino cephalosporinic acid (100 gm) was added and cooled the slurry to -50°C. To the reaction mass sodium hydroxide solution (29 gm NaOH in 200 ml water) was added at -50°C and stirred for 60 minutes at 40±2°C. After completion of reaction the pH of reaction was adjusted to 7.0 to 8.0 using dilute HCl. Temperature of this reaction mass was raised to 0°C by the addition of saturated  
25       sodium bicarbonate solution (800 ml) followed by (fur-2-yl)-2-methoxyimino acetic acid mass from step (i) at 0-2°C. After completion of reaction, pH was adjusted to 2.0 using dilute HCl (80 ml). The product formed was filtered, washed with water

followed by dichloromethane and dried the product under vacuum at 45°C to get the title compound of formula (VI) (116 – 118 gm-) in pure form.

**Step (ii): Preparation of (6R,7R)-3-carbamoyloxymethyl-7-[(Z)-2-(fur-2-yl)-2-methoxyiminoacetamido]-ceph-3-em-4-carboxylic acid (cefuroxime acid):**

(6R,7R)-7-[Z-2-(Fur-2-yl)-2-methoxyiminoacetamido]-3-hydroxymethyl ceph-3-em-4-carboxylic acid (100 gm) obtained from step (i) was dissolved in THF (480 ml) at 0°C and cooled to -50°C. To the cooled solution chlorosulphonyl isocyanate (59 gm in 100 ml THF) solution was added at -50°C and stirred at the same temperature for 60 minutes. The reaction mass was poured into precooled water at 10°C. Stirred the mass at 10°C till completion of reaction. The reaction mass was washed with ethyl acetate and then aqueous layer was subjected to charcoal treatment. The pH of aqueous solution was adjusted to 2.0 using dilute HCl. The product formed was filtered and washed with water followed by isopropyl alcohol to produce the title compound of formula (II) (105 gm).

**Step (iii) Preparation of (6R,7R)-3-carbamoyloxymethyl-7-[(Z)-2-(fur-2-yl)-2-methoxyiminoacetamido]-ceph-3-em-4-carboxylic acid sodium (cefuroxime sodium):**

(6R,7R)-3-carbamoyloxymethyl-7-[Z-2-(fur-2-yl)-2-methoxyimino acetamido]-ceph-3-em-4-carboxylic acid ( 100 gm ) was dissolved in a mixture of acetone (650 ml) and water (80 ml) at 25°C. Activated carbon was added and stirred for 15 minutes at 25°C. The carbon was filtered and washed the bed with acetone /water. The solution was then passed through series of micron filters in a sterile area. The solution was warmed to 35°C. A mixture of sodium lactate solution (23 gm) (60% solution in water) and sodium acetate (16.5 gm) in ethanol (25 ml) was added to the

reaction mixture slowly at 35°C and stirred for 30 minutes. To the thick slurry acetone (900 ml) was charged at 35°C. The product obtained was filtered and washed with ethanol followed by acetone. The product was dried under vacuum to get sterile cefuroxime sodium (98 gm) in pure form.

5 **Example (2):**

**Preparation of (6R,7R)-3-carbamoyloxymethyl-7-[Z-2-(fur-2-yl)-2-methoxy iminoacetamido]-ceph-3-em-4-carboxylic acid sodium (cefuroxime sodium):**

10 (6R,7R)-3-carbamoyloxymethyl-7-[Z-2-(fur-2-yl)-2-methoxyimino acetamido]-ceph-3-em-4-carboxylic acid ( 100 gm ) was dissolved in a mixture of acetone (650 ml)/water (80 ml) at 25°C. Activated carbon was added and stirred for 15 minutes at 25°C. The carbon was filtered and washed the bed with acetone /water. The solution was then passed through series of micron filters in a sterile area. The solution was  
15 warmed to 35°C. A mixture of sodium lactate solution (23 gm) (60% solution in water) and sodium acetate (16.5 gm) in methanol (450 ml) was added to the reaction mixture slowly at 35°C and stirred for 30 minutes. The product obtained was filtered and washed with methanol (200 ml) followed by acetone. The product was dried under vacuum to get sterile cefuroxime sodium (98 gm) in pure form.

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**Example (3):**

**Preparation of (6R,7R)-3-carbamoyloxymethyl-7-[Z-2-(fur-2-yl)-2-methoxy iminoacetamido]-ceph-3-em-4-carboxylic acid sodium (cefuroxime sodium):**

25 (6R,7R)-3-carbamoyloxymethyl-7-[Z-2-(fur-2-yl)-2-methoxyiminoacetamido]-ceph-3-em-4-carboxylic acid ( 100 gm ) was dissolved in a mixture of acetone (650 ml)/water (80ml) at 25°C. Activated carbon was added and stirred for 15 minutes at

25°C. The carbon was filtered and washed the bed with acetone /water. To the clear filtrate acetone (950 ml) was added and warmed the solution to  $39 \pm 1^\circ\text{C}$ . A mixture of sodium lactate solution (24 gm) (60% solution in water) and sodium acetate trihydrate (16.8 gm) in methanol (450 ml) was added to the reaction mixture slowly  
5 at 39°C and stirred for 10 minutes. Acetone was decanted from reaction mass, further aqueous acetone was added and decanted till pH of reaction mass becomes 6.5 to 7.0. The product was stirred with IPE (400 ml), filtered, washed with methanol followed by acetone, and dried to produce crystalline cefuroxime sodium.

10 **Advantages:**

The use of non-polar solvent like IPE, toluene cyclohexane, and the like helps in changing the nature of the slurry substantially, hence it is easy to filter the solid.

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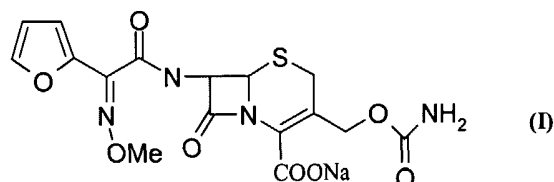
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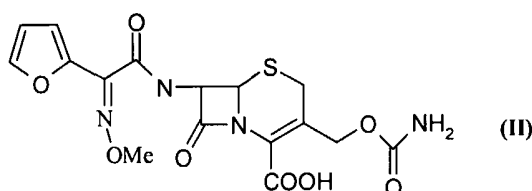
## Claims

- 5 1) A process for the preparation of the cefuroxime sodium of the formula (I)



comprising the steps of:

- (i) dissolving the cefuroxime of the formula (II)



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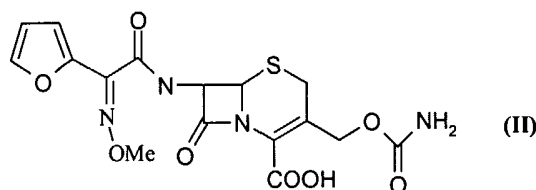
in a water miscible solvent /water at a temperature in the range of 10°C to 50°C,

- (ii) charcoalising the solution followed by micron filtration,  
 (iii) treating the solution with mixture of water soluble sodium salts of two weak  
 15 acids in suitable alcoholic solvent at a temperature in the range of 10°C to 50°C and

- (iv) isolating the precipitated compound of formula (I) in pure form.

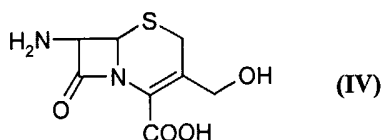
- 2) The process as claimed in claim 1, wherein the water miscible solvent used in step (i) is selected from acetone, THF, acetonitrile, methanol, or ethanol.  
 20 3) The process as claimed in claim 1, wherein the mixture of water soluble sodium salts used in step (iii) is selected from sodium lactate/sodium acetate or sodium 2-ethyl hexanoate/sodium acetate.

- 4) The process as claimed in claim 1, wherein the alcoholic solvent used in step (iii) is selected from methanol, ethanol, isopropyl alcohol or mixtures thereof.
- 5) The process as claimed in claim 1, wherein the solvent used for isolation in step (iv) is acetone, methanol, ethanol, isopropyl alcohol, ethyl acetate, isopropyl ether, hexane, diethyl ether, toluene or mixtures thereof.
- 6) The process as claimed in claim 1, wherein the compound of formula (I) is in crystalline form.
- 7) The process as claimed in claim 1, wherein the compound of formula (I) is a sterile product.
- 8) The process as claimed in claim 1, wherein the compound of formula (I) is a syn isomer.
- 9) A process for the preparation of cefuroxime of the formula (II)

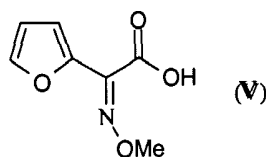


comprising the steps of :

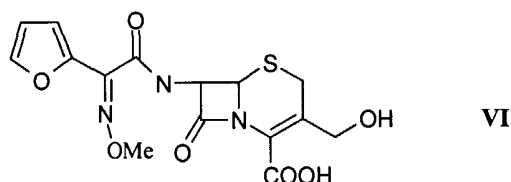
- (i) condensing 3-hydroxymethyl-7-amino cephalosporanic acid of the formula (IV)



with activated (fur-2-yl)-2-methoxyimino acetic acid of the formula (V)



in the presence of an inorganic base in a solvent at a temperature in the range of -40°C to 10°C and isolating the product by adjusting the pH to 1.5 to 2.5 using an acid to produce (6R,7R)-7-[(Z)-2-(furan-2-yl)-2-methoxyiminoacetamido]-3-hydroxymethyl cephalosporanic acid of the formula (VI),



- ii) carbamoylating the compound of formula (VI) with isocyanate of formula (VII)



wherein R is a labile group at a temperature in the range of -60°C to 0°C to get cefuroxime acid of the formula (II).

- 10) The process as claimed in claim 9, wherein the base used in step (i) is selected from sodium hydroxide, sodium bicarbonate, potassium carbonate or sodium carbonate.

- 11) The process as claimed in claim 9, wherein the solvent used in step (i) is selected from methanol, acetone, dichloromethane, THF, water or mixtures thereof.

- 12) The process as claimed in claim 9, wherein the acid used in step (i) is selected from hydrochloric acid, sulphuric acid or ortho phosphoric acid.

- 13) The process as claimed in claim 9, wherein the solvent used in step (ii) is selected from methanol, acetone, dichloromethane, THF, water or mixtures thereof.

14) The process as claimed in claim 9, wherein the labile group represented by R is selected from chlorosulphonyl, mono, di or trichloroacetyl, bromosulphonyl, trichloroethoxycarbonyl, trimethylsilyl or chlorobenzenesulphonyl group.

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