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(54) Title: AN IMPROVED PROCESS FOR THE PREPARATION OF CEFOZOPRAN

(57) Abstract: The present invention relates to an improved process for the preparation of Cefozopran of formula (I), its hydrochloride, its hydrate and its solvate. The present invention more particularly provides a process for preparing Cefozopran hydrochloride IPA solvate, novel crystalline forms of Cefozopran hydrochloride or its hydrate and an improved process for the preparation of pharmaceutical composition of Cefozopran.

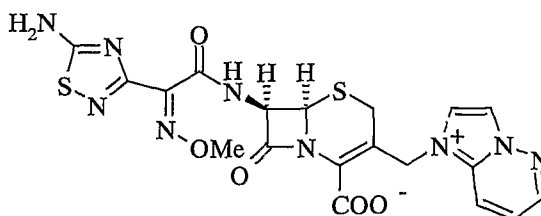


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AN IMPROVED PROCESS FOR THE PREPARATION OF CEFOZOPRAN

Field of the Invention

5 The present invention relates to an improved process for the preparation of Cefozopran of formula (I), its hydrochloride, its hydrate and its solvate. The present invention further provides novel crystalline forms of Cefozopran hydrochloride. The present invention also provides an improved process for the preparation of pharmaceutical composition comprising Cefozopran.



(I)

Background of the Invention

Cefozopran, a semisynthetic parenteral cephalosporin, against acute respiratory tract infections caused by *Klebsiella pneumoniae* DT-S. In the model of chronic respiratory tract infection caused by *K. pneumoniae* 27. The therapeutic effect of cefozopran against urinary tract infections caused by *Pseudomonas aeruginosa* P9. Against thigh muscle infections caused by methicillin-resistant *S. aureus* N133, cefozopran was the most effective agent. The potent therapeutic effect of cefozopran in those experimental infections in mice suggests that it would be effective against respiratory tract, urinary tract, and soft tissue infections caused by a variety of gram-positive and gram-negative bacteria in humans. The chemical designation is 1-[[[(6*R*,7*R*)-7-[[[(2*Z*)-(5-Amino-1,2,4-thiadiazol-3-yl)(methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]imidazo[1,2-*b*]pyridazinium inner salt.

The marketed form of Cefozopran is FIRSTCIN[®] which is a combination of Cefozopran hydrochloride with sodium carbonate and sodium chloride.

Cefozopran is first disclosed in US patent No. US 4,864,022, which also discloses a process for preparing Cefozopran and its hydrochloride. This patent further discloses the preparation of Cefozopran inter from 7-ACA and Cefozopran by reacting Cefozopran inter with activated aminothiadiaazole.

US patent No. 4,978,752 (equivalent to JP patent no. 1,932,035) claims crystalline or crystalline acetone and ethanol solvate of Cefozopran hydrochloride and process for producing thereof. Applicant repeated the process depicted in this patent and found difficult in isolating the solid even with excess of solvent.

US patent No. 6,794,372 claims the nitrate salt of Cefozopran and US 6,642,377 claims a process for the production of Cefozopran hydrochloride by exchanging the respective oxalate salt using alkali earth metal salt of inorganic acids. Conversion of Cefozopran nitrate or oxalate salt into its hydrochloride salt required resin to remove the nitrate or oxalate anion due to which the yield obtained is minimized.

JP patent No. 10,152,490 claims process for the preparation of Cefozopran by condensing Cefozopran inter with acid chloride of aminothiadiaazole using bases like sodium hydroxide, ammonia solution, triethylamine, sodium acetate, potassium acetate, sodium carbonate, and potassium carbonate.

PCT publication No. 97/39002 claims a process for the preparations of Cefozopran inter involving the silylated 7-ACA and imidazo[1,2-b]pyridiazine and silylation of 7-ACA is carried out with hexamethyldisilazane in inert solvent in the presence of sulfur containing acid or an ammonium salt or Lewis acid.

JP patent No. 3,737,642 claims the manufacturing method of cephalosporin injections by dissolving Cefozopran hydrochloride and basic carbonate in water or ethyl alcohol solution, and freeze-drying subsequently, whose basic carbonate is sodium carbonate or sodium bicarbonate. This patent involves the use of organic solvent for

lyophilization which resulted in high residual solvents in the final product and it requires high purity organic solvents with known impurities at lower level leads to higher manufacturing cost. Further the use of secondary solvent like ethanol in the final lyophilization solution tend to operator safety concerns due to high degree of flammability or explosion potential and also have potential adverse environment effect, spoil the vacuum pump, and hence commercially not viable

Conventional process reported for the preparation of Cefozopran involves by the condensation of Cefozopran inter with activated aminothiadiaazole in a solvent like acetone, methanol, THF, water or mixtures thereof and in the presence of an organic amine bases. In order to get pure form of Cefozopran, the conventional process converts Cefozopran into its nitrate or oxalate salts due to which the yield is minimized. Further the conventional process utilizes crystalline acetone or ethanol solvate of Cefozopran HCl, applicant found that the process reported for the isolation of crystalline acetone or ethanol solvate in patents are not re-producible in lab scale itself even after using excess volume of acetone or ethanol. Hence the reported processes are not applicable in commercial point of view.

In our continued research, we have identified an improved process for the preparation of Cefozopran by condensing the intermediate of the formula (II) with activated thioester of formula (III) in a mixture of organic solvent(s) and water in the presence of base and isolating Cefozopran directly from the reaction mixture, which obviates the complexity, associated with the normal work up procedure, and yield Cefozopran with good purity and yield. Further, we have made Cefozopran hydrochloride IPA solvate and novel crystalline forms of Cefozopran hydrochloride which are consistently reproducible in lab as well as in bulk scale, and an improved process for the preparation of the same with enhanced quality and colour especially free of impurities. Moreover pharmaceutical composition of Cefozopran was prepared by dissolving Cefozopran hydrochloride with metal carbonate(s) and salt in a mixture of

water and water miscible organic solvent(s) followed by removal of water miscible organic solvent by extraction with water immiscible organic solvent and isolating the product by freeze-drying or precipitation or spray-drying the obtained solution. This process obviates the complexity associated with the high content of residual solvent in the final product and lyophilization using an organic solvent(s). None of the prior art suggests or even motivates the present invention.

Objectives of the Invention

The primary objective of the invention is to provide an improved process for the preparation of Cefozopran of formula (I) with good purity directly from the reaction mixture.

Another objective of the present invention is to provide a commercial process for direct isolation of Cefozopran

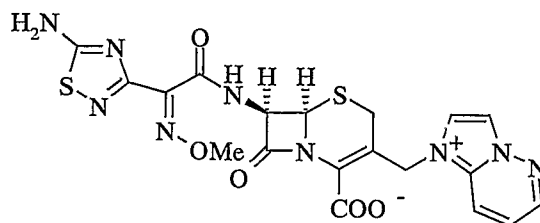
Yet another objective of the present invention is to provide novel Cefozopran hydrochloride hydrate or solvate and novel crystalline forms of Cefozopran hydrochloride or its hydrate.

One more objective of the present invention is to provide novel Cefozopran hydrochloride IPA solvate.

Still another objective of the present invention is to provide an improved process for the preparation of pharmaceutical composition of Cefozopran with sodium carbonate and sodium chloride with pharmaceutically acceptable level of residual solvent.

Summary of the Invention

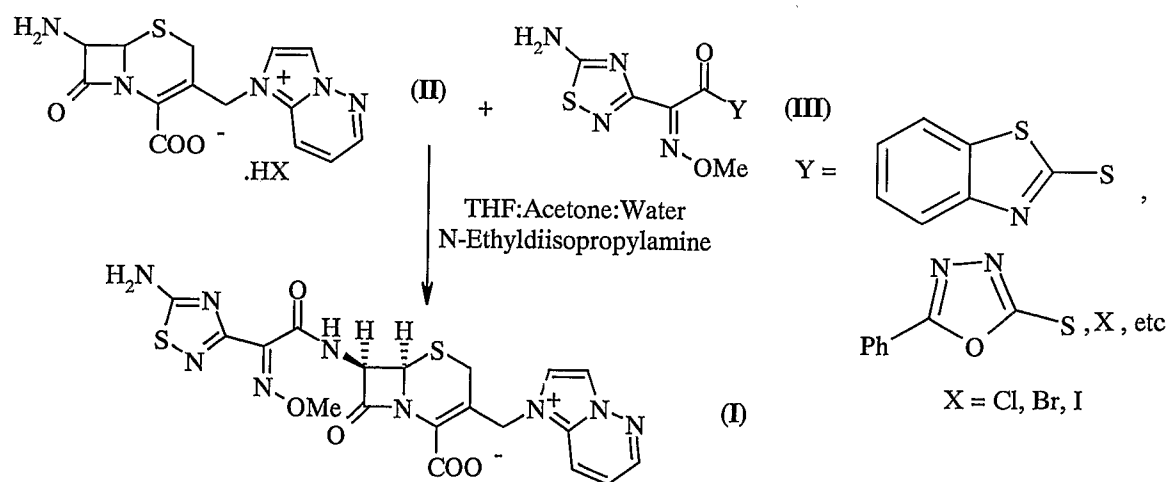
Accordingly, the present invention provides an improved process for the preparation of Cefozopran of formula (I) and its hydrochloride salt



(I)

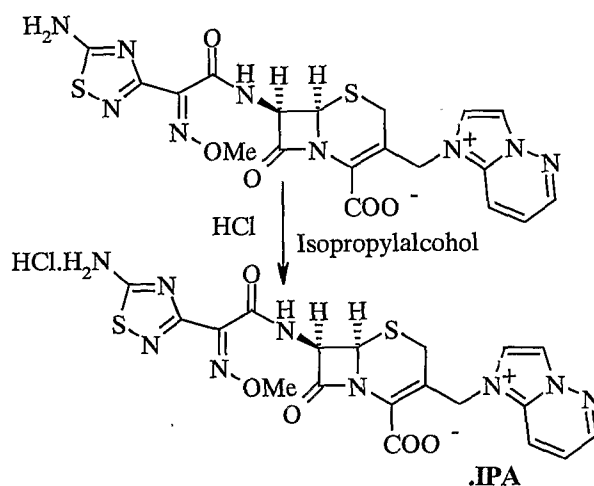
the said process comprising the steps of:

- i) condensing a compound of formula (II) wherein HX represents an acid; with active thioester of aminothiadiazoole acetic acid of formula (III) in a two or more mixtures of water miscible organic solvent and water, in the presence of organic bases; wherein the improvement consists of use of at least two water miscible organic solvent along with water;
- ii) optionally adding water miscible solvents;
- iii) isolating Cefozopran of formula (I) by filtration;
- iv) optionally purifying Cefozopran;
- v) converting Cefozopran into its hydrochloride salt in a solvent;
- vi) mixing the step (v) solution with IPA; and
- vii) isolating Cefozopran hydrochloride IPA solvate.

**Scheme-I**

In another aspect the present invention provides novel Cefozopran hydrochloride IPA solvate, also provides a process for preparing the same. The said process comprising the steps of:

- a) converting Cefozopran into its hydrochloride salt in a solvent;
- b) mixing the step (a) solution with IPA; and
- c) isolating Cefozopran hydrochloride IPA solvate.



Scheme-II

In yet another aspect of the present invention provides a novel crystalline forms of Cefozopran hydrochloride or its hydrate as depicted in Figure-I having moisture content 15-20 % and Figure-II having moisture content 4-8 %, and also provides a process for preparing same; the said process comprising the steps of:

- 1) dissolving Cefozopran hydrochloride IPA solvate in water;
- 2) crystallizing Cefozopran hydrochloride;
- 3) isolating crystalline Cefozopran hydrochloride or its hydrate as depicted in Figure-I having moisture content in the range of 15-20 %; and
- 4) optionally drying the obtained solid in step (3) to get Cefozopran hydrochloride or its hydrate as depicted in Figure-II having moisture content in the range of 4-8 %.

In still another aspect of the present invention also provides an improved lyophilization process for the preparation of pharmaceutical composition comprising Cefozopran, the said process comprising the steps of:

- i) obtaining Cefozopran hydrochloride in a mixture of water and water miscible organic solvent(s);
- ii) adding sodium chloride and sodium carbonate either mixture or independently in the form of solid and/or solution;
- iii) washing the obtained solution in step (ii) with water immiscible organic solvent(s);
- iv) optionally degassing the aqueous solution; and
- v) lyophilizing aqueous solution of step (iii) or step (iv) to get pharmaceutical composition of Cefozopran.

Drawings of the Invention

Figure-1: Powder XRD pattern of crystalline form of Novel crystalline Cefozopran hydrochloride having moisture content in the range of 15-20 %.

Figure-2: Powder XRD pattern of crystalline form of Novel crystalline Cefozopran hydrochloride having moisture content in the range of 4-8 %, analyzed by X-Ray Powder Diffractometer of following features:

Make	BRUKER AXS
Model	D8 ADVANCE
Data handling system	EVA 12.0.0.0.
ANODE	COPPER
RADIATION	COPPER K alpha-1
WAVELENGTH	1.5406 Å°
CURRENT & VOLTAGE	40kV 30mA

Detailed Description of the Invention

In an embodiment of the present invention, activated aminothiadiazole ester of formula (III) used in step (i) for condensation is selected from group comprising 2-(5-Amino-1,2,4-thiadiazol-3yl)-2(Z)-methoxyiminoacetamido-2-mercaptobenzothiazole ester, 2-mercapto-5-methyl-1,3,4-oxadiazolyl-(Z)-2-(5-Amino-1,2,4-thiadiazol-3yl)-2-methoxyimino acetate and the like; alternatively the 2-(5-Amino-1,2,4-thiadiazol-3yl)-2(Z)-methoxyiminoacetic acid activated using its corresponding halo compound.

In another embodiment of the present invention, water miscible organic solvent used in step (i) for condensation is selected from acetone, tetrahydrofuarn, methylethyl ketone, diglyme, butanone, sulfolane, dioxane, DMF, acetonitrile, methanol, ethanol, isopropyl alcohol and the like; preferably tetrahydrofuran, and acetone. Applicant found the use of combination of two water miscible organic solvents and water for the reaction was found to yield good quality product and reaction proceeds smoothly, which constitutes one of the novelty of the present invention.

In still another embodiment of the present invention, base used in step (i) for condensation is selected from triethylamine, diethylamine, diisopropylamine, N-ethyl-diisopropylamine, TMG (1,1,3,3-Tetramethylguanidine), DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene), DBN (1,5-Diazabicyclo[4.3.0]non-5-ene), sodium acetate, sodium 2-ethylhexanoic acid, sodium bicarbonate and the like, preferably N-ethyl-diisopropylamine.

In yet another embodiment of the present invention, isolation of Cefozopran is done by optionally adding water miscible organic solvent or cooling the reaction mixture, preferably adding water miscible organic solvents.

In another embodiment of the present invention, before isolating the product, the reaction mixture was optionally subject to ultrasonic waves, which not only helps to reduce the precipitation time but also ensures the complete precipitation thereby

increasing the yield of the product. The said ultrasonication technology thus found to be useful in terms of reducing crystallization time and also ensures the complete precipitation and hence over all cost and batch cycle time is minimized. The said technology can be extended to any pharmaceutical product, including but not limited to

5 Beta-Lactams antibiotics like cefaclor, cefadroxil, cefalonium, cefaloram, cefamandole, cefaparole, cefatriazine, cefazaflur, cefazedone, cefazolin, cefbuperazone, cefanel, cefcapene, cefclidin, cefdaloxime, cefdinir, cefditoren, cefedrolor, cefempidone, cefepime, cefetamet, cefetecol, cefetriaole, cefivtril, cefixime, cefmatilen, cefmenoxine, cefmepidium, cefmetazole, ceminox, cefodizime, cefonicid, cefoperazone, ceforanide,

10 cefoselis, cefotaxime, cefotetan, cefotiam, cefovecin, cefoxazole, cofoxitin, cefozopran, cefpimizole, cefpiramide, cefpodoxime, cefprozil, cefquinome, cefrotil, cefroxadine, cefsulodin, cefsumide, ceftazidime, cefteram, ceftezole, ceftibuten, ceftioflur, ceftiolene, ceftioxide, ceftioxime, ceftriaxone, cefuracetamime, cefuroxime, cefuzonam, celecoxib, celgosivir, celiprolol, cemadotin, cephacetrile, cephradine, cephalixin, cephaloglycin.

15 Cephaloridine, cephalothin, cephapirin, cepharanthine, cephradine, aztreonam, biapenem, Doripenem, ertapenem, faropenem, Imipenem, Meropenem, Panipenem, sulopenem, sulbactam, tazobactam, piperazilin etc.

In still another embodiment of the present invention, water miscible organic solvent used in step (ii) after condensation is selected from THF, acetone, ethyl methyl

20 ketone, diglyme, butanone, dioxane, DMF (N, N-dimethyl formamide), acetonitrile, methanol, ethanol, isopropyl alcohol and the like, preferably acetone, or THF.

In another embodiment of the present invention, purification of Cefozopran is carried out by converting Cefozopran into its organic acid addition salt or its solvate, by treating Cefozopran with an organic acid and subsequent neutralization to get pure

25 Cefozopran.

In yet another objective of the present invention, organic acid used for the conversion of Cefozopran into its organic acid addition salt is selected from

trifluoroacetic acid, trichloroacetic acid acetic acid, formic acid, and the like, preferably trifluoroacetic acid.

In another objective of the present invention, base used for the neutralization of Cefozopran organic acid addition salt is selected from ammonia, sodium hydroxide, sodium carbonate, sodium acetate, sodium 2-ethylhexanoic acid, sodium bicarbonate, triethylamine, diethylamine, diisopropylamine, N-ethyldiisopropylamine, TMG (1,1,3,3-Tetramethylguanidine), DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene), DBN (1,5-Diazabicyclo[4.3.0]non-5-ene), and the like, preferably ammonia.

In yet another embodiment of the present invention, solvent used in step (v) or step (a) for the conversion of Cefozopran into its hydrochloride is selected from THF, acetone, ethyl methyl ketone, diglyme, butanone, dioxane, DMF, acetonitrile, methanol, ethanol, isopropyl alcohol water and the like or mixtures thereof, preferably mixture of acetone and water. Surprisingly it has been observed that the isolation of Cefozopran Hydrochloride as its IPA solvate found to have more advantages over the reported crystalline acetone or ethanol solvate as it gives better colour, good yield and quality in terms of its purity further pharmaceutical composition of Cefozopran with sodium carbonate and sodium chloride prepared using Cefozopran HCl IPA solvate has enhanced solubility and stability. Apart from this isolation as IPA solvate consistently re-producible in lab scale as well as plant, where as applicant found difficulty in terms of isolation of crystalline acetone or ethanol solvate.

In still another embodiment of the present invention, the novel crystalline Cefozopran hydrochloride as depicted in Figure -I and II are found to have better flow properties, and are thermodynamically more stable, and hence industrially more preferable. The said crystal obtained by dissolving Cefozopran hydrochloride IPA solvate in water or directly from the reaction mixture. Preferably, the solution of Cefozopran hydrochloride in water is obtained by dissolving Cefozopran hydrochloride IPA solvate in water.

In another embodiment of the present invention, crystallizing Cefozopran hydrochloride is by stirring the reaction mixture or by seeding with crystalline Cefozopran hydrochloride and the like, preferably by stirring the reaction mixture.

5 In still another embodiment of the present invention, isolation of crystalline Cefozopran hydrochloride or its hydrate is by filtration, decantation and the like, preferably by filtration. Surprisingly the applicant found that the wet Cefozopran hydrochloride having PXRD as depicted in Figure-I and having moisture content in the range of 15-20 %, further drying the obtained wet Cefozopran hydrochloride having PXRD as depicted in Figure-II and having moisture content in the range of 4-8 %. The
10 above said crystalline forms are not reported and hence constitute one of the novelty of the present invention and found to have better flow properties, and are thermodynamically more stable, and hence industrially more preferable.

In another embodiment of the present invention, before isolating the product, the reaction mixture was optionally exposure to ultrasonic waves, which allows crystallizing
15 the product specifically thereby isolating the product with high purity and narrow particle size distribution, and reduces the time required for completion of crystallization.

The isolated novel crystalline Cefozopran hydrochloride has good purity and stability. Further Cefozopran buffered prepared using the novel crystalline Cefozopran hydrochloride also has good purity and stability.

20 In yet another embodiment of the present invention, water miscible organic solvent used in step (i) for the preparation of pharmaceutical composition of Cefozopran is selected from acetone, methanol, ethanol, THF, isopropyl alcohol and the like or mixtures thereof.

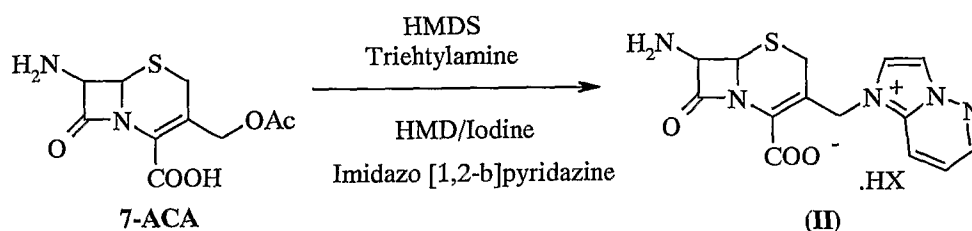
In another embodiment of the present invention, addition of sodium chloride and
25 sodium carbonate is done by either singly or in combination and in the form of solid and/or solution and the order of addition may be reverse.

In still another embodiment of the present invention, water immiscible organic solvent used in step (ii) for the preparation of pharmaceutical composition of Cefozopran is selected from methylene chloride, ethyl acetate, isopropyl acetate, n-butyl acetate and the like or mixtures thereof. The applicant found that the product isolated by freeze-drying the aqueous solution containing pharmaceutical products and an organic solvents have high residual solvent content in the final product and the purity of the isolated product also found to be less. The product isolated by the above said method found to have pharmaceutically acceptable level of residual solvents with good purity and hence constitute one of the novelty of the present invention.

In yet another embodiment of the present invention, removing water miscible organic solvent from the aqueous solution by washing with water immiscible organic solvent before lyophilization can be extended for any pharmaceutical products, including but not limited to Betalactams antibiotics like cefaclor, cefadroxil, cefalonium, cefaloram, cefamandole, cefaparele, cefatriazine, cefazaflur, cefazedone, cefazolin, cefbuperazone, cefanel, cefcapene, cefclidin, cefdaloxime, cefdinir, cefditoren, cefedrolor, cefempidone, cefepime, cefetamet, cefetecol, cefetriaole, cefivtril, cefixime, cefmatilen, cefmenoxine, cefmepidium, cefmetazole, ceminox, cefodizime, cefonicid, cefoperazone, ceforanide, cefoselis, cefotaxime, cefotetan, cefotiam, cefovecin, cefoxazole, cofoxitin, cefozopran, cefpimizole, cefpiramide, cefpodoxime, cefprozil, cefquinome, cefrotil, cefroxadine, cefsulodin, cefsumide, ceftazidime, cefteram, ceftezole, ceftibuten, ceftioflur, ceftiolene, ceftioxide, ceftioxime, ceftriaxone, cefuracetamime, cefuroxime, cefuzonam, celecoxib, celgosivir, celiprolol, cemadotin, cephacetrile, cephadrine, cephalixin, cephaloglycin. Cephaloridine, cephalothin, cephapirin, cepharanthine, cephradine, aztreonam, biapenem, Doripenem, ertapenem, faropenem, Imipenem, Meropenem, Panipenem, sulopenem, sulbactam, tazobactam, piperazilin etc., by using the following improved lyophilization process comprising the steps of:

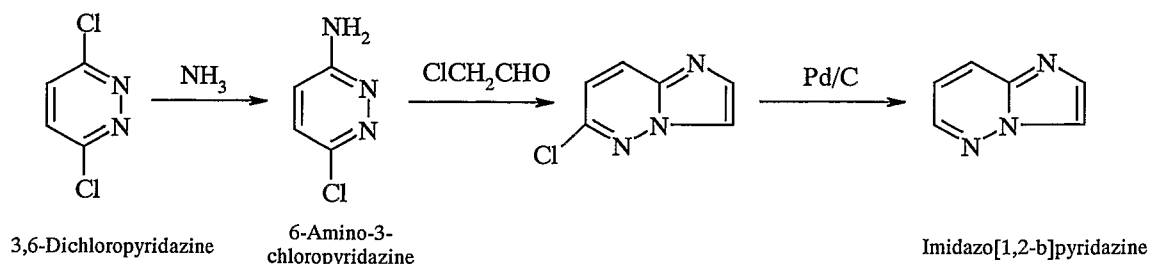
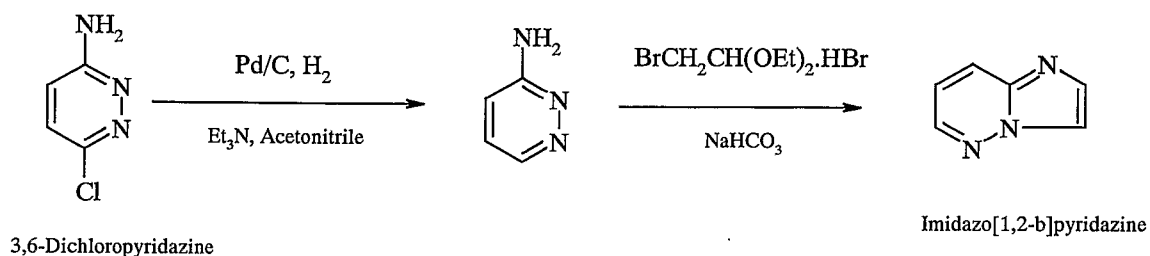
- i) obtaining active pharmaceutical ingredient(s) in a mixture of water and water miscible organic solvent(s);
- ii) optionally adding other excipient(s);
- iii) washing the obtained solution in step (ii) with water immiscible organic solvent(s); and
- iv) isolating pharmaceutical composition by lyophilization.

The starting material used in the present invention is prepared by utilizing the process available in the literature, or by utilizing the process given in Scheme – III.



Scheme-III

Accordingly the starting material of the present inversion is prepared by silylating 7-Aminocephalosporanic acid (7-ACA) using silylating agents like hexamethyldisilazane in an organic solvent preferably in dichloromethane, followed by reacting the silylated 7-ACA with solution of trimethylsilyl iodide (prepared by treating hexamethyldisilane and iodine in an organic solvent, preferably dichloromethane), the ensuing product was reacted with triethylamine and imidazo[1,2-b]pyridazine (which is prepared by utilizing the technique provided in literature or by using the process depicted in Scheme-IV or V). The compound of formula **II** was isolated from reaction mixture by quenching into mixture of methanol and dil.HCl, followed by adjusting the pH (to ~ 3) of aqueous layer using triethylamine. The compound of the formula **II** thus obtained was optionally purified by dissolving the crude compound in mixture of methanol and dil. HCl, followed by subjecting the clear solution to carbon treatment, and adjusting the pH of the aqueous layer to ~3 in the presence of EDTA and sodium dithionite, using TEA.

**Scheme-IV****Scheme-V**

5

Many other beneficial results can be obtained by applying disclosed invention in a different manner or by modifying the invention with the scope of disclosure.

The present invention is provided by the examples below, which are provided by way of illustration only and should not be considered to limit the scope of the invention.

10

Example 1: Preparation of Cefozopran:

Method-A:

To a mixture of THF (125 mL), acetone (62.5 mL) and purified water (62.5 mL) was added compound of formula (II) (25 g) and 2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-methoxyiminoacetamido-2-mercaptobenzothiazole ester (ZAEM) (27.6 g). The pH of the reaction mixture was maintained at 7.0-8.0 using N-ethyldiisopropylamine and at a temperature of 25-35 °C. After completion of the reaction, acetone was added. The precipitated product was filtered and washed with a mixture of acetone, THF & water followed by THF and acetone. Drying under nitrogen afforded Cefozopran (23.1 g; Purity by HPLC 97.98%).

20

Method-B:

Compound of formula (II) (100 g) and ZAEM (113 g) were taken in mixture of water (500 mL) and acetone (2.0 L) at 25-35 °C. Triethylamine was added to maintain pH at 7.0 – 8.0 at 30-40 °C for 1-2 hours. After completion of the reaction, solid formed
5 was filtered, washed with acetone, water and acetone. The wet material was dried to get Cefozopran (95 g).

Method-C:

Compound of formula (II) (100 g) and ZAEM (113 g) were taken in a mixture of
10 water (500 mL) and acetone (2.0 L) at 25-35°C. Triethylamine was added to maintain pH at 7.0 – 8.0 at 30-40 °C for 1-2 hours. The reaction mass was circulated through a set up providing ultrasonic waves with the frequency of 50 Hz, and the precipitated solid was filtered and washed with acetone, water and acetone. The wet material was dried to get Cefozopran (105 g).

Method-D:

To a mixture of water (800 mL) and THF (1300 mL) was added compound of formula (II) (100 g) and ZAEM (152.9 g). Triethylamine (26.0 g) was added slowly to adjust the pH to 7.5 at 25-30 °C. Then the reaction mixture temperature was raised to 30-
20 40° C by simultaneously maintaining the pH between 7.0 and 8.0 till completion of reaction. The reaction mixture was cooled to 25° C and stirred. The crystallized product was filtered and washed with THF (500 mL) followed by acetone (500 mL). The wet product was dried under vacuum afforded Cefozopran (95.0 g).

Purification of Cefozopran:

To a suspension of Cefozopran (40.0 g; Purity: 97.60%) in acetone (or solvent like methanol, ethanol) at 25-30°C was added trifluoroacetic acid to get a clear solution. The clear solution was added into IPA (1.6 L). The precipitate formed was filtered and

washed with IPA. The wet cake was added into water (400 mL) at 25-30°C. After getting a clear solution, pH was adjusted with aqueous ammonia. The crystallized product was filtered and washed with acetone. Drying the solid afforded Cefozopran (34.0 g; Purity: 99.86%)

5

Example 2: Preparation of Cefozopran Hydrochloride IPA solvate:

Method A:

Cefozopran (20 g) was added into a mixture of purified water (80 mL) and acetone
10 (40 mL) at 0-5°C. The pH of the reaction mixture was adjusted to < 0.5 using dil. HCl. To the clear solution was added carbon (2.0 g). The carbon was removed by filtration and washed the bed with purified water. The filtrate was slowly added into isopropyl alcohol (1000 mL). The precipitated IPA solvate of Cefozopran hydrochloride was filtered and washed with isopropyl alcohol. Drying with nitrogen afforded Cefozopran
15 hydrochloride IPA solvate (Solvation: 0.4-0.7 moles with respect to Cefozopran hydrochloride). PXRD of this sample shows that it is amorphous in nature. The solvated IPA was removed by passing moist nitrogen followed by drying with dry nitrogen. PXRD after the removal of IPA shows amorphous nature. (Yield 18.6 g; purity by HPLC 98.6%; IPA content by GC 85 ppm).

20

Method B:

Cefozopran (25.0 g) was stirred in a mixture of water (62.5 mL) and methanol (100 mL) at 25-35°C. To this mixture was added dil. HCl to adjust pH to 0.50-1.50 at 25-35°C and treated with carbon (2.5 g). The carbon was removed by filtration and the
25 clear filtrate was added into IPA at 25-35°C. The product obtained was filtered and washed with IPA. PXRD of this sample showed that it is amorphous in nature. The solvated IPA was removed by passing moist nitrogen followed by drying with dry nitrogen. PXRD after the removal of IPA shows amorphous (Yield: 21.0 g).

Method C:

Cefozopran (25.0 g) was stirred in a mixture of water (62.5 mL) and methanol (100 mL) at 25-35°C. To this mixture was added dil. HCl to adjust pH to 0.50-1.50 at 25-35°C and treated with carbon (2.5 g). The carbon was removed by filtration and the clear filtrate was added into IPA at 25-35°C. The reaction mass was circulated through a set up providing ultrasonic waves with the frequency of 50 Hz. The product obtained was filtered, washed with IPA and dried under moist nitrogen followed by dry nitrogen to get Cefozopran hydrochloride (Yield: 23.0 g).

Example 3: Preparation of Crystalline Cefozopran hydrochloride:**Method-A:**

A solution of Cefozopran hydrochloride IPA solvate (10 g) in water (50 mL) was stirred at 25-30 °C for a time sufficient to crystallize Cefozopran hydrochloride or its hydrate. The crystallized product was filtered and washed with water affording novel crystalline Cefozopran hydrochloride as depicted in Figure-I (moisture content in the range of 15-20 %).

Method-B:

A solution of Cefozopran hydrochloride IPA solvate (10 g) in water (50 mL) was stirred at 25-30 °C for a time sufficient to crystallize Cefozopran hydrochloride or its hydrate. The crystallized product was filtered, washed with water and dried to afford novel crystalline Cefozopran hydrochloride as depicted in Figure-II (moisture content in the range of 4-8 %).

Example 4: Preparation of pharmaceutical composition of Cefozopran with sodium carbonate and sodium chloride:

Method-A:

5 Cefozopran hydrochloride obtained according to example 2 (A) (5 g), sodium chloride (0.56 g) and sodium carbonate (0.96 g) were added into acetone (25 mL). To this purified water (50 mL) was added at 25-30 °C and stirred to get clear solution. The clear solution was washed with dichloromethane (2 x 50 mL). The aqueous layer was treated with carbon and filtered through 0.2 micron filter paper. The clear solution was
10 freeze-dried to get pharmaceutical composition of Cefozopran with pharmaceutically acceptable level of residual solvents.

Residual solvent before washing: Acetone: 25.6 %

Residual solvent after washing: Acetone: 0.17-0.70 %; Dichloromethane: Not detected.

15 **Method-B:**

Cefozopran hydrochloride (5 g) prepared according to example 3A, sodium chloride (0.56 g) and sodium carbonate (0.96 g) were added into ethanol (25 mL). To this purified water (50 mL) was added at 25-30 °C and stirred to get clear solution. The clear solution was washed with dichloromethane (2 x 50 mL). The aqueous layer was
20 treated with carbon and filtered through 0.2 micron filter paper. The clear solution was freeze-dried to get pharmaceutical composition of Cefozopran with pharmaceutically acceptable level of residual solvents.

Method-C:

25 Cefozopran hydrochloride (25 g) was added in acetone (125 mL) and stirred to make slurry. To this slurry, water (125 mL) was added and stirred at 25-30°C to get clear solution. A solution of sodium carbonate (4.8 g) and sodium chloride (2.8 g) in water (62.5 mL) was slowly added to adjust pH to 7.0-9.0. The resulting solution was stirred for

15 min at 25-30°C. The resultant solution is washed with ethyl acetate. The aqueous layer was treated with activated carbon and the carbon was removed by filtration. This filtrate was filtered through 0.2 micron filter and freeze-dried to get Cefozopran buffered.

5 **Method-D:**

Cefozopran hydrochloride (25 g) was added in acetone (125 mL) and stirred to make slurry. To this slurry, water (125 mL) was added and stirred at 25-30°C to get clear solution. A solution of sodium carbonate (4.8 g) and sodium chloride (2.8 g) in water (62.5 mL) was slowly added to adjust pH to 8.0-9.0. The resulting solution was stirred
10 for 60 min at 25-30°C. The resultant solution is washed with dichloromethane. The aqueous layer was treated with activated carbon and the carbon was removed by filtration. This filtrate was filtered through 0.2 micron filter and freeze-dried to get Cefozopran buffered.

15 **Method-E:**

Cefozopran hydrochloride (25 g) was added in acetone (125 mL) and stirred to make slurry. To this slurry, water (125 mL) was added and stirred at 25-30°C to get clear solution. A solution of sodium carbonate (4.8 g) and sodium chloride (2.8 g) in water (62.5 mL) was slowly added to adjust pH to 8.0-9.0. The resulting solution was stirred
20 for 120 min at 25-30°C. The resultant solution is washed with ethyl acetate. The aqueous layer was treated with activated carbon and the carbon was removed by filtration. This filtrate was filtered through 0.2 micron filter and freeze-dried to get Cefozopran buffered.

On reconstitution of the lyophilized product prepared by using acetone as co-
25 solvent gave clear solution even upto three days, however the product prepared by using ethanol (according to example 4 B) gave turbidity after one hour during reconstitution.

Example 5: Preparation of Imipenem monohydrate using Ultrasonic waves:

To a solution of Imipenem p-nitrobenzyl ester hydrochloride in ethanol containing MOPS solution was washed with ethyl acetate and added 10% Pd-C. The resulted
5 suspension was hydrogenated under hydrogen pressure. After completion of reaction, the catalyst was removed by filtration. The aqueous layer was washed with dichloromethane and treated with activated carbon. The carbon was removed by filtration and the carbon bed was washed with water. To the clear filtrate was added cold acetone and the reaction
10 mass was circulated through a set up providing ultrasonic waves with the frequency of 50 Hz for 2-4 hrs to effect complete crystallization of Imipenem monohydrate. The crystals were filtered and washed with aqueous acetone followed by acetone. Drying under vacuum afforded pure crystals of Imipenem monohydrate.

Example 6: Preparation of Meropenem trihydrate Sterile:

15 Into a suspension of Meropenem trihydrate in water was added ammonia solution till to get clear solution. The clear solution was subjected to carbon treatment followed by filtration in sterile area. The pH of the filtrate was adjusted to approximately 2-4 using aqueous formic acid. The resultant mass was circulated through a set up providing
20 ultrasonic waves with the frequency of 50 Hz for 1 hour. The solid obtained was filtered, washed with aqueous tetrahydrofuran, and dried to yield the title compound in pure form. (Purity: 99.00 – 99.88%; water content: 11.4 to 13.4%).

We claim:

1) An improved lyophilization process for the preparation of pharmaceutical composition comprising Cefozopran, the said process comprising the steps of:

5 i) obtaining Cefozopran hydrochloride in a mixture of water and water miscible organic solvent(s);

ii) adding sodium chloride and sodium carbonate either in mixture or independently in the form of solid and/or solution;

10 iii) washing the obtained solution in step (ii) with water immiscible organic solvent(s);

iv) optionally degassing the aqueous solution; and

v) lyophilizing aqueous solution of step (iii) or step (iv) to get pharmaceutical composition of Cefozopran.

15 2) An improved lyophilization process for the preparation of pharmaceutical composition comprising Cefozopran, the said process comprising the steps of:

i) obtaining Cefozopran hydrochloride in a mixture of water and acetone;

ii) adding sodium chloride and sodium carbonate either in mixture or independently in the form of solid and/or solution;

20 iii) optionally washing the obtained solution in step (ii) with water immiscible organic solvent(s);

iv) optionally degassing the aqueous solution; and

v) lyophilizing aqueous solution of step (iii) or step (iv) to get pharmaceutical composition of Cefozopran.

3) An improved lyophilization process comprising the steps of:

- i) obtaining active pharmaceutical ingredient(s) in a mixture of water and water miscible organic solvent(s);
- ii) optionally adding other excepients(s);
- iii) washing the obtained solution in step (ii) with water immiscible organic solvent(s); and
- iv) isolating pharmaceutical composition by lyophilization.

4) A process according to claim 1 and 3, wherein water miscible organic solvent used in step (i) is selected from acetone, methyl ethyl ketone, methyl propyl ketone, methyl isobutyl ketone, dimethyl ketone, methanol, ethanol, THF, propyl alcohol, isopropyl alcohol and the like or mixtures thereof.

5) A process according to claim 1 and 3, wherein the water immiscible organic solvent used in step (iii) is selected from dichloromethane, toluene, ethyl acetate, isopropyl acetate, n-butyl acetate and the like or mixtures thereof.

6) A novel Cefozopran hydrochloride IPA solvate.

7) A process for the preparation of novel Cefozopran hydrochloride IPA solvate, the said process comprising the steps of:

- a) converting Cefozopran into its hydrochloride salt in a solvent;
- b) mixing the step (a) solution with IPA; and
- c) isolating Cefozopran hydrochloride IPA solvate.

8) A novel crystalline Cefozopran hydrochloride essentially as depicted in figure-1 and having moisture content in the range of 15-20 %.

- 9) A novel crystalline Cefozopran hydrochloride essentially as depicted in figure-2.
- 10) A novel crystalline Cefozopran hydrochloride according to claim 8 having moisture content in the range of 4-8 %.
- 5
- 11) A process for the preparation of novel crystalline Cefozopran hydrochloride or its hydrate as depicted in Figure-I having moisture content 15-20 % and Figure II having moisture content 4-8 %, the said process comprising the steps of:
- i) dissolving Cefozopran hydrochloride IPA solvate in water;
 - 10 ii) crystallizing Cefozopran hydrochloride; and
 - iii) isolating crystalline Cefozopran hydrochloride or its hydrate as depicted in Figure-I having moisture content in the range of 15-20 %; and
 - iv) optionally drying the obtained solid in step (iii) to get Cefozopran hydrochloride or its hydrate as depicted in Figure-II having moisture
 - 15 content in the range of 4-8 %.

FIGURE - 1

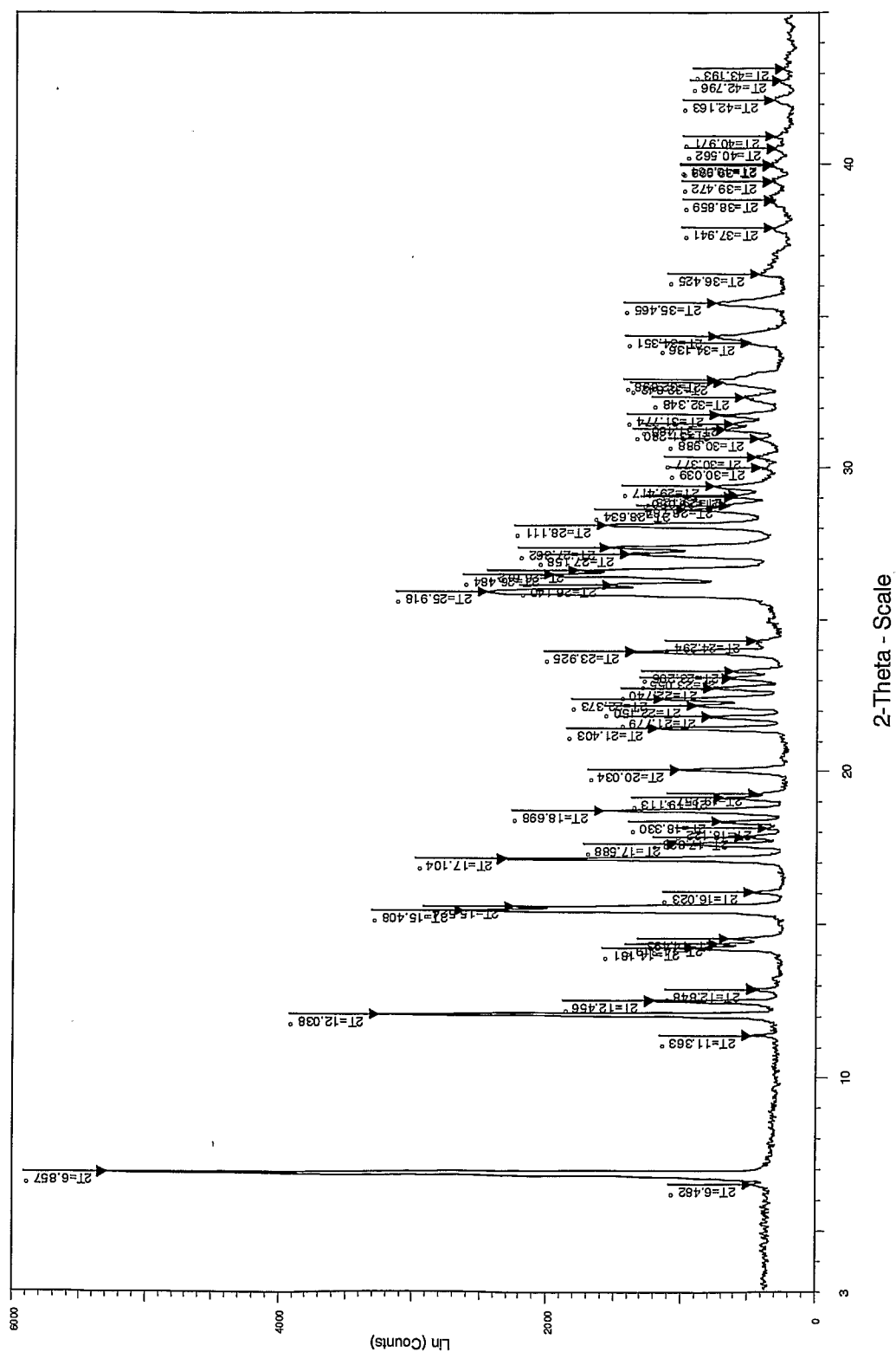


FIGURE - 2

