(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 January 2008 (24.01.2008)

PCT

(10) International Publication Number
WO 2008/010043 A2

(51) International Patent Classification:
C07D 501/36 (2006.01) *C07C 211/27* (2006.01)
C07D 501/18 (2006.01) *C07C 57/32* (2006.01)
C07D 501/20 (2006.01) *C07D 501/32* (2006.01)

(21) International Application Number:
PCT/IB2007/001920

(22) International Filing Date: 10 July 2007 (10.07.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1245/CHE/2006 18 July 2006 (18.07.2006) IN
908/CHE/2007 27 April 2007 (27.04.2007) IN

(71) Applicant *(for all designated States except US)*: **ORCHID CHEMICALS & PHARMACEUTICALS LIMITED** [IN/IN]; Orchid Towers,, 313, Valluvar Kottam High Road, Nungambakkam, Chennai, Tamil Nadu 600 034 (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **UDAYAMPALAYAM, Palanisamy, Senthilkumar** [IN/IN]; Orchid Chemicals & Pharmaceuticals Ltd., 476/14, Old Mahabalipuram Road, Sholinganallur, Chennai, Tamil Nadu 600 119 (IN). **SUNDARAVADIVELAN, Sivakumaran** [IN/IN]; Orchid Chemicals & Pharmaceuticals Ltd., 476/14, Old Mahabalipuram Road, Sholinganallur, Chennai, Tamil Nadu 600 119 (IN). **KONDA, Athmaram, Ramesh** [IN/IN]; Orchid Chemicals & Pharmaceuticals Ltd., 476/14, Old Mahabalipuram Road, Sholinganallur, Chennai, Tamil Nadu 600 119 (IN). **RAJA, Mohamed, Anish, Raja** [IN/IN]; Orchid Chemicals & Pharmaceuticals Ltd., 476/14, Old Mahabalipuram Road, Sholinganallur, Chennai, Tamil Nadu 600 119 (IN). **SAHOO, Prabhat, Kumar** [IN/IN]; Orchid Chemicals & Pharmaceuticals Ltd., 476/14, Old Mahabalipuram Road, Sholinganallur, Chennai, Tamil Nadu 600 119 (IN).

(74) Agents: **DAS, Soumili** et al.; K & S Partners, 84-C, C-6 Lane, Off Central Avenue, Sainik Farms, New Delhi 110 062 (IN).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

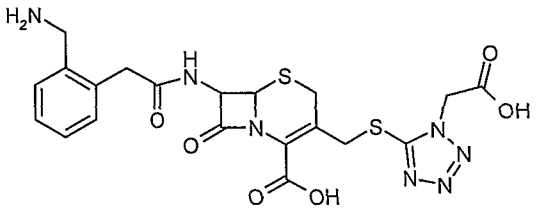
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, 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).

Declaration under Rule 4.17:
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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: IMPROVED PROCESS FOR THE PREPARATION OF CEFORANIDE IN PURE FORM



(I)

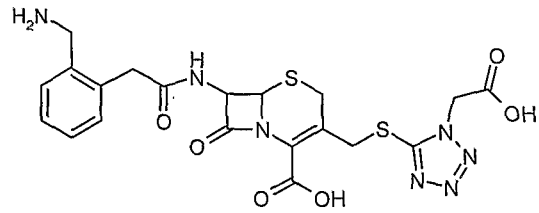
(57) Abstract: The present invention provides an improved process for the preparation of the compound of formula (I) in pure form.

WO 2008/010043 A2

IMPROVED PROCESS FOR THE PREPARATION OF CEFORANIDE IN PURE FORM

Field of the Invention

The present invention provides an improved process for the preparation of the compound of formula (I) in pure form and also provides novel salts of compound of formula (I). The compound of formula (I) is known as Ceforanide.



(I)

The present invention further provides a simple purification process for preparing compound of formula (I) in highly pure form.

Background of the Invention

Ceforanide is a semisynthetic second-generation cephalosporin, and is chemically known as 7-(2-aminomethylphenylacetamido)-3-(1-carboxymethyltetrazol-5-ylthiomethyl) -3-cephem-4-carboxylic acid. Ceforanide, which is administered intramuscularly or intravenously and is found to be useful to treat a wide variety of bacterial infections, such as respiratory tract infections, skin infections and urinary tract infections and is disclosed in US Patent No. 4,100,346.

U.S. Pat. No. 4,118,563 describes the preparation of Ceforanide by the reduction with hydrogen and Raney nickel of the corresponding 2-azidomethyl compound.

The Ceforanide thus prepared according to US 4,100,346 & US 4,118,563 are not suitable for injectable as it contains impurities and even

starting material in the range of up to 10% that are difficult to remove. Hence purification of Ceforanide is inevitable. In order to purify crude Ceforanide, prior art processes utilize column chromatography or extensive carbon treatment plus recrystallization.

US patent No. 4,448,958 claims N,N-dimethylbenzylammonium-7-[.alpha.-(2-aminomethylphenyl)acetamido)-3-[(1-carboxymethyltetrazol-5-ylthio)methyl]-3-cephem-4-carboxylate. Even though this salt is used in the purification of Ceforanide, this salt is not preferable due to the corrosive nature of N,N-Dimethylbenzylamine since it causes burns to the eye on contact and may cause permanent damage. Hence, because of this safety issue this amine is not found to be useful from industrial point of view.

During our continued search we have identified certain novel salts, which yield the compound of formula (I) in good purity, and yield.

Objective of the Invention

The main objective of the present invention is to provide a process for the preparation and purification of the compound of formula (I) in good purity, and quantity.

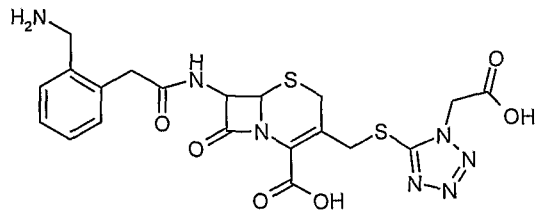
Another objective of the present invention is to provide a N,N-dicylcohexyl ethylenediamine salt of Ceforanide, which are safe to handle in industry.

Still another objective of the present invention is to provide a process for the preparation of novel salts of formula (I), which is easy to implement on commercial scale.

Still another objective of the present invention is to provide an process for the purification of compound of formula (I), which obviates complications associated with conventional processes such as forming salt of Ceforanide.

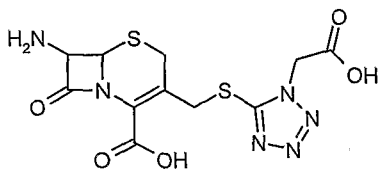
Summary of the Invention

Accordingly, the present invention provide a process for the preparation of compound of formula (I)

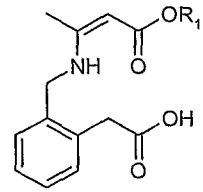


which comprises the steps of:

i) reacting the compound (7-amino-3-[5-(1-carboxymethyl-1,2,3,4-tetrazolyl)thiomethyl]-3 -cephem-4-carboxylic acid) of formula (II) or its reactive derivative with compound of formula (III) or its active derivative wherein R_1 denotes lower alkyl in the presence of organic solvent,



(II)



(III)

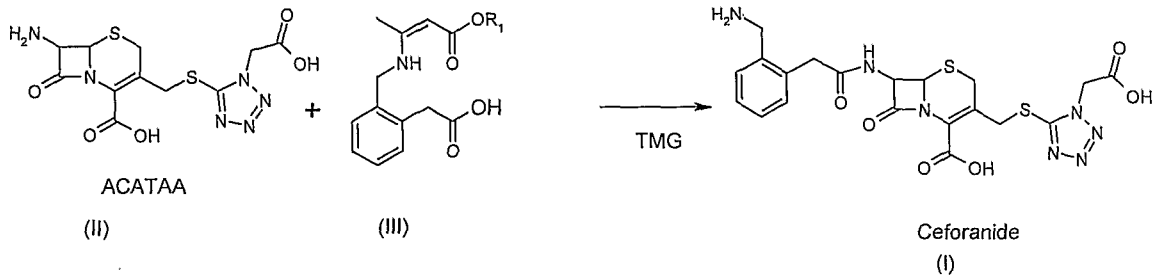
ii) isolating the Ceforanide of formula (I) or N,N-dicylcohexyl ethylenediamine salt of Ceforanide

iii) dissolving the Ceforanide of formula (I) in an organic acid at a temperature in the range of 10°C to 50°C;

iv) adding water to the reaction mass obtained in step (i); and

v) isolating the Ceforanide of formula (I) in pure form.

The process is shown in Scheme-1



Scheme-1

Detailed description of the invention

In an embodiment of the present invention the compound of formula (II) is employed either in free form or in reactive form. The reactive form of compound of formula (II) includes 1) silyl reactive derivative; the silyl derivative was prepared by reacting the compound of formula (II) with silylation agents like hexamethyldisilazane (HMDS), trimethylchlorosilane (TMCS), trimethylsilyl iodide (TMSI), N,O-bis-(trimethylsilyl)-acetamide (BSA), methyltrimethylsilyltrifluoroacetamide (MSTFA), N,O-bis-(trimethylsilyl)trifluoroacetamide (BSTFA) or mixtures there of; 2) salt of compound of formula (II), the salts of compound of formula include trimethylamine, dimethylethylamine, triethylamine, N-methylmorpholine, pyridine, diisopropylethylamine, N-methylpiperidine, N-ethylpiperidine, tetramethylguanidine, pentamethylguanidine, tetraethylguanidine, tetramethylethyguanidine, tetramethylbenzylguanidine and methylarylguanidines, 1,5-diazabicyclo(4,3,0)-non-5-ene (DNB) and 1,8-diazabicyclo(5,4,0)-undec-7-ene (DBU) or mixtures there of.

In another embodiment of the present invention compound of formula (III) is activated as acid halides, mixed anhydrides, active esters, and active amides. Mixed anhydrides of compound of formula (III) formed by reacting the carboxylic acid of formula (III) or its salt with a lower-alkyl chloroformate such as ethyl chloroformate, benzyl chloroformate, isobutyl chloroformate or

pivaloyl chloride in the presence or absence of catalytic amount of pyridine hydrobromide, N,N-dimethyl amino pyridine. The mixed carboxylic-carbonic anhydride thus formed is usually used *in situ* to acylate the said compound of formula (II). Alternatively acylation of compound of formula (II) comprises contacting the said compound of formula (III) with the appropriate carboxylic acid in the presence of certain agents known in the art for forming peptide bonds. Such agents include carbodiimides, for example, dicyclohexylcarbodiimide.

In still another embodiment of the present invention, the solvent used in step (i) is selected from methyl formate, methyl acetate, ethyl acetate, propyl acetate, butyl acetate, methyl propionate, acetone, diethyl ether, ethyl propyl ether, ethyl butyl ether, tetrahydrofuran, dioxane, acetonitrile, propionitrile, butyronitrile, isobutyronitrile, toluene, xylene, chlorobenzene and anisole and solvents such as dichloromethane, chloroform, dichloroethane, trichloroethane, dibromoethane, propylene dichloride, carbon tetrachloride, hexane, heptane, cyclopentane, cyclohexane, cycloheptane and cyclooctane, dimethylformamide and dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, etc. These solvents are used singly or in admixture of at least two of them. These solvents may contain water as required. Optionally a base may be present during acylation.

In yet another embodiment of the present invention, the solvent used in step (iii) is selected from ethanol, methanol, isopropanol, acetonitrile, acetone, ethyl acetate, THF, DMAc, DMF, water or mixtures thereof.

The organic acid used in step (iii) for dissolving the compound of formula (I) is selected from acetic acid, propanoic acid, formic acid, methane sulphonic acid and the like or mixtures thereof.

In an aspect of the present invention, the precipitation Ceforanide of formula (I) in step (iv) is effected by adding water to the reaction mass after dissolving the compound of formula (I) in organic acid.

Conventional process utilizes salt formation technique to purify the Ceforanide of formula (I), for example US patent No. 4,448,958 utilizes N,N-Dimethylbenzylammonium-7-[.alpha.-(2-aminomethylphenyl)acetamido)-3-[(1-carboxymethyltetrazol-5-ylthio)methyl]-3-cephem-4-carboxylate to get pure Ceforanide. The present invention obviates theses extra steps and provide a simple process that yield Ceforanide in pure form. The advantage of this process is that it avoids the complexities associated with the conventional process such as elimination of salt formation step of Ceforanide which requires large quantity of acetone for the isolation of salt of Ceforanide followed by execution of additional step for the neutralization of salt of Ceforanide in order to obtain Ceforanide in pure form. However, the process embodied in the present invention requires simple steps of dissolving the crude compound in organic acid followed by precipitation of the compound through the addition of water. Apart from the simplicity associated with the present process, it proves to be effective in getting rid of the unwanted impurities, which are formed during the course of the reaction, and makes the final API compatible with the pharmacopoeia standards.

In one more embodiment of the present invention, the compound of formula (I) is optionally isolated as N,N-dicylcohexyl ethylenediamine salt. Further the said salt is converted into Ceforanide by reacting the salt with acid such as HCl, sulfuric acid, formic acid, acetic acid, perchloric acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenesulfonic acid, methanesulfonic acid, trifluoro acetic acid, or cationic exchange resin like UBK530 resin in the solvent selected from ethanol, methanol, isopropanol, acetonitrile, acetone, ethyl acetate, THF, DMAc, DMF, water or mixtures thereof.

The N,N-dicylcohexyl ethylenediamine salt of Ceforanide is stable and do not have any safety issue that are associated with the known N,N-Dimethylbenzylammonium salt of Ceforanide. Apart from this, cost of preparation of N,N-dicylcohexyl ethylenediamine salt of Ceforanide is less as compared to the known N,N-Dimethylbenzylammonium salt of Ceforanide.

In one more embodiment of the present invention, this invention further provides a process for preparing sterile Ceforanide which comprises dissolving the Ceforanide in water and optionally in the presence of solvent like methanol, acetone, isopropyl alcohol, tetrahydrofuran and the like using a base selected from ammonia, sodium bicarbonate, triethyl amine and the like, subjecting the clear solution to sterile filtration in sterile area, precipitating the product by adjusting the pH using formic acid or acetic acid.

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.

Example 1

7-(2-Aminomethylphenylacetamido)-3-(1-carboxymethyltetrazol-5-ylthiomethyl) -3-cephem-4-carboxylic acid (Ceforanide).

Activation of compound of formula (III) Solution A:

To the suspension of Dane salt of 2-aminomethyl phenyl acetic acid (AMPAA) (24.8 g) {prepared according to US 4,100,346} in methylene chloride (125 mL) were added pyridine hydrobromide (0.3vg) followed by pivaloyl chloride (8.5g) at –15 to –20°C and stirred for 60 min. The reaction mass was cooled to –35 to –40°C and DMF (87.5 mL) was added in drops at –35 to –40°C for 30 min.

Q-salt of compound of formula (II) Solution B:

To 7-amino-3-[5-(1-carboxymethyl-1,2,3,4-tetrazolyl)thiomethyl]-3 -cephem-4-carboxylic acid (ACATAA) (25 g) in methylene chloride (125 mL)

tetramethyl guanidine (16.3 g) was added at –10°C and stirred for 30 min. at 0 to 5°C to get a solution. It was cooled to –20 to –25°C.

Condensation:

The solution A was transferred into solution B and the resulting solution was stirred until completion of reaction at –35 to –40°C (ACATAA < 5.0%). After completion of the reaction, the reaction mass was poured into water (250 mL), the resultant layers were separated and cooled to 10°C. The pH of aqueous layer was adjusted to 2.5 using dilute HCl. The product was filtered and washed with water (150 mL) followed by methanol (150 mL). The wet material was dried under vacuum.

Example 2

7-(2-Aminomethylphenylacetamido)-3-(1-carboxymethyltetrazol-5-ylthiomethyl) -3-cephem-4-carboxylic acid (Ceforanide).

Silylation of compound of formula (II) Solution B:

To ACATAA (10 g) in DMF (50 mL) BSA (21.9g) was added at 0 to 5°C. The temperature was increased to 20 to 25°C and stirred for 60 min. to get a solution and then reaction mass was cooled to 0 to 5°C.

Activation of compound of formula (III) Solution A:

To the suspension of Dane salt of 2-aminomethyl phenyl acetic acid (10.32 g) {prepared according to US 4,100,346} in methylene chloride (80 mL) DMF (10 mL) N-methyl morpholine, ethyl chloroformate (4.1g) were added at –55°C.

Condensation:

The cooled solution B was added into solution A and the reaction mass was stirred at –45 to –55°C till completion of the reaction (ACATAA < 5%). After completion of reaction the mass was poured into mixture of 1:1 HCl (25 mL) and water (175 mL) followed by separation of layers. The pH of aqueous layer

was adjusted to pH to 2.5 at 15 to 20°C using ammonia. The precipitate was stirred for an hour at 0 to 5°C and then it was filtered. The wet material was washed with water (50 mL) followed by methanol (50 mL). It was dried under vacuum.

Example 3

Purification of Crude Ceforanide

Ceforanide (100 g) was added to formic acid (500 mL) and stirred to get a clear solution. To the clear solution was added water (500 mL) and stirred to get a precipitate. The precipitate obtained was filtered, washed with water followed by acetone. The wet material was dried under vacuum to yield the title compound. (Yield = 92.0 g and Purity > 99.50%; purity before purification is 99.48%)

Example 4

Preparation of Sterile Ceforanide

Ceforanide (100 g) was added to water (100 mL) and stirred at 15-20° C to get a solution. The pH of reaction mass was adjusted to about 7.8 using ammonia solution to get clear solution. The clear solution was subjected to carbon treatment followed by sterile filtration. The pH of the filtrate was adjusted to 2.5 using formic acid at 15-20° C. The precipitated Ceforanide was stirred for an hour and then it was filtered and washed with water followed by acetone. This was dried under vacuum (M/C <1%). This sterile Ceforanide is blended with sterile L-Lysine.

Sterile L-Lysine preparation:

To water (200 mL) non-sterile L-lysine (100 g) was added stirred to get clear solution. The clear solution was subjected to carbon treatment followed by sterile filtration. After filtration the filtrate was added slowly into isopropyl alcohol (5000 mL). The precipitated sterile L-Lysine was filtered washed with isopropyl alcohol dried under vacuum. (Moisture content <1%).

Example 5

Preparation of N, N,-cyclohexyl ethylenediamine Ceforanide

To the suspension of crude Ceforanide {which may contain 8.6% of ACATAA} (5.0g) in a mixture of acetone (25 mL) and water (25 mL), N,N'-dicyclohexylethylenediamine (2.16 g) was added and stirred for 15 min to get a solution. To the clear solution acetone was added. The precipitated N,N,-cyclohexyl ethylenediamine Ceforanide was stirred for 30 min and filtered. This was washed with acetone (25 mL) and dried under vacuum to get N,N'-dicyclohexylethylenediamine salt of Ceforanide. Yield: 5.1g; Purity: 98.26%-99.5%

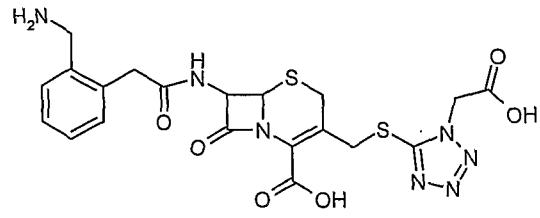
Example 6

Preparation of Pure Ceforanide

To water (50 mL) N, N,-dicyclohexyl ethylenediamine Ceforanide salt was added and stirred in at 25°C to get a solution. The pH of the clear solution was adjusted to 2.5 using dil. HCl. The precipitated pure Ceforanide was stirred for an hour and then it was filtered and washed with water (25 mL) followed by acetone (25 mL). This was dried under vacuum.

We Claim:

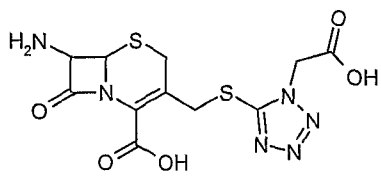
1) An improved process for the preparation of Ceforanide of formula (I),



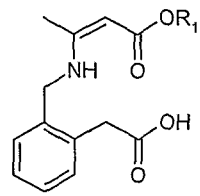
(I)

which comprising the steps of:

i) reacting the compound (7-amino-3-[5-(1-carboxymethyl-1,2,3,4-tetrazolyl)thiomethyl]-3 -cephem-4-carboxylic acid) of formula (II) or its reactive derivative with compound of formula (III) or its active derivative wherein R_1 denotes lower alkyl in the presence of solvent;



(II)



(III)

ii) isolating the Ceforanide of formula (I) or N,N-dicylcohexyl ethylenediamine salt of Ceforanide of formula (I);

iii) dissolving the Ceforanide of formula (I) in an organic acid at a temperature in the range of 10°C to 50°C;

iv) adding water to the reaction mass obtained in step (i); and

v) isolating the Ceforanide of formula (I) in pure form.

2) A process as claimed in claim 1, wherein R_1 in compound of formula (III) represents a lower alkyl group selected from ethyl, methyl, benzyl, isobutyl or pivaloyl.

3) A process as claimed in claim 1, wherein the solvent used in step (i) selected from methyl formate, methyl acetate, ethyl acetate, propyl acetate, butyl

acetate, methyl propionate, acetone, diethyl ether, ethyl propyl ether, ethyl butyl ether, tetrahydrofuran, dioxane, acetonitrile, propionitrile, butyronitrile, isobutyronitrile, toluene, xylene, chlorobenzene and anisole, such as dichloromethane, chloroform, dichloroethane, trichloroethane, dibromoethane, propylene dichloride, carbon tetrachloride, hexane, heptane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, dimethylformamide, dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water or mixtures there of.

4) A sterile process for the preparation of sterile Ceforanide, the said process comprising the steps of:

i) dissolving Ceforanide in water and in the presence or absence of solvent using a base;

ii) filtering through micron filtration;

iii) adjusting pH using an organic acid to yield sterile Ceforanide.

5) A process as claimed in claim 4, wherein the base used is selected from ammonia, TEA, sodium bicarbonate.

6) A process as claimed in claim 4, wherein the organic acid used is selected from formic acid or acetic acid.

7) A process for the purification of Ceforanide of formula (I), which comprising the steps of:

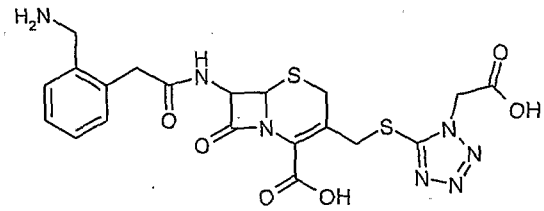
(i) dissolving the Ceforanide of formula (I) in an organic acid at a temperature in the range of 10° C to 50° C,

(ii) adding water to the reaction mass; and

(iii) isolating the Ceforanide of formula (I).

8) A process as claimed in claim 1 or 7, wherein the organic acid used in step (iii) or (i) is selected from acetic acid, propanoic acid, formic acid, methane sulphonic acid and the like or mixtures thereof.

9) N,N-dicylcohexyl ethylenediamine salt of Ceforanide of formula (I):



10) Use of N,N-dicylcohexyl ethylenediamine salt of Ceforanide of formula (I) in the preparation of Ceforanide in pure form.