(54) Title: PURIFICATION OF CEFUROXIME ACID

(57) Abstract: The present invention relates to a process for the purification of cefuroxime acid \{(6R,7R)-3-carbamoyloxy-methyl-7-[\{(Z)-2-(fur-2-yl)-2-methoxy-iminoacetamido\}ceph-3-em-4-carboxylic acid\}} of formula (I).
"PURIFICATION OF CEFUROXIME ACID"

Field of the Invention:
The present invention is in the field of chemistry and more particularly the invention deals with the process for the purification of cefuroxime acid \((6R, 7R)-3\)-carbamoyloxymethyl-7-\([(Z)-2-(fur-2-yl)-2\text{-methoxy-iminoacetamido}]\) ceph-3-em-4-carboxylic acid\) of general formula (I).

\[
\begin{align*}
\text{OH}_3
\end{align*}
\]

(I)

Background of the Invention:
Cefuroxime acid is a key intermediate for the industrial synthesis of cefuroxime sodium (for the injection administration) and cefuroxime axetil (for the oral administration). These compounds have a valuable broad spectrum and having activity against wide range of gram-positive and gram-negative microorganisms. Their effectiveness is advantageously combined with remarkable resistance to \(\beta\)-lactamases.

Cefuroxime can be prepared by condensation of 3-hydroxymethyl-7-amino cephalosporanic acid with (fur-2-yl)-2-methoxyiminoacetic acid to produce \((6R,7R)-7-[(Z)-2-(fur-2-yl)-2\text{-methoxyiminoacetamido}]\)-3-hydroxymethyleneceph-3-em-4-carboxylic acid followed by carbamoylation of resulting acid with isocyanate of formula RNCO wherein \(R\) is a labile substituent to get \((6R,7R)-3\text{-carbamoyloxymethyl-7-[(Z)-2-(fur-2-yl)-2\text{-methoxyimino acetamido}] ceph-3-em-4\text{-carboxylic acid (cefuroxime acid)}}.

In prior art pure crystalline cefuroxime axetil is obtained by cefuroxime sodium from either 3-hydroxy cefuroxime or cefuroxime. Therefore, the said process involves an additional step of preparing sodium cefuroxime and therefore it is not economical.
If purification of cefuroxime axetil or cefuroxime sodium is done without purifying cefuroxime then the yield of the final product will be low. Purify the compound on penultimate stage is more economical rather than on the final stage.

Hence, there is unmet need to develop a simple and environment friendly process for the purification of cefuroxime acid, which is convenient to perform on a commercial scale, operationally safe and provide the product in pure form.

**Objects of the Invention:**

An object of the present invention is to provide a simple and environment friendly process for the purification of cefuroxime acid of formula (I) with good yield, high purity and color absorbance of less than 0.1 at 410 nm.

**Summary of the Invention:**

The present invention provides process for the process for the purification of cefuroxime acid \((6R, 7R)-3-carbamoyloxymethyl-7-[(Z)-2-(fur-2-yl)-2-methoxy-iminoacetamido] ceph-3-em-4-carboxylic acid\) of general formula (I).

**DETAILED DESCRIPTION OF THE INVENTION**

Accordingly, the present invention provides a simple and environment friendly process for the preparation of cefuroxime acid of formula (I) with high purity and improved color. Cefuroxime acid with color absorbance of less than 0.1 at 410 nm is useful for manufacturing of cefuroxime axetil having acceptable quality in terms of purity and color. The spray drying process for making amorphous cefuroxime axetil always result in the enhancement of color hence it is utmost important to control the color of cefuroxime acid to get acceptable quality of amorphous cefuroxime axetil.

The process for purification of cefuroxime acid of formula (I),
Which comprises the steps of:

(i) dissolving impure cefuroxime acid of formula (I) in a mixture of water and polar aprotic solvent,

(ii) adjusting the pH of the mixture in the range 6.0 to 7.0 by adding a base to get a clear solution,

(iii) treating the solution with activated charcoal followed by filtration,

(iv) adjusting the pH of the filtrate to 3.5-3.6 by adding dilute acid and;

(v) isolating the precipitated product by adjusting pH 1.5-2.5 by adding dilute acid at a temperature range 0 to 5°C.

Moreover, the acid product can easily be converted into the corresponding pharmaceutically acceptable salt or ester, preferably into cefuroxime salt and cefuroxime axetil, by using conventional techniques known to those skilled in the art.

For purposes of this invention, polar aprotic solvent is selected from the group of acetonitrile, dioxane, tetrahydrofuran, alcohol or acetone.

Base used in this invention is selected from the group of alkali/alkaline earth metal hydroxides like sodium hydroxide, potassium hydroxide.

Preferably, dissolution is carried out in the temperature range of 0 to 5°C. The above solution is then charcoalised with activated carbon followed by filtration. Preferably, the charcoalisation is carried out in the temperature range of 0 to 5°C.

Finally, the acid used for adjusting pH from 1.5-2.5 is selected from the group of hydrochloric acid or sulphuric acid, more preferable pH to isolate the cefuroxime acid of formula (I) in pure form having color absorbance less than 0.1 at 410 nm and purity more than 99.0% in the range of 2.0±0.05 at a temperature in the range of 0 to 5°C.

The invention is illustrated by the following examples which are only meant to illustrate the invention and not act as limitations. All embodiments apparent to a process their in the art are deemed to fall within the scope of the present invention.
Examples

Example 1
Crude cefuroxime acid [(10.0 g), purity: 98.73%, Color absorbance: 2.263] was added to the mixture of water (130 ml) and ACN (30 ml) at 25-30°C. The pH of the solution was adjusted to 6.0 to 7.0 by adding 10% sodium hydroxide solution and was stirred for 60 minutes at 0 to 5°C to get the clear solution. Activated charcoal was added and stirred for 30 minutes at 0 to 5°C. The solution was filtered and washed with 10 ml of water. The pH of the filtrate was adjusted to 3.5 to 3.6 by adding 5% HCl and was stirred for 30 minutes at 0 to 5°C. Finally, the pH was adjusted to 1.5 to 2.1 by adding 5% HCl solution and was stirred for 60 minutes at 0 to 5°C. The product was filtered and washed with a mixture of ACN and water. The product was dried to get cefuroxime acid (6.0 g) in pure form. HPLC purity: 99.50%, Color absorbance: 0.04.

Example 2-9
The reaction was conducted in the similar manner as explained in example 1 by using different solvents. Results are given in Table 1.

Table 1

<table>
<thead>
<tr>
<th>Examples</th>
<th>Solvents</th>
<th>Color absorbance</th>
<th>% purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.</td>
<td>Acetone</td>
<td>0.11</td>
<td>99.21</td>
</tr>
<tr>
<td>3.</td>
<td>IPA</td>
<td>0.12</td>
<td>99.15</td>
</tr>
<tr>
<td>4.</td>
<td>Ethyl alcohol</td>
<td>0.13</td>
<td>99.21</td>
</tr>
<tr>
<td>5.</td>
<td>THF</td>
<td>0.10</td>
<td>99.30</td>
</tr>
<tr>
<td>6.</td>
<td>Cyclohexane</td>
<td>1.01</td>
<td>98.64</td>
</tr>
<tr>
<td>7.</td>
<td>Toluene</td>
<td>1.14</td>
<td>98.95</td>
</tr>
<tr>
<td>8.</td>
<td>Chloroform</td>
<td>1.33</td>
<td>98.88</td>
</tr>
<tr>
<td>9.</td>
<td>MDC</td>
<td>1.14</td>
<td>98.98</td>
</tr>
</tbody>
</table>

Abbreviations:
ACN : Acetonitrile
HCl : Hydrochloric acid
IPA : Isopropyl alcohol
THF : Tetrahydrofuran
MDC : Dichloromethane
We Claim:

1) A process for the purification of cefuroxime acid of general formula (I) comprising the steps of:
   (i) dissolving impure cefuroxime acid of formula (I) in a mixture of water and polar aprotic solvent
   (ii) adjusting the pH of the mixture in the range of 6.0 to 7.0 by adding a base to get a clear solution,
   (iii) treating the solution with activated charcoal followed by filtration,
   (iv) adjusting the pH of the filtrate to 3.5 to 3.6 by adding dilute acid and;
   (iv) isolating the precipitated product by adjusting pH 1.5-2.5 by adding dilute acid at a temperature range 0 to 50°C.

2) The process as claimed in claim 1, wherein the polar aprotic solvent used in step (i) is selected from the group of acetonitrile, Tetrahydrofuran, acetone, dioxane or mixture thereof.

3) The process as claimed in claim 2, wherein the preferred polar aprotic solvent is acetonitrile.

4) The process as claimed in claim 1, wherein said base used in step (ii) is selected from alkali or alkaline earth metal hydroxides like sodium hydroxide, potassium hydroxide.

5) The process as claimed in claim 4, wherein the preferred base is sodium hydroxide.

6) The process as claimed in claim 1, wherein the acid used in step (iv) is selected from the group of hydrochloric acid or sulphuric acid.
7) The process as claimed in claim 1, wherein the said pure cefuroxime acid having the color absorbance less than 0.1 at 410 nm.

8) Cefuroxime acid having the color absorbance less than 0.1 at 410 nm.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

**IPC**: C07D 501/34 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

**IPC**: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Wpi, Epodoc, TXT, Erribase, Pubmed

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<td>X</td>
<td>WO2004/050663A2 (ORCHID CHEMICALS &amp; PHARM LTD) 17 June 2004 (17.06.2004) <em>e.g. page 2 top and bottom, Step (H), Claims 1,9, 13</em></td>
<td>1-6</td>
</tr>
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<td>WO2000/053609A1 (RANBAXY LAB LTD) 14 September 2000 (14.09.2000) <em>e.g. page 4 line 30 to page 5 line 4, page 3 line 19 to 25</em></td>
<td>1-6</td>
</tr>
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</table>

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* "A" document defining the general state of the art which is not considered to be of particular relevance

* "E" earlier application or patent but published on or after the international filing date

* "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

* "O" document referring to an oral disclosure, use, exhibition or other means

* "P" document published prior to the international filing date but later than the priority date claimed

* "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

* "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

* "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

* "&" document member of the same patent family

Date of the actual completion of the international search 10 September 2008 (10.09.2008)

Date of mailing of the international search report 24 September 2008 (24.09.2008)

Name and mailing address of the ISA/ A T

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Form PCT/ISA/210 (second sheet) (January 2004)
Continuation of first sheet

Continuation No. II:

Observations where certain claims were found unsearchable

(Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

Claims Nos.: 7,8 because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claims 7 and 8 are unclear due to the term "color absorbance" which is not a suitable technical feature for the characterization of cefuroxime or its purity. The subject matters of claims 7 and 8 therefore had to be excluded from the search as well as in the establishment for novelty, inventive step and industrial applicability.
<table>
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<th>Patent family member(s)</th>
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Form PCr/ISA/210 (patent family annex) July 1998; reprint January 2004