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(54) Title: PROCESS FOR THE PURIFICATION OF BIAPENEM

(57) Abstract: The present invention relates to a process for the purification of biapenem.

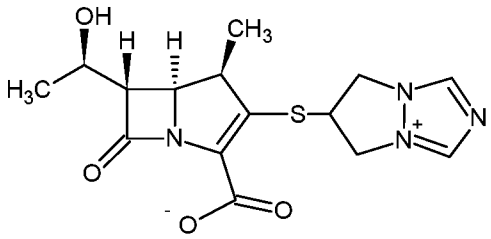
PROCESS FOR THE PURIFICATION OF BIAPENEM

Field of the Invention

The present invention relates to a process for the purification of biapenem.

Background of the Invention

Biapenem is chemically known as 6-[[2(4R,5S,6S)-carboxy-6-[(lR)-hydroxyethyl]-4-methyl-7-oxo- 1-azabicyclo[3.2.0]hept-2-en-3-yljthio]6,7-dihydro-5H-pyrazolo[l,2-a][l,2,4]triazol-4-ium inner salt, and is represented by Formula 1. It is indicated for the treatment of bacterial infection and sepsis.



Formula 1

U.S. Patent No. 4,866,171, in Example 6, discloses the purification of biapenem using chromatography and/or lyophilization techniques. This patent also describes a process for the conversion of amorphous biapenem into a crystalline form by dissolving the amorphous biapenem in water while heating, followed by cooling, then washing the obtained crystals with a 50% aqueous ethanol solution.

U.S. Patent No. 5,241,073 describes a process for the purification of biapenem involving column chromatography and crystallization with ethanol.

U.S. Patent No. 5,286,856 describes a process for the crystallization of biapenem from an aqueous solution, comprising maintaining the temperature of the aqueous solution from eutectic temperature (-10°C to -2°C) to a temperature lower than 0°C, followed by lyophilization.

The *Journal of Organic Chemistry*, 63(23):8145-8149 (1998) describes the purification of biapenem involving resin chromatography.

The present invention provides an alternate process for the purification of biapenem that avoids making use of tedious techniques like chromatography and lyophilization. At the same time, it results in a high yield and high purity of the final

product. Advantageously, the crystalline biapenem of this invention can be directly isolated from the reaction mixture. Further, the process of the present invention involves fewer steps, is easily scalable, and industrially advantageous.

Summary of the Invention

The present invention provides a process for the purification of biapenem comprising the steps of:

(a) treating an aqueous solution of biapenem with charcoal;

(b) filtering the mixture obtained in step (a);

(c) adjusting the pH of the filtrate obtained in step (b) to 4.5 to 5.5; and

(d) adding an antisolvent to the solution obtained in step (c).

The present invention also provides a process for the purification of biapenem which comprises a step of crystallizing biapenem by adding an antisolvent to an aqueous solution of biapenem at a pH range of 4.5 to 5.5.

Detailed Description of the Invention

The term "about", as used herein, refers to any value which lies within the range defined by a variation of up to ±10% of the value.

The term "base", as employed herein, is meant to comprise sodium hydroxide, potassium hydroxide, magnesium hydroxide, ammonia solution, dipotassium hydrogen orthophosphate, magnesium carbonate, sodium carbonate, potassium carbonate, pyridine, trimethylamine, triethylamine, diisopropylethylamine, N-methyl morpholine, and the like.

The term "antisolvent", as employed herein, is meant to comprise a solvent which is capable of crystallizing out biapenem from an aqueous solution of biapenem. Some of the non-limiting examples of "antisolvent" are acetone, ethyl methyl ketone, methanol, ethanol, propanol, isopropanol, and the like.

The present invention can be explained by way of the following aspects.

A first aspect of the present invention provides a process for the purification of biapenem comprising the steps of:

(a) treating an aqueous solution of biapenem with charcoal;

(b) filtering the mixture obtained in step (a);

(c) adjusting the pH of the filtrate obtained in step (b) to 4.5 to 5.5; and

(d) adding an antisolvent to the solution obtained in step (c).

According to one embodiment of this aspect, the aqueous solution of biapenem can be prepared by dissolving biapenem in water.

In another embodiment, the filtration of the mixture obtained in step (a) can be performed through a hyflo bed and/or a filter paper.

In another embodiment, the pH of the filtrate obtained in step (b) can be adjusted to a range of 4.5 to 5.5 by the addition of a base.

In another embodiment, an antisolvent is added to the solution obtained in step (c) to crystallize out biapenem.

In another embodiment, the antisolvent is acetone.

Accordingly, an aqueous solution of biapenem is prepared by dissolving biapenem in water while heating at a temperature of about 60°C to about 70°C, followed by cooling to a temperature of about 25°C to about 35°C within 10 minutes. To this aqueous solution of biapenem, activated charcoal (enoantichromos carbon) is added and the resultant mixture is filtered. The filtration can be performed through a hyflo bed and/or a filter paper. The pH of the filtrate is then adjusted to a range of 4.5 to 5.5 by adding a base. An antisolvent is added to the resultant solution to crystallize out biapenem, which is then filtered, washed, and dried under vacuum to obtain the purified biapenem.

The term "purified", as employed herein, refers to a purity of greater than 99% as determined by HPLC.

This aspect of the present invention provides biapenem with greater than 80% yield and greater than 99% HPLC purity.

A second aspect of the present invention provides a process for the purification of biapenem which comprises a step of crystallizing biapenem by adding an antisolvent to an aqueous solution of biapenem at a pH range of 4.5 to 5.5.

According to one embodiment of this aspect, an aqueous solution of biapenem can be prepared by dissolving biapenem in water.

In another embodiment, the pH of the solution can be adjusted to a range of 4.5 to 5.5 by the addition of a base.

In another embodiment, the antisolvent is acetone.

Accordingly, an aqueous solution of biapenem is prepared by dissolving biapenem in water while heating at a temperature of about 60°C to about 70°C, followed by cooling to a temperature of about 25°C to about 35°C within 10 minutes. This solution is treated with activated charcoal (enoantichromos carbon) and filtered. The pH of the filtrate is adjusted to a range of 4.5 to 5.5 by adding a base. An antisolvent is added to the resultant solution to crystallize out biapenem, which is then filtered, washed, and dried under vacuum to obtain the purified biapenem.

This aspect of the present invention provides biapenem with greater than 80% yield and greater than 99% HPLC purity.

The biapenem to be purified (starting material) can be obtained using known methods, for example, the processes described in U.S. Patent Nos. 4,866,171 or 5,241,073.

While the present invention has been described in terms of its specific aspects, certain modifications and equivalents will be apparent to those skilled in the art, and are intended within the scope of the present invention.

EXAMPLES

Example 1: Purification of Biapenem

Biapenem (12 g) was added into water (300 mL) at 65°C, stirred for 5 minutes, and cooled to 30°C within 10 minutes. Enoantichromos carbon (0.6 g) was added to the reaction mixture and stirred for 10 minutes to 15 minutes at 25°C to 30°C. The reaction mixture was filtered through a hyflo bed and washed with water (36 mL). The filtrate obtained was passed through a 0.45 micron filter, and its pH was adjusted to 5.5 using 5% aqueous sodium hydroxide solution at 10°C to 15°C. Acetone (336 mL) was added to the reaction mixture at 5°C to 10°C. The resultant slurry was stirred for 3 hours at 5°C to 10°C, filtered, and the obtained solid was washed with acetone (60 mL). The solid was dried under reduced pressure (720 mmHg) at 30°C to 35°C to obtain the title product as white crystals.

Yield: 84%

HPLC Purity: 99.87%

Example 2: Purification of Biapenem

Biapenem (18 g) was added into water (450 mL) at 65°C, stirred for 5 minutes, and cooled to 30°C within 10 minutes. Enoantichromos carbon (0.9 g) was added to the reaction mixture and stirred for 30 minutes at 25°C to 30°C. The reaction mixture was filtered through a hyflo bed and washed with water (54 mL). The filtrate obtained was passed through a 0.45 micron filter and its pH was adjusted to 4.9 using 5% aqueous sodium hydroxide solution at 10°C to 15°C. Acetone (504 mL) was added to the reaction mixture at 10°C to 15°C. The resultant slurry was stirred for 3 hours at 5°C to 10°C, filtered, and the obtained solid was washed with acetone (90 mL). The solid was dried under reduced pressure (720 mmHg) at 35°C to 40°C to obtain the title product as white crystals.

Yield: 81.77%

HPLC Purity: 99.80%

We Claim:

1. A process for the purification of biapenem comprising the steps of:
   (a) treating an aqueous solution of biapenem with charcoal;
   (b) filtering the mixture obtained in step (a);
   (c) adjusting the pH of the filtrate obtained in step (b) to 4.5 to 5.5; and
   (d) adding an antisolvent to the solution obtained in step (c).

2. The process of claim 1, wherein the filtration is performed through a hyflo bed and/or a filter paper.

3. The process of claim 1, wherein the pH is adjusted to 4.5 to 5.5 by the addition of a base.

4. The process of claim 1, wherein an antisolvent is added to crystallize out biapenem.

5. The process of claim 1 or claim 4, wherein the antisolvent is acetone.

6. A process for the purification of biapenem which comprises a step of crystallizing biapenem by adding an antisolvent to an aqueous solution of biapenem at a pH range of 4.5 to 5.5.

7. The process of claim 6, wherein the pH is adjusted to 4.5 to 5.5 by the addition of a base.

8. The process of claim 6, wherein the antisolvent is acetone.

9. The process of claim 6, wherein the aqueous solution of biapenem is formed by treating an aqueous solution of biapenem with charcoal and filtering the resulting mixture.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2013/061157

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D477/20
ADD.

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)
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)
EPO-Internal , WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02/057266 A1 (MERCK & CO INC [US] ; WILLIAMS JOHN M [US] ; SKERLJ RENATO [US]) 25 July 2002 (2002-07-25) page 13, line 2 - line 11; example 1	1-9
Y	WO 2009/047604 A1 (ORCHID CHEMICALS & PHARM LTD [IN] ; UDAYAMPALAYAM PALANISAMY SENTH [IN]) 16 April 2009 (2009-04-16) page 6, line 34 - page 7, line 5	1-9
Y	CN 102 268 025 A (HAINAN MEILAN SMITH KLINE PHARMACEUTICAL CO., LTD.) 7 December 2011 (2011-12-07) abstract & machine translation of CN102268025A provided by Google	1-9

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2013/061157

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