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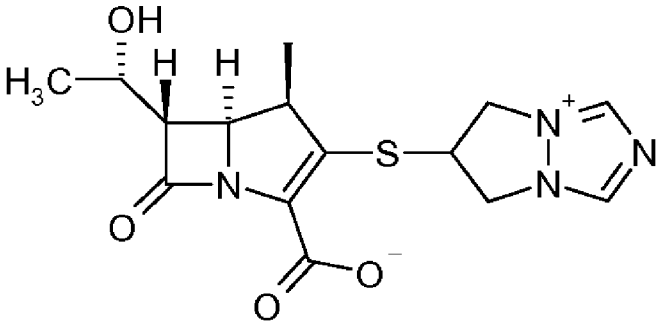
(54) Title: AN IMPROVED PROCESS FOR THE PREPARATION OF CARBAPENEM ANTIBIOTIC



(I)

(57) Abstract: The present invention relates to an improved process for the preparation of Biapenem of Formula (I) having reconsti - tution time less than 25 seconds. (Formula (I))

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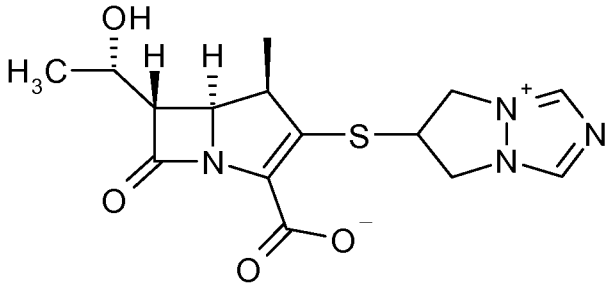
AN IMPROVED PROCESS FOR THE PREPARATION OF CARBAPENEM ANTIBIOTIC

Field of the Invention

The present invention provides an improved process for the preparation of carbapenem antibiotic namely Biapenem of formula (I). Further the process of the present invention provides Biapenem having reconstitution time less than 25 seconds.



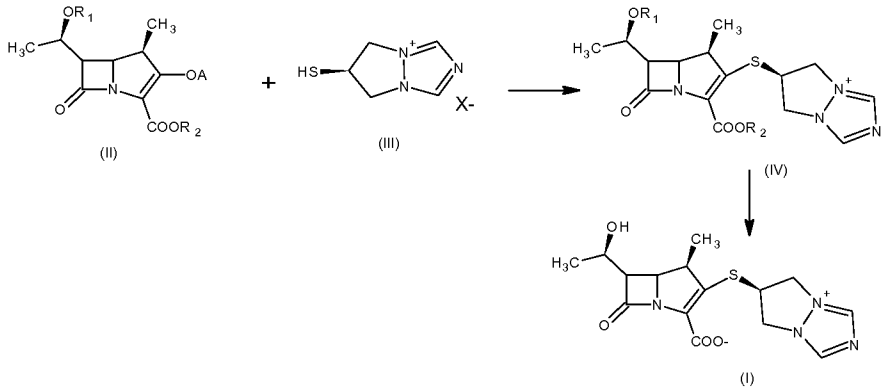
(I)

Background of the Invention

Biapenem is a synthetic broad-spectrum carbapenem antibiotic which suppresses bacterial growth by inhibiting the enzymes responsible for bacterial cell wall synthesis, and shows broad-spectrum antibacterial activity both against gram-positive bacteria and gram-negative bacteria. Biapenem is chemically known as (4R,5S,6S)-3-(6,7-dihydro-5H-pyrazolo[l,2-a][l,2,4] triazol-8-ium-6-ylsulfanyl)-6-(1-hydroxyethyl)-4-methyl-7-oxo- 1-azabicyclo [3.2.0]hept-2-ene-2-carboxylate and marketed in Japan as OMEGACIN®.

Various methods are reported in the prior art for the preparation of Biapenem of formula (I) which includes the condensation of compound of formula (II) with compound of formula (III) and subsequent deprotection of the protecting group as shown in scheme-1.

Scheme-1



wherein R^1 is hydrogen or hydroxy protecting group such as tert-butyl dimethyl silyl and the like, R^2 is hydrogen or carboxyl protecting group such as p-nitrobenzyl, p-methoxy benzyl, allyl and the like, A is an activating group such as $P(0)(OR)_2$, $S0_2R$ and the like wherein R is selected from substituted or unsubstituted Ci_{-6} alkyl, aralkyl or aryl to form the compound of formula (II). The X^- in compound of formula (III) is halogen selected from Br or CI.

Biapenem was first disclosed in US 4,866,171 and the said patent also discloses a process for the preparation of the same. US 5,241,073 disclosed the method for the preparation of compound of formula (III) followed by condensation with compound of general formula (II) using base such as N-ethyldiisopropylamine and subsequent deprotection yields Biapenem which was isolated by column chromatography followed by crystallization from ethanol.

EP 0289801 discloses a process for the preparation of crystalline Biapenem wherein Biapenem was dissolved in water and lyophilized to get amorphous compound. The amorphous compound was dissolved in water at 40° C followed by cooling to get crystalline product. This patent further provides the PXRD values of the crystalline Biapenem. The Biapenem obtained according to the process provided in this patent takes longer time for reconstitution and hence not suitable.

US 5,286,856 and US 5,424,069 provide a process for the crystallization of Biapenem which utilizes freeze-drying technique and vial lyophillisation method respectively. These patents disclose (refer para 1, lines 10-33 of US' 856) that the process provided in EP 0289801 results with Biapenem crystals which take relatively longer time for dissolution during use. To overcome the above issues, these patents utilize the freeze-drying and vial lyophillisation methods. The said methods involve freezing of the solution containing Biapenem followed by raising the temperature and repeating the cooling and heating process followed by lyophillisation to get the crystalline product. Lyophillisation and related process are capital intensive techniques and uneconomical in commercial scale operations.

All the above said prior arts utilize either the lyophillisation technique or preparing the amorphous material and crystallizing it from water to get crystalline Biapenem.

Biapenem is available as powder for injection which needs to be reconstituted with water or saline solution before injection. The process of preparing a solution having an appropriate concentration of an active ingredient for the administration is called "reconstitution". The reconstitution time (RCT) plays a critical role in injectable powders. Short reconstitution time is preferable for both a member of medical center and patients. If the reconstitution time is too long, it will increase the preparation time thus making it difficult to administrate it to many patients at the same, which will eventually lower the competitiveness of the drug. The problem before the applicants is to find economic and robust process for the preparation of Biapenem with high purity and yield which should dissolve in water in less than 25 seconds (reconstitution time).

With our continued intensive and diligent research for developing a process for the preparation of Biapenem having high purity and yield with reconstitution time of less than 25 seconds, we have identified an improved process which is commercially viable and eliminates the issues associated with reconstitution time. The process of this invention is simple and obviates the use of freeze crystallization. Further the present invention fulfils the need for a process for the manufacture of Biapenem which is convenient to operate in commercial scale.

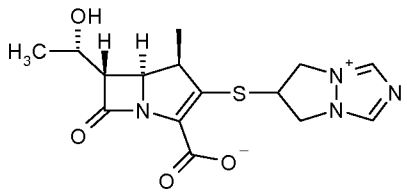
Objectives of the Invention

The main objective of the present invention is to provide a simple and commercially viable, industrially scalable process for the crystallization of Biapenem of formula (I) with high purity and good yield.

Yet another objective of the present invention is to provide a simple and commercially suitable process for the preparation of Biapenem of formula (I) with reconstitution time less than 25 seconds. The reconstitution time is calculated by the time taken to dissolve 300 mg of Biapenem in 100 ml of water or saline solution.

Summary of the invention

Accordingly the primary aspect of the present invention is to provide an improved process for the preparation of Biapenem of formula (I)



(I)

the said process comprises;

(i) obtaining a solution of Biapenem in water containing co-solvent; and

(ii) adding anti-solvent in to the solution of step (i) or *vice-versa* to crystallize Biapenem followed by filtration.

Detailed Description

In an embodiment of the present invention, the co-solvent used in step (i) is selected from alcoholic solvents consisting of methanol, ethanol, isopropyl alcohol, n-propanol, n-butanol and iso-butanol or mixtures thereof; preferably methanol, ethanol and isopropyl alcohol; more preferably methanol.

In another embodiment of the present invention the anti-solvent used in step (ii) is selected from acetone, methyl ethyl ketone, methyl isobutyl ketone, ethyl acetate, methyl acetate, butyl acetate, tetrahydrofuran or mixtures thereof; preferably acetone.

In yet another embodiment of the present invention, the solution of Biapenem in step (i) can be obtained by (a) dissolving Biapenem in water followed by addition of co-solvent (b) dissolving Biapenem in water containing the co-solvent (c) the aqueous solution containing Biapenem can be obtained directly from the reaction mass followed by addition of co-solvent (d) the aqueous solution of Biapenem containing co-solvent can be obtained directly from the reaction mass. The said solutions, if necessary can be subjected to sterile filtration before the addition of anti-solvent. Thus the present invention provided a process for the preparation of sterile Biapenem having reconstitution time less than 25 seconds, more preferably less than 15 seconds.

The prior art lyophillisation process for the preparation of Biapenem requires capital investment and high operating cost due to the involvement of repetitive heating and cooling process which is tedious technology in commercial scale operations. The reported prior art process for the crystallization of Biapenem of formula (I) from water results in the formation of crystalline powder which takes longer time for dissolution in water or saline solution (reconstitution time). Surprisingly, applicant found that the use of co-

solvents during the crystallization of Biapenem results with Biapenem having reconstitution time of less than 25 seconds. This constitutes the novelty of the present invention.

In this present invention the Biapenem of formula (I) is obtained as crystalline solid with purity above 99.0 % by HPLC with good stability and further can be easily filled in vials.

The following examples are provided by way of illustration only and should not be construed to limit the scope of the invention.

Crystallization of (4R,5S,6S)-3-(6J-dihvdro-5H-pyrazolori,2-al fl,2,41 triazol-8-ium-6-ylsulfanyl)-6-(l-hvdroxyethyl)-4-methyl-7-oxo-l-azabicyclo [3.2.01 hept-2-ene-2-carboxylate [Biapenem of formula (1)1:

Example -1:

To water (4 lit), Biapenem (100 g) was added at 40° C and dissolved to get a clear solution. Activated carbon and EDTA were added to the clear solution and filtered through hi-flow bed, washed with water followed by filtration through micron filters in sterile area. To the filtrate, methanol (600 mL) was added followed by acetone under stirring. To the reaction mass, Biapenem seed material was added and stirred. The crystallized product was filtered, washed with aqueous acetone and dried under vacuum to get crystalline Biapenem.

Yield: 85 g Purity by HPLC: 99.5%
Reconstitution time (RCT): < 15 seconds

Example -2:

To water (4 lit), Biapenem (100 g) was added at 40° C and dissolved to get a clear solution. To the filtrate, isopropyl alcohol (500 ml) was added followed by acetone under stirring. The mass was cooled and stirred. The crystallized

product was filtered, washed with aqueous acetone and dried under vacuum to get crystalline Biapenem.

Yield: 83 g Purity by HPLC: 99.6%
Reconstitution time: < 15 seconds.

Example -3:

To water (4 lit), Biapenem (100 g) was added at 40° C and dissolved to get a clear solution. The solution was filtered through micron filters. To the filtrate, ethanol (600 ml) was added followed by acetone and stirred. The crystallized product was filtered, washed with aqueous acetone and dried under vacuum to get crystalline Biapenem.
Yield: 84 g Purity by HPLC: 99.5%
Reconstitution time : < 15 seconds

Example -4:

To water (4 lit), Biapenem (100 g) was added at 40° C and dissolved to get a clear solution. The solution was filtered through hi-flow bed, washed with water followed by filtration through micron filters. To the filtrate, methanol (450 ml) was added followed by acetone and stirred. The crystallized product was filtered, washed with aqueous acetone and dried under vacuum to get crystalline Biapenem.

Yield: 87 g Purity by HPLC: 99.4%
Reconstitution time (RCT): < 15 seconds

Reference example -1:

Preparation of Biapenem (Non-Sterile)

Step-I: Preparation of p-Nitrobenzyl (4R,5S,6S)-3-(6,7-dihydro-5H-Pyrazolo[l,2-al[l,2,41triazol-8-ium-6-ylsulfanyl)-6-(l-hvdroxyethyl)-4-methyl-7-oxo-l-azabicvclo[3.2.01hept-2-ene-2-carboxylate [Compound of formula (IV)1

To a mixture of acetonitrile and DMF, P-Nitrobenzyl (4R,5S,6S)-3-(diphenyloxy)phosphoryloxy-6-[(lR)-l-hydroxyethyl]-4-methyl-7-oxo-l-azabicyclo[3,2,0]hept-2-ene-2-carboxylate (compound of formula II) and 6,7-dihydro-6-mercapto-5H-pyrazolo[l,2-a] [1,2,4] triazole chloride (compound of formula III) were added and cooled to 0-5° C. To this mixture, N-ethyldiisopropyl amine was added and stirred till the completion of the reaction, followed by the addition of dichloromethane to crystallize the p-Nitrobenzyl (4R,5S,6S)-3-(6,7-dihydro-5H-pyrazolo[1,2-a][1,2,4]triazol-8-ium-6-ylsulfanyl)-6-(l-hydroxyethyl)-4-methyl-7-oxo-l-azabicyclo[3.2.0] hept-2-ene-2-carboxylate which was filtered and dried under nitrogen.

Step-II: Preparation of Biapenem

To a solution of MOPS buffer and THF, p-Nitrobenzyl (4R,5S,6S)-3-(6,7-dihydro-5H-pyrazolo[l,2-a][l,2,4]triazol-8-ium-6-ylsulfanyl)-6-(l-hydroxy ethyl)-4-methyl-7-oxo-l-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (Compound of formula-IV) was added at pH 7-8 and cooled to 5-10° C. The mixture was hydrogenated using palladium on carbon as catalyst. The catalyst was filtered and the filtrate was treated with activated carbon and filtered. The filtrate was extracted with dichloromethane and the layers separated. The aqueous layer was degassed. To the aqueous layer, acetone was added to crystallize Biapenem at 20-25° C. The product was filtered, washed with aqueous acetone and dried under vacuum to get Biapenem (Non-Sterile).

Reference example -2:

Crystallization of Biapenem

Example -1 was repeated without the addition of methanol.

Yield: 84 g Purity by HPLC: 99.5%

Reconstitution time : > 90 seconds

The reconstitution time is calculated by the time taken to dissolve 300 mg of Biapenem in 100 ml of water or saline solution.

Table-1:

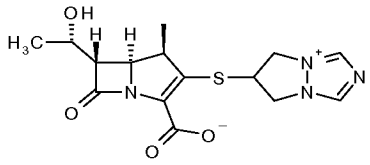
Comparative Data:

Experiment	Co-solvent	Anti-solvent	Reconstitution time (RCT)
Example-1	Methanol	Acetone	< 15 seconds
Example-2	Isopropyl alcohol	Acetone	< 15 seconds
Example-3	Ethanol	Acetone	< 15 seconds
Reference example-2	No co-solvent	Acetone	> 90 seconds
Example-7 of EP 0289801	No co-solvent	No-antisolvent	> 150 seconds

The comparative data provided in the table-1 clearly indicates that the addition of co-solvent during crystallization provides Biapenem with reconstitution time less than 25 seconds.

We Claim:

1. An improved process for the preparation of Biapenem of formula (I)



(I)

the said process comprises;

(i) obtaining a solution of Biapenem in water containing co-solvent; and

(ii) adding anti-solvent in to the solution of step (i) or *vice-versa* to crystallize Biapenem followed by filtration.

2. The process as claimed in claim 1, wherein the co-solvent used in step (i) is selected from methanol, ethanol, isopropyl alcohol, n-propanol, n-butanol , iso-butanol or mixtures thereof.

3. The process as claimed in claim 1, wherein the anti-solvent used in step (ii) is selected from acetone, methyl ethyl ketone, methyl isobutyl ketone, ethyl acetate, methyl acetate, butyl acetate, tetrahydrofuran or mixtures thereof.

4. The process as claimed in claim 1, wherein the Biapenem obtained is having reconstitution time of less than 25 seconds.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2013/051721

A. CLASSIFICATION OF SUBJECT MATTER

C07D 519/06 (2006.01) C07B 63/04 (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)

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)

STN (Registry, CAPlus): Search based upon the registry number for Biapenem (120410-24-4) limited to the preparation thereof or by the keyword crystal (using truncations)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C [X] **See patent family annex**

* Special categories of cited documents:

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

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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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Date of the actual completion of the international search	Date of mailing of the international search report
12 **July** 2013	12 **July** 2013
Name and mailing address of the ISA/All	**Authorised officer**
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustralia.gov.au Facsimile No.: +61 2 6283 7999	Gavin Bartell AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. 0262223647

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	CN 101935321 A (SHENZHEN HAIBIN PHARMACEUTICAL CO LTD) 05 January 2011 & CNFULL Accession Number 2010093910 Examples 5-13, formula lib	1-2, 4
X	CN 102268025 A (U S LAN SHIKE HAINAN PHARMACEUTICAL CO LTD) 07 December 2011 & CNFULL Accession Number 201120173 1 The whole document, in particular the examples	1-2, 4
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A	EP 0 533 149 A1 (TAKEDA CHEMICAL INDUSTRIES LTD) 24 March 1993 The whole document, in partcular the working examples	1-4

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/IB2013/051721

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
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End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.