Abstract:
The present invention provides an improved process for the preparation of methyl carbapenem derivative of formula (I) or its pharmaceutically acceptable salts or hydrates thereof in a pure form.
AN IMPROVED PROCESS FOR THE PREPARATION OF MEROPENEM

Field of the Invention

The present invention provides an improved process for the preparation of methylcarbapenem derivative of formula (I) or its pharmaceutically acceptable salts or hydrates thereof in a pure form.

![Chemical Structure](image)

The compound of the formula (I) is generically known as meropenem and is used as antibiotic agent in the treatment of pneumonia, urinary tract infections, intra-abdominal, gynecological, skin, and soft tissue infections, meningitis, septicemia and febrile neutropenia.

Background of the Invention

EP 126587 discloses an amorphous powder of Meropenem which is obtained by lyophilization. The product obtained according to this patent has insufficient stability in storage, so that long-term storage under typical storage conditions disadvantageously leads to decrease of its antibiotic potency.
In our Indian patent, 198820, we have provided preparation of Meropenem wherein biphasic solvent system such as Water-THF-Ethyl acetate was utilized for deprotection (where $R'$ is allyloxy carbonyl). After deprotection of the protecting groups, the aqueous layer was subjected to lyophilization to afford the crude product which was crystallized by the addition of THF to yield Meropenem trihydrate.

U.S. Pat. No. 4,888,344 discloses the compound of formula (I) in crystalline form and its use as an antibiotic agent. The crystalline Meropenem prepared according to this patent was in trihydrate form. As per US 4,888,344 in example 1, Meropenem is dissolved in water, whereupon small amount of Meropenem crystals formed and further addition of acetone yielded Meropenem trihydrate. Since the sterile preparation requires complete dissolution, this technique is not suitable for sterile preparation.

In our co-pending application 1301/CHE/2005, Non-sterile Meropenem trihydrate dissolved in water optionally in the presence of organic solvent using ammonia. The solution obtained was subjected to sterile filtration and then pH of the filtrate was adjusted to using aqueous formic acid. Addition of organic solvent yields the title compound in pure form.

It has been, however, still desired to develop a process more suitable for the production of the desired carbapenem compounds (I) as sterile product in high yield with desired reconstitution time on larger scale. With our continued intensive and diligent research on this study, we have come up with an improved process which involves use of methanol for dissolution of Meropenem trihydrate. None of the prior art discloses the present invention.
Objectives of the Invention

The main objective of the present invention is to provide a simple and commercially viable process for the preparation of compound of the formula (I) or its pharmaceutically acceptable salts or hydrates thereof as sterile product in pure form.

Another objective of the present invention is to provide a simple and commercially viable process for the preparation of compound of the formula (I), in higher yield on larger scale.

Another objective of the present invention is to provide a simple and commercially viable process for the preparation of compound of the formula (I), with desired characteristic of rapid reconstitution time.

Summary of the Invention

Accordingly, the present invention provides an improved process for the compound of formula (I) its pharmaceutically acceptable salts or hydrates thereof,

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\text{H}_3\text{C}\begin{array}{c}
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\end{array}\begin{array}{c}
\text{N} \\
\text{S} \\
\text{COOH} \\
\text{CH}_3 \\
\end{array}\begin{array}{c}
\text{OH} \\
\text{CH}_3 \\
\text{N-CH}_3 \\
\text{H}_3\text{C} \\
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\]

which comprises,

a. dissolving Meropenem trihydrate in an alcohol to obtain the clear solution;
b. optionally treating with carbon;
c. optionally filtering through micron filter;
d. optionally adding water; and
e. isolating the Meropenem trihydrate.

Description of the Invention

In an embodiment of the present invention, the alcohol used in the step (a) is selected from methanol, ethanol, isopropanol, 1-propanol and the like or mixtures thereof; preferably methanol.

In another embodiment of the present invention optionally the solution of Meropenem in methanol is cooled to lower temperature preferably 10° C, more preferably below 5° C, to yield methanol solvate of Meropenem.

In another embodiment of the present invention, the clear solution of Meropenem trihydrate in methanol was treated with EDTA and sodium hydro sulphite to remove the impurities.

In yet another embodiment of the present invention, isolation of Meropenem trihydrate is carried out either by adding anti-solvent or by cooling.

In still another embodiment of the present invention, the anti-solvent used for the isolation of meropenem trihydrate is selected from acetone, THF, methyl ethyl ketone, methanol, isopropanol, 1-propanol, ethanol, water and the like or mixtures thereof.
The improved process disclosed found to be attractive from commercial and technological perspective. It has been observed that, Sterile product obtained by the present invention has high purity as well as desired reconstitution time (RCT). Reconstitution has direct implications on patient safety, making it a critical parameter to evaluate powder for injection formulations. A short and reproducible reconstitution time will save the precious time. An incompletely dissolved product can be hazardous to the patient, thereby making reconstitution a critical performance parameter for these products. For some drugs a prolonged reconstitution time might be detrimental to drug stability. Therefore, special inputs from scientists are required to optimize the reconstitution time during the development of these dosage forms.

Advantages of the present invention:

- High yield
- Reconstitution time (RCT) less than 60 sec
- High purity
- Good Colour, flow-properties of the obtained product

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.

The key starting materials for the preparation of Meropenem namely (2S,4S)-2-dimethylaminocarbonyl-4-mercapto-l-p-nitrobenzyloxycarbonyl pyrrolidone (VII) and (4R,5S,6S)-3-(diphenyl-oxy)phosphoryloxy-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-l-azabicyclo[3,2,0]hept-2-ene-2-carboxylate) (XIII)
can be synthesized following the conventional method reported in the prior arts or by the reference examples provided in the present application.

**Example 1:**

**Preparation of compound of formula (I):**

Meropenem trihydrate non-sterile (50 gm) was added in cold methanol and stirred to get clear solution. To this clear solution, EDTA (0.25 gm), sodium hydro sulphite followed by ENO carbon was added and it is filtered to remove the carbon. The carbon bed was washed with chilled methanol (25 ml). The solution was filtered through 0.2 micron filter paper. To filtrate, water was added at 10 -13°C followed by the addition of acetone. The reaction mass was further cooled to 3-5°C, the product obtained was filtered and washed with chilled mixture of Acetone and water (3: 1) to yield Meropenem trihydrate in pure form.

Yield: 95%;  RCT < 60 sec

**Preparation of Sterile Meropenem trihydrate:**

**Reference example 1:**

Meropenem trihydrate (50 g) was added to cooled water (375 mL) at 0-5°C and the pH of slurry was adjusted to 9.0-9.2 with dil. Ammonia solution for complete dissolution. The pH was readjusted to 8.0-8.2 with dilute Formic acid. To the solution Carbon, EDTA and hydrose was added, stirred, filtered and washed with water. The filtrate was again filtered through 0.2 micron filter. To this filtrate 0.5 to 5.0 volume (with respect to starting material) alcohol (like ethanol, isopropanol or methanol; preferably about 0.5 to 1.0 V of methanol) was added at 10-15°C and pH was adjusted to 5.6-5.7. The solution was optionally seeded with Meropenem trihydrate. To this slurry, acetone was added slowly at 10-15°C and cooled to 0-
5°C. The obtained product was filtered, washed with aqueous Acetone and dried to get sterile Meropenem trihydrate.
Yield = 40-45 g
RCT: ~ 40 to 60 sec

Reference example 2:
Into a cold suspension of non-sterile Meropenem trihydrate (100 g) in water (750 mL) ammonia solution was added drop-wise till clear solution was obtained. The clear solution was subjected to carbon treatment followed by filtration in sterile area and pH of filtrate was adjusted to approximately 5 to 6 using aqueous formic acid. THF was added to the resultant mass. The solid obtained was filtered, washed with aqueous tetrahydrofuran, and dried to yield the title compound in pure form. (Purity: 99.00 - 99.88 %)

Reference example-3
The process for the synthesis of (2S,4S)-2-Dimethylaminocarbonyl-4-mercapto-l-\(\text{p}\)-nitrobenzyloxyacarbonyl pyrrolidine (VII) is shown in Scheme-I
**Scheme-I**

Step - 1

**Preparation of (2S,4R)-2-carboxy-4-hydroxy-L-p-nitrobenzyloxycarbonyl pyrrolidine (III)**

Trans-4-hydroxy-L-proline (II) was added to a solution of sodium hydroxide in water at 0-5°C, and stirred to get a clear solution, followed by p-nitrobenzyloxycarbonyl chloride in dichloromethane (MDC) was added and stirred till completion of reaction at 0-5°C. To this reaction mass sodium hydroxide solution was added and the layers were separated. To the aqueous layer methanol was added and pH was adjusted to acidic using sulphuric acid at 0-5°C. The solid
obtained was filtered, washed with water and dried in vacuum at 50°C to afford the title compound (III) as colorless crystals.

**Step-2**

**Preparation of (2S,4R)-2-dimethylamino carbonyl-4-hydroxy-l-p-nitrobenzylxoycarbonyl pyrrolidine (IV)**

(2S,4R)-2-carboxy-4-hydroxy-1-p-nitrobenzylxoycarbonyl pyrrolidine (III) obtained in step-I was dissolved in dichloromethane and cooled to -20 to -30 °C. Triethylamine followed by isopropylcarbonyl chloride were added and maintained at the same temperature. Dimethylamine hydrochloride was added and stirred till the completion of reaction. The mass was quenched with water and the organic layer was separated, washed with brine, dried over anhydrous magnesium sulphate, filtered and the filtrate containing compound (IV) was taken for next step without purification.

**Step-3:**

**(2S,4R)-2-dimethylamino carbonyl-4-mesyloxy-l-p-nitrobenzylxoycarbonyl pyrrolidine (V)**

To the solution of (2S, 4R)-2-Dimethylaminocarbonyl-4-hydroxy-l-p-nitrobenzylxoycarbonylpyrrolidine (IV) in MDC was added triethylamine followed by methanesulphonyl chloride at -20°C and maintained till the completion of the reaction. The reaction mixture was quenched with water and the separated organic phase was washed with sodium bicarbonate solution followed by brine solution. The organic layer was concentrated to get residue, which was recrystallized using toluene to get (2S,4R)-2-dimethylamino carbonyl-4-mesyloxy-l-p-nitrobenzylxoycarbonyl pyrrolidine (V)
**Step-4**

**Preparation of (2S,4S)-4-acetyl thio-2-dimethylamino carbonyl-l-(p-nitrobenzyloxy carbonyl)pyrrolidine (VI)**

To a solution of (2S,4R)-2-dimethylamino carbonyl-4-mesyloxy-l-p-nitrobenzyloxy carbonyl pyrrolidine (V) in dimethylformamide, potassium thioacetate was added and the resulted suspension was heated to 70-80°C and maintained till completion of the reaction. The reaction mass was added to water and the obtained solid was filtered and recrystallized from methanol-water mixture to get (2S,4S)-4-acetyl thio-2-dimethylamino carbonyl-l-(p-nitrobenzyloxy carbonyl)pyrrolidine (VI).

**Step-5**

**Preparation of (2S,4S)-2-dimethylaminocarbonyl-4-mercapto-l-p-nitrobenzyloxy carbonylpyrrolidine (VII)**

To a methanolic solution of (2S,4S)-4-acetyl thio-2-dimethylamino carbonyl-l-(p-nitrobenzyloxy carbonyl)pyrrolidine (VI) obtained from step-4, an aqueous solution of sodium hydroxide was added at 5-10°C and stirred. The pH of the reaction mass was adjusted to 2 with dilute hydrochloric acid and the solid obtained was filtered, washed with water, dried and recrystallised from a solvent mixture of ethanol-ethyl acetate-light petroleum to get a white crystalline product of (2S,4S)-2-dimethylaminocarbonyl-4-mercapto-1-p-nitrobenzyloxy carbonylpyrrolidine (VII).

**Reference example-4**

The process for the synthesis of (4R,5S,6S)-3-(diphenyl-oxy)phosphoryloxy-6-[(IR)-l-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3,2,0]hept-2-ene-2-carboxylate (XIII) is shown in Scheme-II.
Scheme-II

(3S,4S)-3-((R)-(tert-Butyldimethyl-silyloxy)ethyl)-4((R)-carboxyethyl)-2-azetidinone (VIII) was reacted with carbodimide and Magnesium mono-p-nitrobenzyl malonate in acetonitrile and quenched with water and extracted with ethylacetate. The ethyl acetate layer containing compound (IX) was treated with dilute hydrochloric acid to remove the tert-butyldimethyl silyl group and quenched with water. The ethyl acetate layer was separated, dried over anhydrous sodium sulphate. The ethyl acetate layer containing the desilylated intermediate (X) was reacted with dodecylbenzene sulfonylazide (70% solution in toluene) using triethylamine as base. The reaction mass was quenched with water and the organic
layer was separated and evaporated to get a residue of compound (XI), which was dissolved in acetone and cyclised using rhodium octanoate dimer under reflux to get compound (XII). The reaction mass containing compound (XII) was cooled to -30°C and N,N-Diisopropylethyl amine, zinc iodide followed by diphenylchlorophosphate were added. The reaction mass was quenched by adding phosphoric acid followed by phosphate buffer and isopropyl ether. The solid obtained was filtered and purified using methanol to get (4R,5S,6S)-3-(diphenyloxy)phosphoryloxy-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (XIII).

**Reference example-5**

The process for the synthesis of Meropenem is shown in Scheme-III

![Scheme-III](image-url)

In a stirred solution of (4R,5S,6S)-3-(diphenyloxy)phosphoryloxy-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (XIII) and (2S,4S)-2-dimethylaminocarbonyl-4-mercapto-1-p-nitrobenzyloxycarbonyl pyrrolidine (VII) in N-Methylpyrrolidone (or a mixture of N-Methylpyrrolidone
and acetonitrile) was added N,N-Diisopropylethylamine at -25°C and stirred till the completion of the reaction. The mass was quenched in phosphate buffer and ethyl acetate and the pH was adjusted to 4 with phosphoric acid. The ethyl acetate layer containing compound (XIV) was treated with carbon and filtered. The ethyl acetate layer containing compound (XIV) was hydrogenated with Palladium on carbon using aqueous solution of 3-(N-morpholino)propanesulfonic acid buffer. The ethyl acetate layer was separated and the aqueous phase containing Meropenem (XV) was treated with carbon and filtered. The filtrate was cooled to 5°C and pH was adjusted using dilute hydrochloric acid (or other organic acids like formic acid, acetic acid etc.) to 3-4 and crystallized the product by adding acetone (or solvents like methanol, ethanol, isopropyl alcohol, 1-propanol or mixtures thereof). The solid was filtered and dried under vacuum to get Meropenem.

The above process can be extended for the preparation of Ertapenem by reacting (4R,5S,6S)-3-(diphenyloxy)phosphoryloxy-6-[(lR)-l-hydroxyethyl]-4-methyl-7-oxo-l-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (XIII) and the corresponding mercaptan namely 3-[[[(2S,4S)-4-mercapto-l-(4-nitrobenzyloxy)carbonyl-2-pyrrolidinyl] carbonyl]amino]benzoic acid by having modification in the workup. After the condensation of Compound (XIII) and mercaptan and workup, the ethyl acetate layer containing diprotected compound (XVI) was treated with Sodium -2-ethylhexanoate (or other alkali metal salts like sodium acetate, sodium carbonate and sodium bicarbonate) followed by 3-(N-morpholino)propanesulfonic acid buffer and the mass was hydrogenated using palladium on carbon till completion of the reaction. After filtration of Pd/C the filtrate was washed with ethyl acetate (by adjusting the pH of the aqueous phase to 6 to 7.5 with alkali hydroxide or carbonate solution). The pH was of aqueous phase was readjusted to 5 to 6 with acid followed by adding the solvents as mentioned above to crystallize the Ertapenem sodium.
P' & P'' - p-Nitrobenzyl
We claim:

1. An improved process for the preparation of compound of formula (I) 
   its pharmaceutically acceptable salts or hydrates thereof,

   which comprises,
   
   a. dissolving Meropenem trihydrate in an alcohol to obtain the clear solution;
   b. optionally treating with carbon;
   c. optionally filtering through micron filter;
   d. optionally adding water; and
   e. isolating the Meropenem trihydrate.

2. A process as claimed in claim 1, wherein the alcohol used in step (a) is selected from methanol, ethanol, isopropanol, 1-propanol or mixtures thereof; preferably methanol.

3. A process as claimed in claim 1, wherein the isolation of Meropenem trihydrate is carried out either by the addition of anti-solvent or by cooling.
4. A process as claimed in claim 3, wherein the anti-solvent used is selected from acetone, THF, methyl ethyl ketone, methanol, isopropanol, 1-propanol, ethanol, water or mixtures thereof.
A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.
C07D 477/20 (2006.01) A61P 31/00 (2006.01) BOID 9/02 (2006.01)
A61K 31/40 (2006.01) A61P 31/04 (2006.01)

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

B. FIELDS SEARCHED

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN Registry and Caplus: Search based on Registry Number 96036-03-2 and related compounds, Keyword search based on (crystallisation, purification, isolation, charcoal, activated carbon and like terms); EPODOC, WPIDS: Keyword Search based on (Meropenem, crystallisation, activated carbon, charcoal, alcohol, ethanol, methanol, propanol, isopropanol, butanol and like terms)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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