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(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING CILASTATIN, A CHELATING AGENT AND OPT. A PEN-EM ANTIBIOTIC

(57) Abstract: The present invention refers to a stable pharmaceutical composition comprising cilastatin, a chelating agent and opt. a penem antibiotic (preferably imipenem). Additionally, the composition can also contain a buffer.



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Pharmaceutical composition comprising cilastatin, a chelating agent and opt. a penem antibiotic

Field of the Invention

The present invention relates to stable pharmaceutical compositions containing Cilastatin or its sodium salt and Imipenem commercially available as Primaxin®. Such compositions are useful for intravenous administration as antibiotics for hospitalized patients with serious infections. Specifically, this invention relates to a stable pharmaceutical composition further including an aminocarboxylic acid chelating agent, for example, ethylene diamine tetraacetic acid (EDTA), or a pharmaceutically acceptable salt thereof, and optionally citrate. The pharmaceutical compositions described herein normally have enhanced stability during storage of the reconstituted solution.

Background of the Invention

Most of the Carbapenem antibiotics are administered parenterally, for example, via intramuscular injection, intravenous injection or continuous subcutaneous infusion, for which the drug should be stable upon reconstitution.

These formulations for parenteral administration of carbapenem antibiotic, however, have been reported to have various disadvantages or drawbacks, especially in terms of meeting stability requirements during storage of reconstituted solution. There are various factors that affect the stability of the reconstituted solution. One of which is due to the presence of trace amount of heavy metal. Carbapenem antibiotics have been generally reported to be sensitive to light and oxygen. For example, carbapenem antibiotic undergoes oxidation in the presence of oxygen to form multiple degradation products.

In addition, parenteral carbapenem antibiotic formulations typically changes color on storage. Such discoloration generally indicates a lack of stability and/or safety of the formulation. While a relatively impurity-free formulation is clear and colorless or almost clear and colorless, slight yellow is an acceptable color for a parenteral levomepromazine formulation. However, objectionable colors, such as dark yellow and salmon pink, which easily intensify to produce brown color on storage, have been reported with many parenteral carbapenem antibiotic formulations that have been exposed to oxygen and heat.

The origin of trace amount of heavy metals in finished pharmaceutical products is from the reaction vessels that are made up of metal. The presence of these heavy metals causes sever damage to the drug product resulting in unwanted product by degradation of active pharmaceutical ingredients.

Accordingly, there has been a significant need to develop a formulation for parenteral administration of carbapenem antibiotic having an improved stability of reconstituted solution, thereby preventing or reducing the formation and accumulation of degradation products in the formulation or discoloration of the formulation and assuring a longer shelf life. There is a further need to provide these formulations more effectively, at less cost, and in a more convenient manner with respect to administration, than previous formulations.

Chelating agents or buffers are scavengers for trace amounts of metal ions. Chelation refers to the formation of an unusual stable bond between an organic compound and an ion or other polar group. Many reactions, including many oxidation and decomposition reactions, are catalyzed by trace amounts of metallic ions present in solutions. Many drugs can be degraded through oxidation and hydrolytic reactions, which

are catalyzed by metal ions. The presence of metallic ions can therefore significantly accelerate the degradation of these drugs. Chelating agents or buffers are useful in preventing degradation of drugs in solution. EDTA (ethylene diamine tetraacetic acid) and its salts and buffer such as citric acid and its salts are examples of powerful chelating agents.

Objectives of the Invention

The main objective of the present invention is to provide a stable pharmaceutical composition comprising Cilastatin and Imipenem.

Another objective of the present invention is to provide stable pharmaceutical composition comprising Cilastatin, Imipenem and chelating agents.

Yet another objective of the present invention is to provide a process for the preparation of said pharmaceutical composition.

Summary of the Invention

According to the present invention there is provided a stable pharmaceutical composition comprising Cilastatin and chelating agent.

In another embodiment, the pharmaceutical composition according to the present invention further comprising carbapenem antibiotic.

According to the present invention there is further provided a stable pharmaceutical composition comprising Cilastatin, Imipenem and Chelating agent.

Detailed Description of the Invention

In an embodiment of the present invention, wherein the chelating agent is selected from but not limited to ethylenediaminetetraacetic acid (EDTA), diethylenetriaminepentaacetic acid (DTPA), hydroxyethylenediaminetriacetic acid (HEDTA), nitrilotriacetic acid (NTA) O,O'-bis(2-aminoethyl)ethyleneglycol-N,N, N',N'-tetraacetic acid (EGTA), trans-1,2-diaminocyclohexane-N,N,N',N'-tetraacetic acid (CyDTA) or a pharmaceutically acceptable salt thereof (normally as a sodium salt).

In another embodiment of the present invention, the chelating agent such as EDTA is added in a concentration of from 0.001 percent to 10 percent by weight of total active pharmaceutical product; more preferably from 0.01 to 1 percent by weight.

In still another embodiment of the present invention the pharmaceutical composition further comprising Imipenem preferably in the form monohydrate, which is a carbapenem antibiotic. The pharmaceutical composition comprising Cilastatin sodium, Imipenem monohydrate and EDTA according to the present invention found to be more stable upon reconstitution. It has been observed that the degradation pattern of pharmaceutical composition containing only Imipenem monohydrate and cilastatin sodium is more, particularly one of the impurity viz. BP impurity A (as per British pharmacopoeia version-2007) is raising upon reconstitution. This observation varies from batch to batch. Upon analyzing this, it has been noted that the presence of trace amount of heavy metal in some batches inducing the degradation. Accordingly the present invention provides pharmaceutical compositions which contain EDTA along with Cilastatin sodium and Imipenem monohydrate. The presence of chelating agent like EDTA avoids such degradation and hence the stability of reconstituted solution meets pharmaceutical requirement.

In yet another embodiment of the present invention, the reconstitution stability of Cilastatin and Imipenem was studied with and without EDTA and found that the level of impurities are less in a sample containing EDTA than the sample without EDTA.

In one more embodiment of the present invention, the reconstitution stability of Imipenem Cilastatin sodium for injection was studied with and with out EDTA and found more specifically that the BP impurity A of Cilastatin (Both diastereomer-I and II) is increased substantially when stored at 25 °C for 4 hours and 2-8 °C for 24 hours for the sample that does not containing EDTA than the sample containing EDTA.

In yet another embodiment of the present invention, the pharmaceutical composition may further contain buffer such as sodium citrate, sodium bicarbonate, sodium carbonate, in a concentration of from 0.001 percent to 10 percent by weight, more preferably from 0.1 to 5 percent by weight.

Starting material can be prepared according to the reported method or by the method provided in the reference example.

The present invention is illustrated with the following examples, which should not be construed as limiting to the scope of the invention.

Example 1

Preparation of pharmaceutical composition of Imipenem Cilastatin sodium for Injection:

Imipenem monohydrate sterile, Cilastatin sodium sterile and sodium bicarbonate sterile were mixed in a proportion in such a way that 1080 mg of the mixture containing

each 500 mg of Imipenem and Cilastatin. A sample from the blended mixture is tested for reconstitution studies and the results are tabulated below.

Example 2

Preparation of pharmaceutical composition of Imipenem Cilastatin sodium for Injection containing EDTA:

Imipenem monohydrate sterile, Cilastatin sodium sterile, sodium bicarbonate sterile and Sterile EDTA were blended until to get uniform mixture. A sample from the blend was tested for reconstitution stability studies and the results are tabulated below.

Imipenem Cilastatin for Injection	EP Impurity-A1	EP Impurity-A2	EP Impurity-A1	EP Impurity-A2
	Initial		After 4 Hours at 25 °C	
Prepared in Example-1	0.07	0.07	0.32	0.16
Prepared in Example-2	0.07	0.07	0.12	0.10

Reference Example 1:

Preparation of Cilastatin Sodium:

To Cilastatin acid (20 gm) in methanol (100 mL) was added sodium methoxide (3.6 gm) at ambient temperature. The reaction mass was stirred with carbon and EDTA. The carbon was removed by filtration. The filtrate was again filtered through sterile micron (0.2 μ) filter. The resulted clear solution was added slowly into acetone (800 mL) at 25 to 30°C and stirred. The precipitated Cilastatin sodium was filtered and washed with acetone. The obtained Cilastatin sodium was optionally dried under nitrogen pressure, followed by drying under vacuum at 50 to 65°C.

We claim:

- 1) A pharmaceutical composition comprising Cilastatin or its sodium salt and chelating agent.
- 2) A pharmaceutical composition according to claim 1, further comprising carbapenem antibiotic.
- 3) A pharmaceutical composition according to claim 2, where in the carbapenem antibiotic is Imipenem monohydrate.
- 4) A pharmaceutical composition comprising Cilastatin or its sodium salt, Imipenem and chelating agent.
- 5) A pharmaceutical composition according to claim 1 and 4, the chelating agent is selected from ethylenediaminetetraacetic acid (EDTA), diethylenetriaminepentaacetic acid (DTPA), hydroxyethylenediaminetriacetic acid (HEDTA), nitrilotriacetic acid (NTA) O,O'-bis(2-aminoethyl)ethyleneglycol-N,N, N',N'-tetraacetic acid (EGTA), trans-1,2-diaminocyclohexane-N,N,N',N'-tetraacetic acid (CyDTA) or a pharmaceutically acceptable salt thereof (preferably sodium salt).
- 6) A pharmaceutical composition according to claim 1 and 4, further comprising buffer.
- 7) A pharmaceutical composition according to claim 6, wherein the buffer is selected from sodium bicarbonate, or sodium citrate.

INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER

IPC⁸: **A61K 31/407** (2006.01); **A61K 31/155** (2006.01); **A61K 31/194** (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)

IPC⁸: A61K

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)

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2004/072815 A1 (KOPPEL) 15 April 2004 (15.04.2004) <i>paragraphs [0090],[0092],[0194],[0201],[0205]; claim 1</i> --	1-7
X	US 6630510 B1 (BALKOVEC et al.) 7 October 2003 (07.10.2003) <i>column 18, line 4; column 19, lines 38-41; claim 1</i> --	1-4,6,7
X	US 2002/019543 A1 (BALKOVEC et al.) 14 February 2002 (14.02.2002) <i>paragraph [0037]; claim 1,15-28</i> --	1-4,6,7

☒ Further documents are listed in the continuation of Box C.☒ 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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"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

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6221859 B1 (DORSO et al.) 24 April 2001 (24.04.2001) <i>column 10, lines 20-42; column 13, line 66; column 15, lines 15-29; claim 1</i> -----	1,2,5-7

INTERNATIONAL SEARCH REPORT
Information on patent family members

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Patent document cited in search report			Publication date		Patent family member(s)	Publication date
US	A	2004072815			US A1 2004072815	2004-04-15
US	A	6630510			US A1 2003207859	2003-11-06
					US A1 2003078418	2003-04-24
					WO A1 0130148	2001-05-03
					JP T 2003527332T	2003-09-16
					ES T3 2283327T	2007-11-01
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US	A	2002019543			US A1 2002019543	2002-02-14
US	A	6221859			US B1 6221859	2001-04-24