(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 July 2015 (16.07.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/105720 A1

(51) **International Patent Classification**:
A61K 47/40 (2006.01)

(21) **International Application Number**:
PCT/US2014/072996

(22) **International Filing Date**:
31 December 2014 (31.12.2014)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
IN62/CHE/2014 7 January 2014 (07.01.2014) IN

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(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

WO 2015/105720 A1

(54) **Title**: STABILISED CARBAPENEM COMPOSITIONS

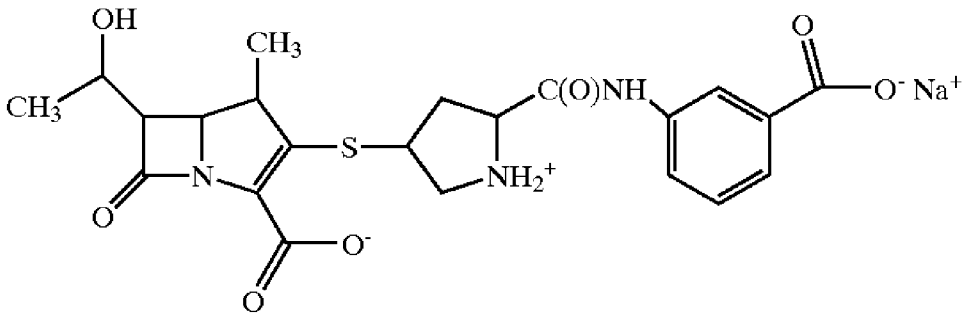
(57) **Abstract**: A composition comprising a carbapenem, a buffer (preferably a carbonate buffer or citrate buffer), and a stabiliser, wherein the stabilise is a cyclic oligosaccharide or a polysaccharide (preferably a cyclic polysaccharide, cyclodextrin, sulfobutyleth-er-p-cyclodextrin, hydroxyethyl starch or a dextran) is provided. Also described is a method of producing a stabilised carbapenem compositionincluding combining in a buffered solution: a stabiliser, wherein the stabiliser is a cyclic oligosaccharide or a polysac-charide and a carbapenem wherein the stabilised carbapenem composition comprises less than about 8%, preferably less than about 5% total degradation products after 24 hours at 0-20 degree C.

Stabilised Carbapenem Compositions

Background to the invention

Carbapenems are a class of β-lactam antibiotics which includes, for example imipenem, meropenem, ertapenem and doripenem. The structure of the monosodium salt of ertapenem, a representative carbapenem, is shown below as Formula I:

I

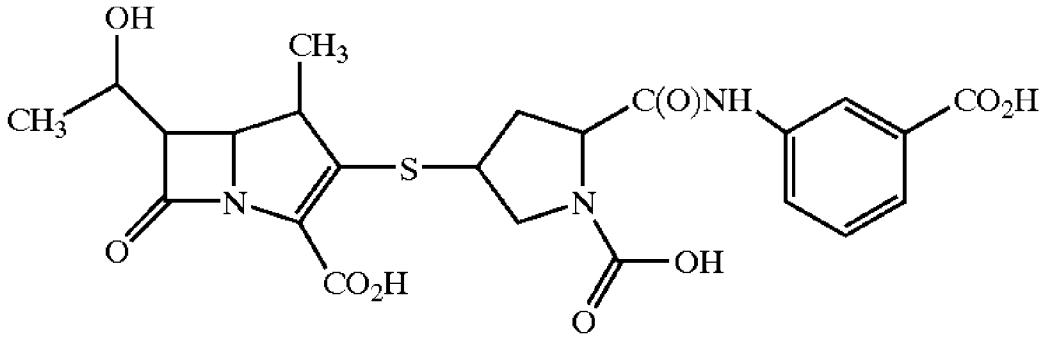


The compound of formula 1 is relatively unstable at ambient conditions and remains unstable above approximately -20°C. In addition, during production, carbapenems in bulk solution are unstable at room temperature, degrading into a number of open-ring and dimer by-products, complicating manufacture of the final drug products. The open-ring and dimer degradation products for ertapenem are set out in Sajonz *et al.* J. Liq. Chrom. & Rel. Technol., 24(19), 2999-3015 (2001), which is incorporated herein by reference.

A current approach to increase the stability of carbapenem compounds, used for example in the production of the

ertapenem product Invanz™ (Merck), is to form a reversible carbon dioxide-carbapenem adduct during manufacture. For example, a carbon dioxide-ertapenem adduct can be formed by use of a carbon dioxide source, such as a carbonate buffer (e.g. sodium carbonate or sodium bicarbonate) in the course of manufacture of the drug product. This process is described in detail in US 09/064426 and US 09/698808 (incorporated herein by reference). The more stable carbon dioxide-ertapenem structure is set out as Formula II below:

II



Following bulk production of such more stable carbon dioxide-carbapenem adducts, the formulations are lyophilised for long term storage at room temperature (approximately 20-25°C). Nevertheless, when employing the carbon dioxide adduct technique for stabilisation during manufacture, an excess of active substance of up to 6% is required to compensate for degradation during manufacture, and a further excess of up to 4% is required to allow for degradation during the "in-use" storage period (*i.e.* following reconstitution of the lyophilised product).

Moreover, utilization of the carbon dioxide source to stabilize carbapenems such as ertapenem results in the

formation of an undesirable oxazinone degradation impurity in the final drug product.

For these reasons there remains a need for more stable carbapenem compositions.

Summary of Invention

The present application provides such more stable compositions and methods of producing them. Carbapenem compositions according to the present invention allow a greater holding time of the bulk carbapenem solution (Bulk solution) prior to lyophilisation, provide a final lyophilised product with lower levels of degradation products and provide a greater “in-use” storage period once reconstituted.

In a first aspect, the invention provides a composition comprising a carbapenem, a buffer, and a stabiliser, wherein the stabiliser is a cyclic oligosaccharide or a polysaccharide. In one embodiment, the buffer comprises a carbonate source, for example a carbonate and/or a bicarbonate buffer. In one such embodiment, the buffer is sodium bicarbonate.

In another embodiment, the buffer does not comprise a carbonate source. In one such embodiment the buffer is a citrate buffer, for example sodium citrate.

In one embodiment, the composition further comprises sodium chloride, preferably in a ratio of between about 90 milligrams to about 180 milligrams of sodium chloride per

gram of carbapenem, preferably about 180 milligrams of sodium chloride per gram of carbapenem.

In one embodiment the stabiliser is a cyclic oligosaccharide, preferably a cyclodextrin, more preferably sulfobutylether-β-cyclodextrin (SBECD). In an alternative embodiment, the stabiliser is a polysaccharide. In one such embodiment, the polysaccharide is preferably a dextran or, equally preferably, a hydroxyethyl starch. In one embodiment the stabiliser is present in a ratio of between about 0.5 grams to about 5 grams of stabiliser per gram of carbapenem, preferably between about 1 gram to about 3 grams of stabiliser per gram of carbapenem.

In one embodiment, the carbapenem is ertapenem.

In one embodiment, the bulk solution composition comprises less than about 8%, preferably less than about 5% total degradation products after being stored at 0-2°C for 24 hours.

In one embodiment, the composition is lyophilised. In one such embodiment, the lyophilised composition comprises less than about 5% total degradation products, preferably less than about 4% total degradation products. In a further such embodiment, the lyophilised composition has an in-use shelf life of more than 6 hours at 25°C.

In one embodiment the composition is a pharmaceutical composition.

In a second aspect, the invention provides a method of producing a stabilised carbapenem composition, the method comprising combining in a buffered solution:

(a) a stabiliser, wherein the stabiliser is a cyclic oligosaccharide or a polysaccharide; and

(b) a carbapenem;

wherein the stabilised carbapenem composition comprises less than about 8%, optionally less than about 5% total degradation products after 24 hours at 0-2°C.

In a third aspect, the invention provides a method of producing a stabilised carbapenem composition, the method comprising combining in a buffered solution:

(a) a stabiliser, wherein the stabiliser is a cyclic oligosaccharide or a polysaccharide; and

(b) a carbapenem;

optionally wherein the stabilised carbapenem composition is lyophilised; wherein, when lyophilised, the stabilised carbapenem composition comprises less than about 5% total degradation products, optionally less than about 4% total degradation products.

In one embodiment of the second and third aspects of the invention, the buffer comprises a carbonate source, for example a carbonate and/or a bicarbonate buffer. In one such embodiment, the buffer is sodium bicarbonate.

In another embodiment of these aspects, the buffer does not comprise a carbonate source. In one such embodiment the buffer is a citrate buffer, for example sodium citrate.

In one embodiment, the composition further comprises sodium chloride, preferably in a ratio of between about 90 milligrams to about 180 milligrams of sodium chloride per gram of carbapenem, preferably about 180 milligrams of sodium chloride per gram of carbapenem.

In one embodiment of these aspects the stabiliser is a cyclic oligosaccharide, preferably a cyclodextrin, more preferably sulfobutylether-β-cyclodextrin (SBECD). In an alternative embodiment, the stabiliser is a polysaccharide. In one such embodiment, the polysaccharide is preferably a dextran or, equally preferably, a hydroxyethyl starch. In one embodiment the stabiliser is present in a ratio of between about 0.5 grams to about 5 grams of stabiliser per gram of carbapenem, preferably between about 1 gram to about 3 grams of stabiliser per gram of carbapenem.

In one embodiment, the carbapenem is ertapenem.

All embodiments relate to each and all of the above aspects and embodiments, alone or in combination with any one or more other embodiments, unless otherwise specified.

Definitions

“Stabiliser” as used herein is any substance which, when included in a composition comprising a carbapenem, the carbapenem in that composition is more stable than in the same carbapenem composition without the stabiliser.

The stability of a carbapenem in a carbapenem composition is determined by the rate at which degradation products or

impurities are accumulated in the carbapenem composition. The respective degradation products/impurities for a particular carbapenem are known to the skilled person. For example, for ertapenem, the major degradation products are Dimer I, Dimer II, Dimer III, Dimer-H_2Oa, Dimer-H_2Ob, Dimer V and the open-ring degradation product, as detailed in Sajonz *et al.* J. Liq. Chrom. & Rel. Technol., 24(19), 2999-3015 (2001). These impurities form the majority of the degradation products for ertapenem, although small amounts of other impurities can also be formed.

The total amount of degradation products/impurities in a carbapenem composition can be determined by methods known in the art, for example reverse-phase high-performance liquid chromatography (HPLC).

The "in-use" shelf life of a carbapenem composition is the length of time following reconstitution of a lyophilised carbapenem composition before total degradation products exceed acceptable levels, when the reconstituted composition is stored at approximately 25°C. An example of unacceptable levels of degradation products is when total degradation products exceed approximately 8.0% of the active carbapenem.

The "bulk solution" of a carbapenem composition is the final formulated solution which is to be filled into vials prior to lyophilisation.

A pharmaceutical composition as used herein includes the bulk solution prepared during the manufacture of the final pharmaceutical composition product.

Detailed description

Carbapenem antibiotics exhibit significant instability, especially in solution state, degrading into hydrolysed open-ring structures and forming dimerised impurities. The present invention relates to carbapenem compositions comprising a stabiliser, the effect of which is to reduce the rate at which the carbapenem degrades into such degradation products. Carbapenems suitable for use in compositions and methods according to the invention include imipenem, meropenem, ertapenem and doripenem, preferably ertapenem.

Compositions according to the invention may have a concentration of carbapenem of between 5-50% w/v, optionally 15-40% w/v, optionally 20%-30% w/v, optionally about 20% w/v. If the composition is a bulk solution for manufacture of a final product, the composition may contain an excess of carbapenem of up to 6%, 5%, 4%, 3%, 2% or up to 1% w/v compared to the intended concentration of the final product.

The stabiliser used in compositions according to the invention is a cyclic oligosaccharide, preferably a cyclodextrin, for example sulfobutylether-β-cyclodextrin, hydroxypropyl-β-cyclodextrin, or gamma cyclodextrin. Alternatively, the stabiliser is a polysaccharide, for example a dextran, a hydroxyethyl starch, a dextrin or maltodextrin. The amount of stabiliser used in the compositions or methods of the invention may be between about 0.5g to about 5g of stabiliser per 1g of carbapenem, preferably between about 1g to about 3g of stabiliser per 1g of carbapenem. For example, the amount of stabiliser may be

about 0.5g, about 1g, about 2g, about 3g, about 4g, or about 5g of stabiliser per 1g of carbapenem.

Buffers suitable for use in the compositions and methods of the invention may be buffers that provide a carbon dioxide source when in solution. Such buffers may be carbonate buffers, for example sodium carbonate or sodium bicarbonate.

Alternatively, the buffer or buffers used in the compositions and methods of the invention may be buffers that do not provide a carbon dioxide source when in solution. Such buffers may be citrate buffers, for example sodium citrate. Other suitable buffers would be familiar to the person skilled in the art and include phosphate buffers, or ammonium acetate.

The amount of buffer used in the compositions or methods of the invention may be in the range of between about 0.1g-0.3g per gram of carbapenem, for example about 0.1g, about 0.15g, about 0.175g, about 0.18g, about 0.2g, about 0.25g, or about 0.3g of buffer per 1g of carbapenem.

In one embodiment, compositions according to the invention or produced by methods according to the invention may further comprise sodium chloride. In one such embodiment, compositions according to the invention wherein the buffer is a carbon dioxide source, for example sodium bicarbonate, further comprise sodium chloride.

In an alternative such embodiment, compositions according to the invention wherein the buffer is not a carbon dioxide

source in solution, for example sodium citrate, may further comprise sodium chloride.

The amount of sodium chloride used in compositions according to any of these embodiments may be about 90mg, about 100mg, about 120mg, about 150mg, about 180mg, or about 200mg of sodium chloride per 1g of carbapenem.

In a particular embodiment, an ertapenem composition according to the invention comprising 3g of SBECD per gram of ertapenem and a carbonate buffer can be manufactured as follows:

1. Preparation of sodium hydroxide solution: A 2N solution of sodium hydroxide was prepared by dissolving sodium hydroxide NF pellets in required amount of Water for Injection (WFI) (80 g sodium hydroxide in 1000 mL WFI yields a 2N sodium hydroxide solution). The sodium hydroxide solution was chilled to a temperature of about 5°C.
2. In a beaker, WFI quantity equivalent to 50% of the batch size is taken. 3g of SBECD per gram of ertapenem is added into WFI and stirred for about 15 minutes to obtain a clear solution and then sodium bicarbonate is added and further mixed for 5 minutes to obtain a clear solution and then the solution is chilled to about 5°C.
3. The Ertapenem bulk drug was thawed from -20°C for approximately 30 minutes and then divided into 5 equal portions. The 5 portions of bulk drug were added to the above step 2 solution over a period of about 1 hour, while adding the sodium hydroxide solution to keep the pH of the bulk drug solution between 7.5 and 7.8.

4. At the end of the bulk drug addition, the solution was mixed for an additional 5 minutes and WFI at a temperature of about 5°C was added to bring the solution to about 90% of the batch size, and 2N NaOH titrations were performed to maintain the pH of the bulk solution at about 7.5. After mixing, WFI at a temperature of about 5°C was added to bring the solution to about 100% of the batch size and stirred for 10 minutes. If necessary, the pH was adjusted to the target pH of 7.5 by addition of 2N NaOH solution.

In an alternative embodiment, an ertapenem composition according to the invention comprising 3g of SBECD per gram of ertapenem and a citrate buffer, optionally also including 180mg of sodium chloride per gram of ertapenem, can be manufactured as follows:

1. Preparation of sodium hydroxide solution: A 2N solution of sodium hydroxide was prepared by dissolving sodium hydroxide NF pellets in required amount of Water for Injection (WFI) (80 g sodium hydroxide in 1000 mL WFI yields a 2N sodium hydroxide solution). The sodium hydroxide solution was chilled to a temperature of about 5°C.
2. In a beaker, WFI quantity equivalent to 50% of the batch size is taken. 3g of SBECD per gram of ertapenem is added into WFI and stirred for about 15 minutes to obtain a clear solution and then sodium citrate is added and further mixed for 5 minutes to obtain a clear solution, optionally 180mg of sodium chloride per gram of ertapenem is added to the solution and stirred for 5 minutes. Then the solution is chilled to about 5°C.

3. The Ertapenem bulk drug is thawed from -20°C for approximately 30 minutes was then divided into 5 equal portions. The 5 portions of bulk drug were added into the above step 2 solutions over a period of about 50 minutes, while adding the sodium hydroxide solution to keep the pH of the bulk drug solution at about 7.8.

4. At the end of the bulk drug addition, the solution was mixed for an additional 5 minutes and WFI at a temperature of about 5°C was added to bring the solution to about 90%, and 2N NaOH titrations were performed to maintain the pH of the bulk solution at about 7.8. After mixing, WFI at a temperature of about 5°C was added to bring the solution to about 100% of the batch size and stirred for 10 minutes.

In one embodiment, compositions according to the invention are used in therapy. In a further embodiment, compositions according to the invention are used in the treatment of bacterial infections. In one embodiment, the compositions according to the invention are suitable to be administered parenterally, optionally intramuscularly, optionally intravenously.

In one embodiment, the invention provides a method of treating a subject, optionally a mammalian subject, for example a human, comprising administering to the subject a therapeutic amount of a composition according to the invention.

The invention will be further understood by reference to the following non-limiting examples.

Examples

Example 1

The stability of the bulk solution of ertapenem manufactured according to the techniques known in the art was assessed to establish a baseline reference.

A bulk solution was manufactured as disclosed in US patent 6,548,492. This formulation contains 175 mg of sodium bicarbonate as the carbonate source for the formation of the claimed reversible carbon dioxide adduct and sodium hydroxide solution is used to maintain the pH of the bulk solution between 7.0 and 8.0 during the bulk solution compounding process. The detailed manufacturing process is set out below:

Manufacturing Process:

1. Preparation of sodium hydroxide solution: A 2N solution of sodium hydroxide was prepared in a 50 Litre stainless steel vessel by dissolving 2.1 kg of sodium hydroxide NF pellets in 14 Litres of WFI while mixing and finally Water for Injection was added to produce the final solution of 15 litres. The sodium hydroxide solution was chilled utilizing a Chiller to a temperature of 5°C.
2. Into a 100 litre, stainless steel, jacketed compounder, 30 Litres of the Water for Injection was charged and cooled to a temperature about 5°C. Sodium bicarbonate USP in an amount of 2.10 kg was dissolved in the compounder while continuously stirring until complete

dissolution occurred, wherein the pH of the solution measured 8.5.

3. The Ertapenem bulk drug in an amount of 12.72 kg was thawed from -20°C for approximately 30 minutes was then divided into 5 equal portions. The 5 portions of bulk drug were added to the compounder over a period of about 40 minutes, while adding the sodium hydroxide solution to keep bulk drug solution in the compounder close to the a target pH of 7.5.
4. At the end of the bulk drug addition, the solution was mixed for an additional 15 minutes, and 2N NaOH titrations were preformed to maintain the pH at about 7.5. After mixing for 15 minutes, Water for injection at a temperature of about 5°C was added to bring the solution to about 97% of the batch size, based on 100% batch size. While still mixing the solution, the pH thereof was adjusted to 7.5 by addition of 2N NaOH solution, ensuring that the mole ration of NaOH to bulk drug is about 0.85. The volume of the solution was adjusted to 100 percent of the final batch volume by addition of WFI at a temperature about 5°C, and then mixed for another 10 minutes.
5. The compounder was then sealed and pressurized to NMT 2 bar to initiate filtration, and the solution was filtered through a Durapore 0.22 micron sterilizing filter into a sterile receiving vessel. The filtered solution exhibited a density of about 1.12 g/ml at 5°C.The stability of this bulk solution was evaluated by holding at 0°C and is provided in below Table 2.

The composition of bulk solution formulations made according to this process is set out in Table 1:

Table 1. Control formulation composition

Component	Quantity per 5.0 mL (in g)	Quantity per 60.0 Litre (in kg)
Ertapenem sodium equivalent to Ertapenem acid	1.0	12.72[#]
Sodium bicarbonate USP*	0.175	2.10
Sodium hydroxide NF**	q.s to pH 7.5	1.20[##]
Water for Injection USP***	q.s to 5.0 mL	q.s to 60.0 Litre

[#] Includes 6% excess to the theoretical weight to compensate the degradation during manufacturing
* quantity corresponds to 1 mole equivalent to Ertapenem
** diluted in Water for Injection, USP and used as 2N solution for pH control
[##] quantity for preparation of 15 Litres of 2N sodium hydroxide solution
*** removed during lyophilization process

The bulk composition of the control formulation was held at about 0°C and sampled every 6 hours up to 18 hours, with the levels of impurities in each sample measured by HPLC. The results are set out in Table 2. (For HPLC conditions please see Example 5)

There was a significant dimerization and hydrolytic degradation observed during the storage of the control formulation bulk solution.

Table 2. Stability of the Bulk Solution of composition manufactured as per U.S. Patent No. 6,548,492

Test	Hold time stability of bulk solution at about 0-2°C			
	Initial	6 hour	12 hour	18 hour
Description	Clear, pale yellow color solution	Clear, pale yellow color solution	Clear, pale yellow color solution	Clear, pale yellow color solution
pH of solution	7.3	7.3	7.3	7.3
Assay (%)	104.8	102.4	101.8	99.7
Related Substances (By % of Ertapenem)				
Oxazinone Impurity	0.2	0.3	0.5	0.7
Hydrolyzed Impurity	1.9	2.2	2.6	2.9
Dimer I &Dimer II	0.7	1.4	2.2	3.0
Dimer III	0.2	0.2	0.3	0.4
Dimer IV*	0.1	0.1	0.2	0.3
Dimer V	<LOQ	0.07	0.1	0.1
Any unspecified degradation product	Not detected	0.06	0.06	0.08
Total degradation Products	3.5	4.9	6.2	8.0

* Dimer IV is a combination of Dimer-H_2Oa and Dimer-H_2Ob as defined in Sajonz *et al.* J. Liq. Chrom. & Rel. Technol., 24(19), 2999-3015 (2001).

Example 2

Stabilised carbapenem compositions according to the invention wherein the stabiliser is sulfobutylether-β-cyclodextrin (SBECD) were manufactured as follows:

1. Preparation of sodium hydroxide solution: A 2N solution of sodium hydroxide was prepared by dissolving sodium hydroxide NF pellets in required amount of Water for Injection (WFI) (80 g sodium hydroxide in 1000 mL WFI yields a 2N sodium hydroxide solution). The sodium hydroxide solution was chilled to a temperature of about 5°C.
2. In a beaker, WFI quantity equivalent to 50% of the batch size is taken. SBECD is added into WFI and

stirred for about 15 minutes to obtain a clear solution and then sodium bicarbonate is added and further mixed for 5 minutes to obtain a clear solution and then the solution is chilled to about 5°C.

3. The Ertapenem bulk drug was thawed from -20°C for approximately 30 minutes and then divided into 5 equal portions. The 5 portions of bulk drug were added to the above step 2 solution over a period of about 1 hour, while adding the sodium hydroxide solution to keep the pH of the bulk drug solution between 7.5 and 7.8.
4. At the end of the bulk drug addition, the solution was mixed for an additional 5 minutes and WFI at a temperature of about 5°C was added to bring the solution to about 90%, and 2N NaOH titrations were performed to maintain the pH of the bulk solution at about 7.5. After mixing, WFI at a temperature of about 5°C was added to bring the solution to about 100% of the batch size and stirred for 10 minutes. If necessary, the pH was adjusted to the target pH of 7.5 by addition of 2N NaOH solution.

Bulk solutions of stabilised ertapenem compositions each comprising 1g, 2g, or 3g of SBECD per gram of ertapenem were manufactured according to the above method. The compositions of these formulations are shown in Table 3.

Table 3.

Component	Formulation 1: Composition with 1 g SBECD		Formulation 2: Composition with 2 g SBECD		Formulation 3: Composition with 3 g SBECD	
	Quantity per 5 mL (in g)	Quantity per 300 mL (in g)	Quantity per 10.0 mL (in g)	Quantity per 360 mL (in g)	Quantity per 10.0 mL (in g)	Quantity per 600 mL (in g)
Ertapenem sodium equivalent to Ertapenem acid	1.0	63.6#	1.0	38.2#	1.0	63.6#
Sodium bicarbonate USP*	0.175	10.5	0.175	6.3	0.175	10.5
Betadex Sulfobutyl Ether Sodium NF (SBECD)	1.0	60.0	2.0	72.0	3.0	180.0 g
Sodium hydroxide NF**	q.s to pH 7.5	4.8##	q.s to pH 7.5	2.4$	q.s to pH 7.5	4.8##
Water for Injection USP***	q.s to 5.0 mL	q.s to 300 mL	q.s to 10.0 mL	q.s to 360 mL	q.s to 10.0 mL	q.s to 300 mL

Includes 6% excess to the theoretical weight to compensate the degradation during manufacturing
* quantity corresponds to 1 mole equivalent to Ertapenem
** diluted in Water for Injection, USP and used as 2N solution for pH control
quantity for preparation of 60 mL of 2N sodium hydroxide solution
$ quantity for preparation of 30 mL of 2N sodium hydroxide solution
*** removed during lyophilization process

The stability of these stabilised formulations at 0°C was measured as for the control formulation of Example 1. The results are shown in Table 4.

Compared to the control formulation, the stability of formulations 1-3 containing SBECD was significantly improved, especially upon increasing the quantity of the SBECD.

Table 4. Bulk solution stability of the compositions having varying quantities of SBECD added to the compositions disclosed as per US patent 6,548,492

	Formulation 1: Composition with 1 g SBECD and 175 mg Sodium Bicarbonate per gram of Ertapenem				Formulation 2: Composition with 2 g SBECD and 175 mg Sodium Bicarbonate per gram of Ertapenem			Formulation 3: Composition with 3 g SBECD and 175 mg Sodium Bicarbonate per gram of Ertapenem			
	Bulk Solution Stability at about 0-2℃										
Time period	**0 hr**	**6th hr**	**12th hr**	**24th Hr**	**0 hr**	**12th hr**	**24th Hr**	**0 hr**	**6th hr**	**12th hr**	**24th Hr**
Related Substances (By % of Ertapenem)											
Oxazinone	0.09	0.32	0.55	0.89	0.03	0.10	0.15	0.06	0.13	0.21	0.30
Hydrolyzed Impurity	0.78	1.18	1.62	2.39	0.61	1.15	1.37	0.74	0.99	1.29	1.72
Dimer-I & II	0.68	1.29	1.98	2.85	0.47	1.11	1.49	0.47	0.70	0.91	1.20
Dimer-III	0.17	0.24	0.31	0.40	0.14	0.17	0.16	0.15	0.18	0.20	0.22
Dimer-IV	0.11	0.13	0.14	0.16	0.10	0.11	0.10	0.10	0.11	0.11	0.11
Dimer-V	0.03	0.09	0.14	0.20	ND	ND	0.05	0.03	0.04	0.05	0.07
Any unspecified Degradation Product	ND	0.06	0.10	0.14	ND	0.06	0.04	ND	ND	0.05	0.06
Total Degradation Products	**1.9**	**3.4**	**5.0**	**7.2**	**1.5**	**2.7**	**3.4**	**1.6**	**2.2**	**2.8**	**3.7**
Assay (%)	103.9	101.9	98.4	96.9	104.5	100.7	99.0	101.2	105.8	103.8	103.8
pH	7.6	7.5	7.3	7.3	7.5	7.5	7.5	7.6	7.6	7.8	7.6

ND: Not detected

Example 3

Alternate ertapenem compositions using different amounts of SBECD as a stabiliser, but which do not have any carbonate source to form a carbon dioxide adduct, were also evaluated. In these formulations sodium citrate was used as the buffering agent and the pH was adjusted with sodium hydroxide solution during the compounding process. The formulations were manufactured according to the following process, with the final compositions as set out in Table 5.

1. Preparation of sodium hydroxide solution: A 2N solution of sodium hydroxide was prepared by dissolving sodium hydroxide NF pellets in required amount of Water for Injection (WFI) (80 g sodium hydroxide in 1000 mL WFI yields a 2N sodium hydroxide solution). The sodium hydroxide solution was chilled to a temperature of about 5°C.

2. In a beaker, WFI quantity equivalent to 50% of the batch size is taken. SBECD is added into WFI and stirred for about 5-15 minutes to obtain a clear solution and then sodium citrate is added and further mixed for 5 minutes to obtain a clear solution and then the solution is chilled to about 5°C.

3. The Ertapenem bulk drug was thawed from -20°C for approximately 30 minutes was then divided into 5 equal portions. The 5 portions of bulk drug were added into the above step 2 solutions over a period of about 50 minutes, while adding the sodium hydroxide solution to keep the pH of the bulk drug solution at about 7.5.

4. At the end of the bulk drug addition, the solution was mixed for an additional 5 minutes and WFI at a temperature of about 5°C was added to bring the solution to about 90%, and 2N NaOH titrations were performed to maintain the pH of the bulk solution at about 7.5. After mixing, WFI at a temperature of about 5°C was added to bring the solution to about 100% of the batch size and stirred for 10 minutes. If necessary, the pH was adjusted to the target pH of 7.5 by addition of 2N NaOH solution.

Table 5. Bulk solution formulations with SBECD and without carbonate source

Component	Formulation 4: Composition with 1 g SBECD and 200 mg sodium citrate per gram of Ertapenem		Formulation 5: Composition with 2 g SBECD and 200 mg sodium citrate per gram of Ertapenem		Formulation 6: Composition with 3 g SBECD and 200 mg sodium citrate per gram of Ertapenem	
	Quantity per 5 mL (in g)	Quantity per 200 mL (in g)	Quantity per 10.0 mL (in g)	Quantity per 400 mL (in g)	Quantity per 10.0 mL (in g)	Quantity per 400 mL (in g)
Ertapenem sodium equivalent to Ertapenem acid	1.0	42.4[#]	1.0	42.4[#]	1.0	42.4[#]
Sodium Citrate NF*	0.20	8.0	0.20	8.0	0.20	8.0
Betadex Sulfobutyl Ether Sodium NF (SBECD)	1.0	40.0	2.0	80.0	3.0	120.0
Sodium hydroxide NF**	q.s to pH 7.5	2.4[##]	q.s to pH 7.5	3.2[$]	q.s to pH 7.5	3.2[$]
Water for Injection USP***	q.s to 5.0 mL	q.s to 200 mL	q.s to 10.0 mL	q.s to 400 mL	q.s to 10.0 mL	q.s to 400 mL

[#] Includes 6% excess to the theoretical weight to compensate the degradation during manufacturing
** diluted in Water for Injection, USP and used as 2N solution for pH control
[##] quantity for preparation of 30 mL of 2N sodium hydroxide solution
$ quantity for preparation of 40 mL of 2N sodium hydroxide solution
*** removed during lyophilization process

The stability of these non-carbonate stabilised formulations at 0°C was measured as for the control formulation of Example 1. The results are shown in Table 6.

The stability of these formulations significantly improved upon increasing the quantity of SBECD.

Table 6. Bulk solution stability of the compositions having varying quantities of SBECD and without any carbonate source

	Formulation 4: Composition with 1 g SBECD and 200 mg sodium citrate per gram of Ertapenem				Formulation 5: Composition with 2 g SBECD and 200 mg sodium citrate per gram of Ertapenem			Formulation 6: Composition with 3 g SBECD and 200 mg sodium citrate per gram of Ertapenem			
	Bulk Solution Stability at about 0-2°C										
Time period	**0 hr**	**6th hr**	**12th hr**	**24 hr**	**0 hr**	**6th hr**	**24 hr**	**0 hr**	**6th hr**	**13th hr**	**24 hr**
Related Substances (By % of Ertapenem)											
Oxazinone impurity	0.02	0.02	0.03	0.03	0.02	0.02	0.03	0.02	0.02	0.02	0.03
Hydrolyzed Impurity	0.63	0.74	0.86	0.84	0.68	0.83	1.08	0.76	0.85	0.9	1.1
Dimer-I	0.06	0.16	0.23	0.41	0.06	0.15	0.31	0.05	0.09	0.13	0.18
Dimer-II	1.36	3.72	5.55	9.33	0.95	3.04	7.29	0.81	1.85	2.68	4.53
Dimer-III	0.15	0.17	0.19	0.24	0.14	0.14	0.08	0.15	0.15	0.15	0.19
Dimer-IV	0.12	0.15	0.17	0.23	0.11	0.13	0.18	0.12	0.12	0.13	0.14
Dimer-V	0.04	0.07	0.08	0.13	0.03	0.04	0.06	0.03	0.04	0.04	0.05
Any Unspecified Degradation Product	ND	0.05	0.14	0.55	0.1	0.08	0.27	0.08	0.07	0.06	0.11
Total degradation Products	**2.4**	**5.1**	**7.3**	**11.8**	**2.1**	**4.4**	**9.6**	**2.0**	**3.2**	**4.1**	**6.4**
Assay (%)	103.2	100.0	96.7	88.2	99.9	101.8	93.8	100.8	97.0	96.9	95.6
pH	7.1	7.3	7.3	6.9	7.1	7.2	7.0	7.2	7.2	7.1	7.1

ND: Not detected

Further it was observed that the addition of sodium chloride to Formulation 6 improved the stability of the formulation, without any carbonate source. Formulations including sodium chloride were manufactured according to the following method. Their final composition is shown in Table 7 and the stability of the bulk solutions with sodium chloride is shown in Table 8.

1. Preparation of sodium hydroxide solution: A 2N solution of sodium hydroxide was prepared by dissolving sodium hydroxide NF pellets in required amount of Water for Injection (WFI) (80 g sodium hydroxide in 1000 mL WFI yields a 2N sodium hydroxide solution). The sodium hydroxide solution was chilled to a temperature of about 5°C.

2. In a beaker, WFI quantity equivalent to 50% of the batch size is taken. SBECD is added into WFI and stirred for about 15 minutes to obtain a clear solution and then sodium citrate is added and further mixed for 5 minutes to obtain a clear solution and then finally sodium chloride was added to the solution and stirred for 5 minutes. Then the solution is chilled to about 5°C.

3. The Ertapenem bulk drug (as anhydrous free acid) was thawed from -20°C for approximately 30 minutes was then divided into 5 equal portions. The 5 portions of bulk drug were added into the above step 2 solutions over a period of about 50 minutes, while adding the sodium hydroxide solution to keep the pH of the bulk drug solution at about 7.8.

4. At the end of the bulk drug addition, the solution was mixed for an additional 5 minutes and WFI at a temperature of about 5°C was added to bring the solution to about 90%, and 2N NaOH titrations were performed to maintain the pH of the bulk solution at about 7.8. After mixing, WFI at a temperature of about 5°C was added to bring the solution to about 100% of the batch size and stirred for 10 minutes.

Table 7. Formulations with SBECD, sodium citrate and sodium chloride

Component	Formulation 7: 3 g SBE-β-CD, 200 mg Sodium Citrate and 90 mg Sodium chloride per gram of Ertapenem		Formulation 8: 3 g SBE-β-CD, 200 mg Sodium Citrate and 180 mg Sodium chloride per gram of Ertapenem	
	Quantity per 10 mL (in g)	Quantity per 550 mL (in g)	Quantity per 10.0 mL (in g)	Quantity per 550 mL (in g)
Ertapenem sodium equivalent to Ertapenem acid	1.0	58.3#	1.0	58.3#
Sodium Citrate NF*	0.20	11.0	0.20	11.0
Betadex Sulfobutyl Ether Sodium NF (SBECD)	3.0	165.0	3.0	165.0
Sodium Chloride USP	0.09	4.95	0.18	9.9
Sodium hydroxide NF**	q.s to pH 7.5	4.8##	q.s to pH 7.5	5.6$
Water for Injection USP***	q.s to 10.0 mL	q.s to 550 mL	q.s to 10.0 mL	q.s to 550 mL

Includes 6% excess to the theoretical weight to compensate the degradation during manufacturing
** diluted in Water for Injection, USP and used as 2N solution for pH control
quantity for preparation of 60 mL of 2N sodium hydroxide solution
$ quantity for preparation of 70 mL of 2N sodium hydroxide solution
*** removed during lyophilization process

The experimental data shows that the compositions with SBECD and sodium citrate, when used along with sodium chloride, had improved stability compared to the control formulation.

Table 8. Bulk solution stability of the compositions comprising SBECD and varying quantities of sodium chloride

	Formulation 7: 3 g SBE-β-CD , 200 mg Sodium Citrate and 90 mg Sodium chloride per gram of Ertapenem				**Formulation 8: 3 g SBE-β-CD , 200 mg Sodium Citrate and 180 mg Sodium chloride per gram of Ertapenem**			
Bulk Solution Stability at 0-2℃								
Time period	0 hr	6th hr	12th hr	24thhr	0 hr	6th hr	12thhr	24thhr
Related Substances (By % of Ertapenem)								
Oxazinone	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Hydrolyzed Impurity	0.81	1.06	1.31	1.86	0.79	1.04	1.28	1.80
Dimer-I	0.03	0.06	0.09	0.13	0.03	0.06	0.08	0.13
Dimer-II	0.50	0.93	1.52	2.65	0.50	0.96	1.46	2.46
Dimer-III	0.18	0.18	0.17	0.16	0.17	0.17	0.16	0.15
Dimer-IV	0.12	0.12	0.12	0.12	0.11	0.11	0.12	0.12
Dimer-V	0.02	0.02	0.01	0.01	0.02	0.02	0.02	0.01
Any unspecified Degradation Product	0.08	0.05	0.06	0.07	0.07	0.05	0.06	0.07
Total Degradation Products	**1.8**	**2.5**	**3.3**	**5.1**	**1.7**	**2.5**	**3.2**	**4.9**
Assay (%)	102.6	101.2	100.3	97.2	104.6	102.7	100.1	97.2
pH	8.2	8.2	8.3	8.4	8.1	8.3	8.3	8.2

Example 4

The bulk solutions of formulations 1, 3 and 7 were filtered, filled into vials and lyophilized. The level of impurities in the various lyophilized products was tested with the HPLC method and the comparative data is provided in the Table 9. The lyophilised commercial product Invanz® was also tested.

Table 9. Comparative Lyophilized Product Related Substances Data

	RLD Formulation Invanz® 1 g Lot # 2079560 Exp Date: 12/2014	Control Formulation	Formulation 1	Formulation 3	Formulation 7
Related Substances (By % of Ertapenem)					
Oxazinone Impurity	0.6	0.6	0.4	0.2	0.02
Hydrolyzed Impurity	3.3	4.1	2.5	2.1	1.1
Dimer-I & II	**0.7**	**1.6**	**0.9**	**0.6**	**0.7**
Dimer-III	0.1	0.3	0.2	0.2	0.2
Dimer-IV	0.2	0.1	0.2	0.1	0.1
Dimer-V	0.04	0.08	0.06	0.04	ND
Any unspecified Degradation Product	0.1	0.1	0.07	ND	0.1
Total Degradation Products	**5.2**	**7.0**	**4.4**	**3.2**	**2.2**
Assay (%)	**110.9**	**102.2**	**111.6**	**111.2**	**108.9**
pH	7.9	7.7	7.6	7.9	8.3

The data shows that the compositions with SBECD had significantly lower impurity levels than the commercial product (Invanz®) and the control formulation.

The stability of the lyophilized products of Invanz®, control formulation, Formulation 3 and Formulation 7 were evaluated at accelerated stability (40°C/75%RH) condition and the comparative data is provided in Table 11.

Table 11. Comparative Accelerated stability (at 40°C/75%RH condition) of the lyophilized formulations

	INVANZ 1 g Lot # 2079560 Exp Date: 12/2014		Control Formulation			Formulation 3			Formulation 7		
Time period	Initial	3 Month	Initial	1 Month	3 Month	Initial	1 Month	3 Month	Initial	1 Month	3 Month
Related Substances (%)											
Oxazinone Impurity	0.6	1.1	0.6	1.0	1.2	0.2	0.3	0.4	0.02	0.02	0.03
Hydrolyzed Impurity	3.3	6.1	4.1	5.7	6.9	2.1	3.8	4.6	1.1	1.9	2.3
Dimer-I & II	0.7	0.8	1.6	1.7	1.7	0.6	0.6	0.6	0.7	0.7	0.7
Dimer-III	0.1	0.1	0.3	0.3	0.4	0.2	0.2	0.2	0.2	0.2	0.2
Dimer-IV	0.2	0.3	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Dimer-V	0.04	0.04	0.1	0.1	0.1	0.04	0.03	0.03	ND	0.01	0.02
Any unspecified Degradation Product	0.1	0.2	0.1	0.2	0.2	ND	ND	0.08	0.1	0.1	0.2
Total Degradation Products	5.2	9.0	7.0	9.2	10.9	3.2	5.1	6.0	2.2	3.0	3.7
Assay (%)	110.9	107.5	102.2	99.8	98.8	111.2	107.1	106.0	108.9	102.4	103.6
pH	7.9	7.7	7.8	7.8	7.7	7.9	7.8	7.4	8.3	8.3	8.1

The stability data shows that the compositions with SBECD had significantly lower impurity levels than the commercial product (Invanz®) and the control formulation. In addition, the Formulation 7 that did not contain the sodium bicarbonate had significantly lower level of oxazinone impurity.

The "in-use" stability after reconstitution of the lyophilised product was also tested for Invanz® and formulations 3 and 7. Stability of the reconstituted vials at a ertapenem concentration of 20 mg/mL was tested over a

period of up to 24 hours. For the commercial product Invanz®, storage of the reconstituted solution is recommended to be no more than 6 hours at controlled room temperature, as after this point too much degradation has occurred and the level of impurities has increased. The stability data for the reconstituted formulations are provided in Table 10.

Table 10. Comparative in-use stability of the reconstituted formulations

	INVANZ 1 g Lot # 2079560 Exp Date: 12/2014				**Formulation 3**				**Formulation 7**	
	Initial	6th hr	12th hr	24th hr	Initial	6th hr	12th hr	24th hr	Initial	6th hr
Related Substances (%)										
Oxazinone	0.78	0.85	0.95	1.13	0.15	0.21	0.28	0.43	0.03	0.03
Hydrolyzed Impurity	3.97	4.94	6.07	8.41	1.98	3.08	4.13	6.09	0.89	2.33
Dimer-I&II	0.81	1.24	1.70	2.50	0.55	0.87	1.23	1.90	0.60	1.59
Dimer-III	0.14	0.14	0.15	0.16	0.18	0.18	0.18	0.18	0.18	0.17
Dimer-IV	0.29	0.29	0.30	0.28	0.10	0.11	0.12	0.11	0.12	0.12
Dimer-V	0.06	0.04	0.05	0.04	0.03	0.02	0.03	0.03	0.01	0.01
Any unspecified Degradation Product	0.12	0.13	0.13	0.20	ND	0.08	0.10	0.18	0.15	0.13
Total Degradation Products	**6.2**	**7.8**	**9.5**	**12.9**	**3.0**	**4.6**	**6.1**	**9,0**	**2.0**	**4.4**
pH	7.7	7.6	7.5	7.7	7.7	7.7	7.6	7.7	8.0	7.9

These data show that the formulations stabilised with SBECD according to the invention can be stored as “in-use” reconstituted solutions for longer than the commercial product.

Stability of the reconstituted vials at a ertapenem concentration of 20 mg/mL was tested over a period of up to 24 hours.

Example 5

Chromatographic parameters of Related Substances Testing:

(1) Column: Ascentis express C18, 250 x 4.6 mm, 5 µm that contains Octa decyl silane chemically bonded to porous silica particles.

(2) Flow rate: 1.0 mL/min.

(3) Column temperature: Ambient.

(4) Wavelength: 250 nm.

(5) Injection volume: 10 µL.

(6) Sample cooler temperature: 10°C.

(7) Run time: About 55 minutes.

Preparation of Mobile Phase A:

(1) Weigh accurately and dissolve about 3.8 g Ammonium acetate in 1000 mL of HPLC grade water, adjust the pH to 6.5 ± 0.05 with 10%v/v Ortho phosphoric acid.

(2) Filter through 0.45 µm membrane filter and degas for about 10 minutes.

Preparation of Mobile phase B: Use degassed Acetonitrile.

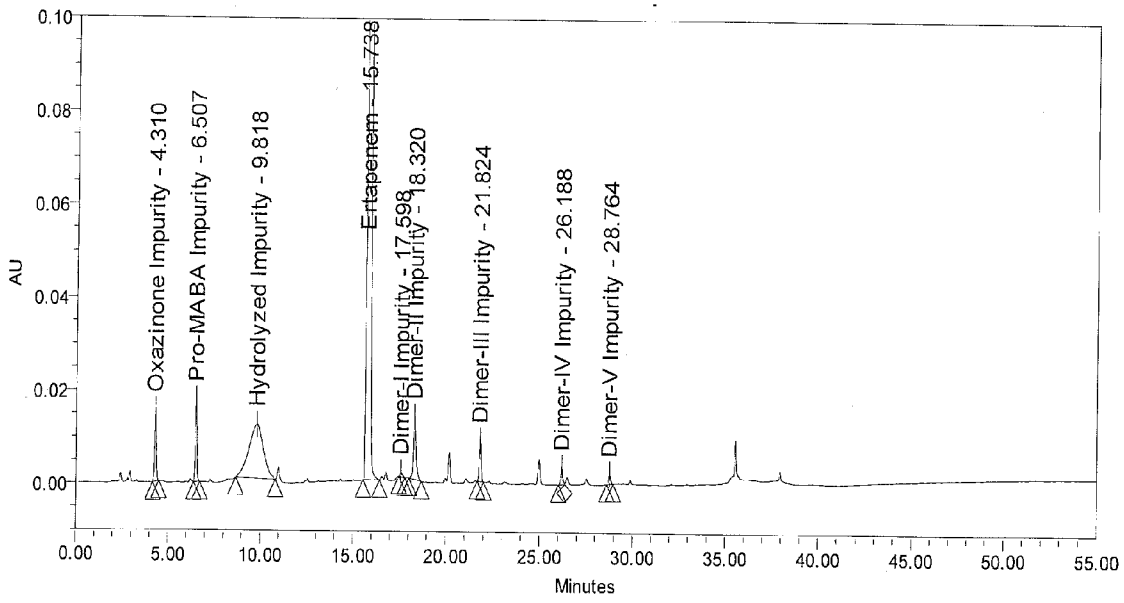
Gradient programme:

Time (min)	% Mobile phase-A	% Mobile phase-B
0	98	2
1	98	2
3	97	3
5	97	3
12	93	7
25	88	12
30	75	25
35	50	50
37	98	2
55	98	2

RRT's of known impurities with respect to Ertapenem

S.No.	Component Name	RRT(About)
1	Oxazinone	0.27
2	PRO-MABA	0.41
3	Hydrolyzed product	0.62
4	Dimer-I impurity	1.12
5	Dimer-II impurity	1.16
6	Dimer-III impurity	1.39
7	Dimer-IV impurity	1.66
8	Dimer-V impurity	1.83

TYPICAL CHROMATOGRAM OF SPIKED SAMPLE



Claims:

1. A composition comprising a carbapenem, a buffer, and a stabiliser, wherein the stabiliser is a cyclic oligosaccharide or a polysaccharide.

2. The composition according to claim 1, wherein the buffer comprises a carbonate source, preferably a carbonate buffer and/or a bicarbonate buffer, preferably sodium bicarbonate.

3. The composition according to claim 1, wherein the buffer does not comprise a carbonate source, preferably wherein the buffer is a citrate buffer, preferably sodium citrate.

4. The composition according to any of claims 1-3, wherein the stabiliser is a cyclic polysaccharide, preferably a cyclodextrin

5. The composition according to claim 4, wherein the stabiliser is sulfobutylether-β-cyclodextrin.

6. The composition according to any of claims 1-3, wherein the stabiliser is a polysaccharide, preferably a dextrin, a hydroxyethyl starch or a dextran.

7. The composition according to any of claims 1-6, wherein the stabiliser is present in a ratio of between about 0.5 grams to about 5 grams of stabiliser per gram of carbapenem, preferably between about 1 gram to about 3 grams of stabiliser per gram of carbapenem.

8. The composition according to any of claims 1-7 further comprising sodium chloride, preferably in a ratio of between about 90 milligrams to about 180 milligrams of sodium chloride per gram of carbapenem, preferably about 180 milligrams of sodium chloride per gram of carbapenem.

9. The composition according to any of claims 1-8, wherein the carbapenem is ertapenem.

10. The composition according to any of claims 1-9, wherein the composition comprises less than about 8%, preferably less than about 5% total degradation products after 24 hours at 0-2°C.

11. The composition according to any of claims 1-10, wherein the composition is lyophilised.

12. The composition according to claim 11, wherein the lyophilised composition comprises less than about 5% total degradation products, preferably less than about 4% total degradation products.

13. The composition according to claim 10 or 11, wherein the lyophilised composition has an in-use shelf life of more than 6 hours at 25°C.

14. The composition according to any of claims 1-13, wherein the stabilised carbapenem composition is a pharmaceutical composition.

15. A method of producing a stabilised carbapenem composition, the method comprising combining in a buffered solution:

(c) a stabiliser, wherein the stabiliser is a cyclic oligosaccharide or a polysaccharide; and

(d) a carbapenem;

wherein the stabilised carbapenem composition comprises less than about 8%, preferably less than about 5% total degradation products after 24 hours at 0-2°C.

16. A method of producing a stabilised carbapenem composition, the method comprising combining in a buffered solution:

(c) a stabiliser, wherein the stabiliser is a cyclic oligosaccharide or a polysaccharide; and

(d) a carbapenem;

optionally wherein the stabilised carbapenem composition is lyophilised,

wherein, when lyophilised, the stabilised carbapenem composition comprises less than about 5% total degradation products, preferably less than about 4% total degradation products.

17. A method according to claim 15 or claim 16, wherein the buffer comprises a carbonate buffer and/or a bicarbonate buffer, preferably sodium bicarbonate.

18. A method according to claim 15 or claim 16, wherein the buffer is not a carbonate source, preferably a citrate buffer, preferably sodium citrate.

19. A method according to any one of claims 15-18, wherein the stabiliser is a cyclic oligosaccharide, preferably a cyclodextrin.

20. A method according to claim 19 wherein the stabiliser is sulfobutylether-β-cyclodextrin.

21. A method according to any one of claims 15-18, wherein the stabiliser is a polysaccharide, preferably a dextrin, a hydroxyethyl starch or a dextran

22. A method according to any one of claims 15-21, wherein the stabiliser and carbapenem are combined in a ratio of between about 0.5 grams to about 5 grams of stabiliser per gram of carbapenem, preferably between about 1 gram to about 3 grams of stabiliser per gram of carbapenem.

23. A method according to any of claims 15-22, wherein the carbapenem is ertapenem.

24. A method according to any one of claims 15-23, wherein the buffered solution further comprises sodium chloride, preferably in a ratio of between about 90 milligrams to about 180 milligrams of sodium chloride per gram of carbapenem, preferably about 180 milligrams of sodium chloride per gram of carbapenem.

25. A composition according to any of claims 10-14, or a method according to any of claims 15-24, wherein the total degradation products are measured by reverse-phase high performance liquid chromatography (HPLC).

26. A composition according to any one of claims 1-14 for use in therapy.

27. A composition according to any one of claims 1-14 for use in treating bacterial infection.

28. A method of treating bacterial infection in a subject comprising administering to the subject a therapeutic amount of a composition according to any one of claims 1-14.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/072996

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 47/40 (2015.01)
CPC - C07D 477/14 (2015.01)
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(8) - A61K 9/19, 47/40; C07D 477/14 (2015.01)
CPC - A61K 9/19, 47/40; C07D 477/14 (2015.01) (keyword delimited)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 34/284; 514/210.13; 536/123.1; 540/350 (keyword delimited)

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

PatBase, Google Patents, Google Scholar.
Search terms used: stable, stabilized, carbapenem, imipenem, meropenem, ertapenem, doripenem, saccharide, cyclodextrin, CD, starch, dextran

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2012/0207762 A1 (KIPP et al) 16 August 2012 (16.08.2012) entire document	1, 2, 4-6
---		---
Y		3, 15-18
Y	US 5,952,323 A (ZIMMERMAN et al) 14 September 1999 (14.09.1999) entire document	3, 18
Y	US 2013/0281427 A1 (CSPC ZHONGQI PHARMACEUTICAL TECHNOLOGY (SHIJIAZHUANG) CO LTD) 24 October 2013 (24.10.2013) entire document	15-18

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

* Special categories of cited documents:
"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	Date of mailing of the international search report
09 March 2015	28 APR 2015
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/072996

Box 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:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
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:

3. ☒ Claims Nos.: 7-14, 19-28
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.