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(54) **CEFTOLOZANE-TAZOBACTAM PHARMACEUTICAL COMPOSITIONS**

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(57) **ABSTRACT**

Pharmaceutical compositions can include ceftolozane lyophilized in the absence of tazobactam.

Figure 1A

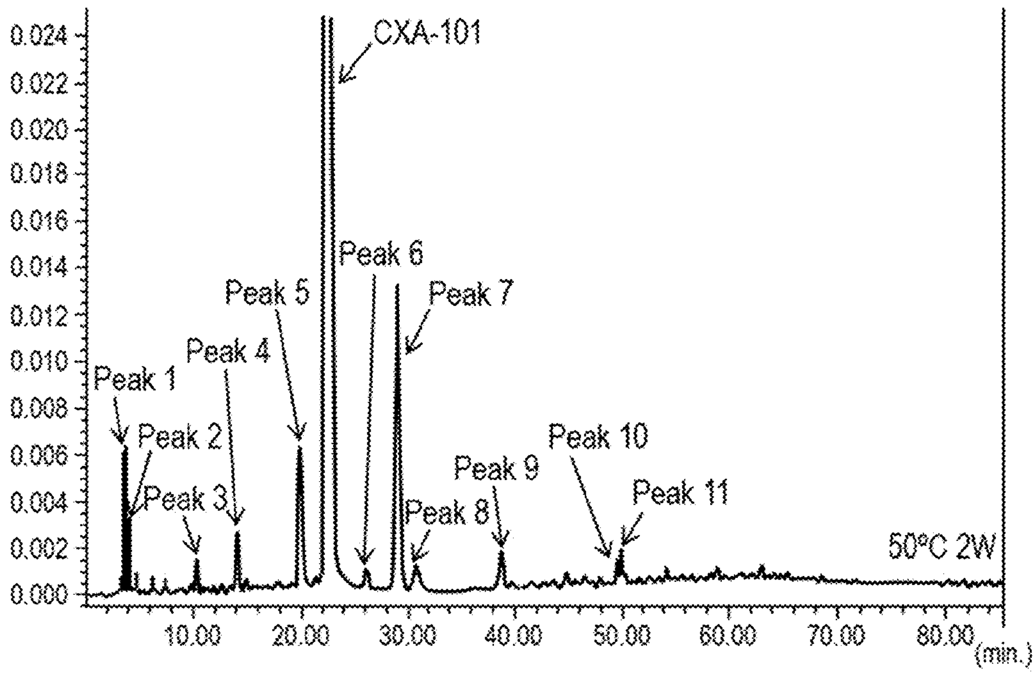

CXA-101
Peak 1
Peak 2
Peak 3
Peak 4
Peak 5
Peak 6
Peak 7
Peak 8
Peak 9
Peak 10
Peak 11
50°C 2W
0.024
0.022
0.020
0.018
0.016
0.014
0.012
0.010
0.008
0.006
0.004
0.002
0.000
10.00
20.00
30.00
40.00
50.00
60.00
70.00
80.00
(min.)

Figure 1B

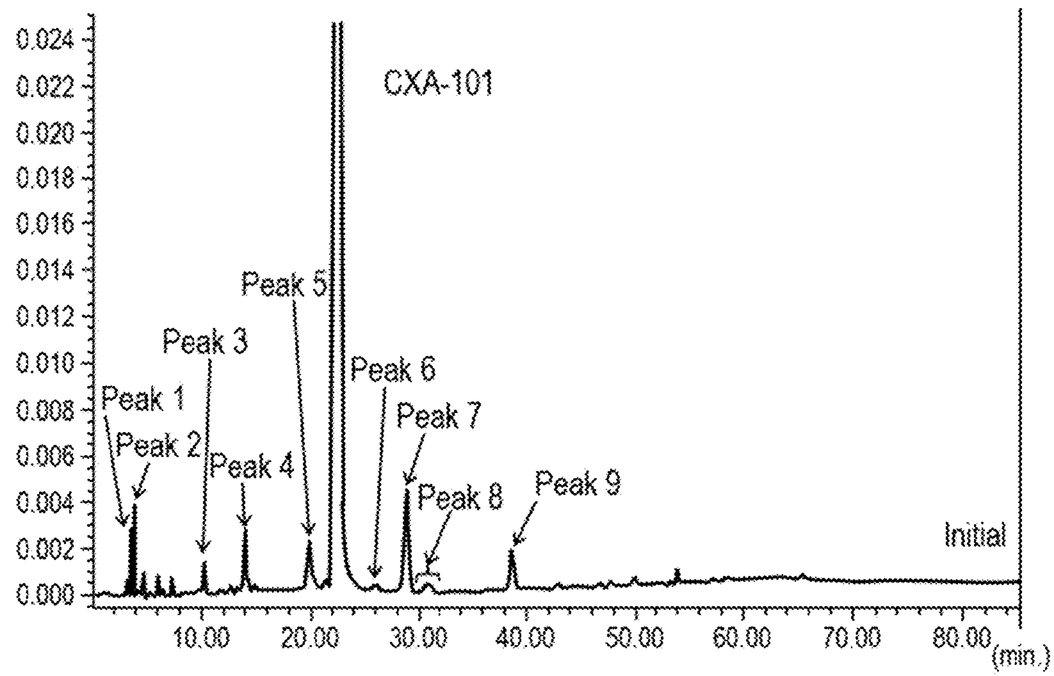

0.024
0.022
0.020
0.018
0.016
0.014
0.012
0.010
0.008
0.006
0.004
0.002
0.000
CXA-101
Peak 1
Peak 2
Peak 3
Peak 4
Peak 5
Peak 6
Peak 7
Peak 8
Peak 9
Initial
10.00
20.00
30.00
40.00
50.00
60.00
70.00
80.00
(min.)

Figure 2

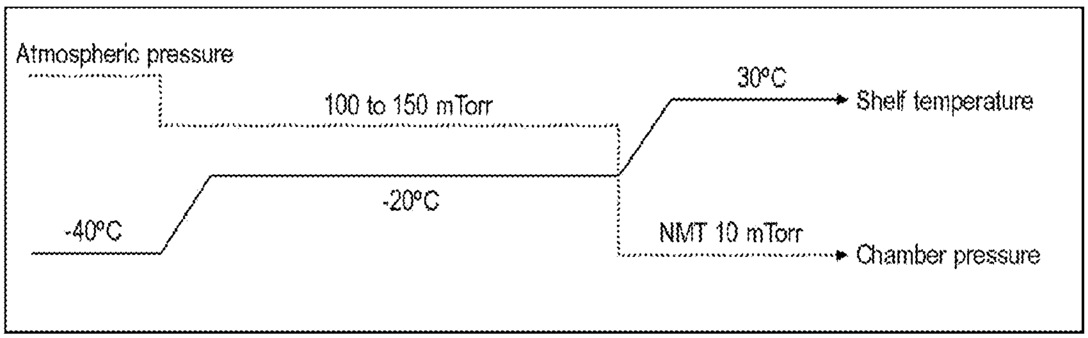

Atmospheric pressure
100 to 150 mTorr
30°C
Shelf temperature
-40°C
-20°C
NMT 10 mTorr
Chamber pressure

Figure 3

Table 1

Impurity	RRT
Peak 1 (P1) [1]	~0.1
Peak 2 (P2)	~0.2
Peak 3 (P3)	~0.4
Peak 4 (P4)	~0.6
Peak 5 (P5)	~0.9
CXA-101 [2]	1.0
Peak 6 (P6)	~1.1
Peak 7 (P7)	~1.3
Peak 8 (P8)	~1.4
Peak 9 (P9)	~1.7
Peaks 10, 11 (P10, 11)	~2.3

1. The absolute retention time for Peak 1 is 3.5 minutes.
2. The absolute retention time for CXA-101 (ceftolozane) is 24 minutes.

Figure 4A

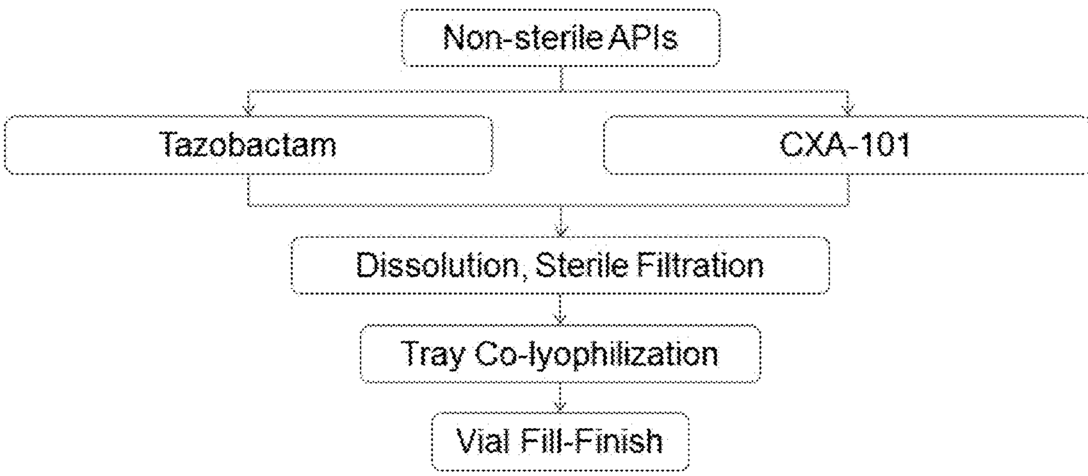

Non-sterile APIs
Tazobactam
CXA-101
Dissolution, Sterile Filtration
Tray Co-lyophilization
Vial Fill-Finish

Figure 4B

Table 2: Compositions of Co-lyophilization Drug Product.

Component	Function	Amount (mg/vial)
CXA-101	Active pharmaceutical ingredient	1000 (potency)
L-arginine	Alkalization reagent	587
Citric acid (anhydrous)	Buffer	21
Sodium chloride	Stabilizer	476
Tazobactam (free acid)	Active pharmaceutical ingredient	500
Sodium bicarbonate	Alkalization reagent	Quantity sufficient[1] for pH 4.8 to 7.0
water	Dissolution solvent	Not more than 4% by HPLC[2]
Nitrogen	Inert gas	Sufficient quantity

1. Sodium content is approximately 78 mg/g of tazobactam in drug product after lyophilization.
2. Water is removed during the lyophilization process and is controlled at no more than 4% by weight.

Figure 5

Table 3

Test	Acceptance Limits (expected value)	Results			
		Sampling	**60 minute**	**120 minute**	**180 minute**
Content: Ceftolozane[1]	30.4%-37.2%	1	34.24	34.07	34.42
		2	34.62	34.21	34.66
		3	34.71	34.60	34.85
		Mean [3]	34.52	34.30	34.64
		RSD%	0.72	0.80	0.63
Content: Tazobactam[2]	15.2%-18.6%	1	17.96	18.20	17.12
		2	16.90	18.26	16.51
		3	17.27	16.93	17.02
		Mean [3]	17.38	17.80	16.89
		RSD%	3.10	4.22	1.96
Ratio of Content (w/w) ceftolozane/tazobactam	2.00[4]	1	1.91	1.87	2.01
		2	2.05	1.87	2.10
		3	2.01	2.04	2.05
		Mean [3]	1.99	1.93	2.05
		RSD%	3.69	5.12	2.2

RSD = relative standard deviation

[1] Theoretical value: 33.96% Acceptance limits are 90% - 110% of the theoretical value.

[2] Theoretical value: 16.99% Acceptance limits are 90% - 110% of the theoretical value.

[3] Three samples are taken at each time point at three places to measure the percentage by weight of ceftolozane and tazobactam. The "Mean" is the average of the percentages or the weight ratios of Ceftolozane/tazobactam.

[4] Acceptance limits were established based on batch history.

Figure 6

Table 4: Formulation composition of the Co-Lyo Combo Drug Product.

CXA-201 Comp.	16.3 g active	ceftolozane
	8.1 g active	Tazobactam free ac.
	15.5 g	L-Arginine
	350 mg	Citric acid
	7.9 g	NaCl
	6.1	pH compounded solution

Figure 7A

Table 5: Stability data Co-Lyo Combo Drug Product at 25 °C.

Test items	Spec. D.P.	T0	T1 25°C	T2 25°C
Related Substances				
-Peak1	≤ 1.50%	0.31%	0.54%	0.71%
-Peak2	≤ 0.40%	0.07%	0.07%	0.09%
-Peak3	≤ 0.30%	<0.03%	<0.03%	<0.03%
-Peak4	≤ 0.80%	0.08%	0.08%	0.09%
-Peak5	≤ 1.00%	0.27%	0.26%	0.29%
-Peak6	≤ 0.15%	<0.03%	<0.03%	<0.03%
-Peak7	≤ 2.00%	0.64%	0.65%	0.66%
-Peak8	≤ 0.15%	<0.03%	<0.03%	<0.03%
-Peak9	≤ 0.60%	0.05%	0.11%	0.10%
-Peak10,11	≤ 0.15% each	0.04%	0.04%	0.04%
-Peak12	≤ 2.00%	<0.03%	<0.03%	<0.03%
Others (RRT 0.43)	≤ 0.15%	<0.03%	<0.03%	0.04%
Others (RRT 1.22)	≤ 0.15%	0.13%	0.30%	0.38%
Others (RRT 2.18)	≤ 0.15%	0.03%	<0.03%	0.05%
Others (RRT 2.77)	≤ 0.15%	<0.03%	0.03%	0.03%
Sing. Unk.	≤ 0.15%	0.05%	0.07%	0.05%
Total	≤ 5.00%	1.67%	2.19%	2.77%
pH	report value	5.5		4.83

Figure 7B

Table 6: Stability data Co-Lyo Combo Drug Product at 40 °C.

Test items	Spec. D.P.	T0	T1 40°C	T2 40°C
Related Substances				
-Peak1	≤ 1.50%	0.31%	1.77%	2.22%
-Peak2	≤ 0.40%	0.07%	0.10%	0.16%
-Peak3	≤ 0.30%	<0.03%	<0.03%	0.06%
-Peak4	≤ 0.80%	0.08%	0.09%	0.09%
-Peak5	≤ 1.00%	0.27%	0.27%	0.30%
-Peak6	≤ 0.15%	<0.03%	<0.03%	<0.03%
-Peak7	≤ 2.00%	0.64%	0.69%	0.78%
-Peak8	≤ 0.15%	<0.03%	<0.03%	0.10%
-Peak9	≤ 0.60%	0.05%	0.09%	0.09%
-Peak10,11	≤ 0.15% each	0.04%	0.04%	0.05%
-Peak12	≤ 2.00%	<0.03%	<0.03%	<0.03%
Others (RRT 0.43)	≤ 0.15%	<0.03%	0.09%	0.15%
Others (RRT 1.22)	≤ 0.15%	0.13%	0.74%	0.97%
Others (RRT 2.18)	≤ 0.15%	0.03%	<0.03%	0.08%
Others (RRT 2.77)	≤ 0.15%	<0.03%	<0.03%	0.04%
Sing. Unk.	≤ 0.15%	0.05%	0.11%	0.25%
Total	≤ 5.00%	1.67%	4.49%	6.32%
pH	report value	5.5		4.09

Figure 8

Table 7: Formulation composition of the blend Drug Product.

	Component	Composition	Quantity as active components
CXA-201 Comp.	**CXA-101 for Injection Bulk (25 g)**	CXA-101	10.8 g
		L-Arginine	6.7 g
		Citric acid	233 mg
		Sodium chloride	5.2 g
	Tazobactam sodium sterile Bulk (6 g)		5.4 g (as Tazo free acid)

Figure 9A

Table 8: Stability data of Blending Combo Drug Product at 25 °C/RH=60%.

Test items	Specifications	T0	T1 25°C	T2 25°C
Related Substances				
-Peak1	≤ 1.50%	0.61%	0.93%	1.08%
-Peak2	≤ 0.40%	<0.03%	<0.03%	<0.03%
-Peak3	≤ 0.30%	<0.03%	<0.03%	<0.03%
-Peak4	≤ 0.80%	0.03%	0.03%	0.04%
-Peak5	≤ 1.00%	0.09%	0.12%	0.13%
-Peak6	≤ 0.15%	<0.03%	<0.03%	<0.03%
-Peak7	≤ 2.00%	1.28%	1.34%	1.35%
-Peak8	≤ 0.15%	<0.03%	<0.03%	<0.03%
-Peak9	≤ 0.60%	0.03%	<0.03%	0.03%
-Peak10,11	≤ 0.30%	<0.03%	0.04%	0.05%
Sing. Unk.	≤ 0.15%	0.13%	0.13%	0.14%
Total	≤ 5.00%	2.49%	3.03%	3.28%
Assay CXA-101	Teor. %=32.6%	32.5%	n.a.	n.a.
Assay Tazobactam	Teor. %=17.4%	18.2%	n.a.	n.a.
Tazobactam Related Compound A	≤ 4.0%	0.07%	0.12%	0.14%
K.F.	≤ 4.0%	2.6%	n.a.	n.a.
pH	5.0-7.0	6.0	5.6	5.1

Figure 9B

Table 9: Stability data of Blending Combo Drug Product at 40 °C/RH=75%.

Test items	Specifications	T0	T1 40°C	T2 40°C
Related Substances				
-Peak1	≤ 1.50%	0.61%	1.66%	2.28%
-Peak2	≤ 0.40%	<0.03%	<0.03%	<0.03%
-Peak3	≤ 0.30%	<0.03%	<0.03%	0.04%
-Peak4	≤ 0.80%	0.03%	0.04%	0.05%
-Peak5	≤ 1.00%	0.09%	0.13%	0.14%
-Peak6	≤ 0.15%	<0.03%	<0.03%	<0.03%
-Peak7	≤ 2.00%	1.28%	1.41%	1.46%
-Peak8	≤ 0.15%	<0.03%	<0.03%	<0.03%
-Peak9	≤ 0.60%	0.03%	<0.03%	0.03%
-Peak10,11	≤ 0.30%	<0.03%	0.08%	0.09%
Sing. Unk.	≤ 0.15%	0.13%	0.14%	0.13%
Total	≤ 5.00%	2.49%	4.21%	5.27%
Assay CXA-101	Teor. %=32.6%	32.5%	n.a.	n.a.
Assay Tazobactam	Teor. %=17.4%	18.2%	n.a.	n.a
Tazobactam Related Compound A	≤ 4.0%	0.07%	0.35%	0.54%
K.F.	≤ 4.0%	2.6%	n.a.	n.a.
pH	5.0-7.0	6.0	5.0	4.4

CEFTOLOZANE-TAZOBACTAM PHARMACEUTICAL COMPOSITIONS

RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Patent Application No. 61/792,092, filed Mar. 15, 2013, and U.S. Provisional Patent Application No. 61/793,007, filed Mar. 15, 2013, both of which are incorporated herein in their entirety.

TECHNICAL FIELD

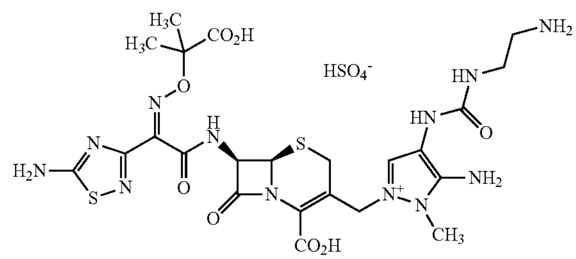
[0002] This disclosure relates to antibacterial compositions comprising ceftolozane and tazobactam.

BACKGROUND

[0003] The pharmaceutical antibiotic composition comprising ceftolozane and tazobactam in a 2:1 weight ratio of ceftolozane active to tazobactam active ("CXA-201") displays potent antibacterial activity, including antibiotic activity against infections caused by many Gram-negative pathogens such as *Pseudomonas aeruginosa* (*P. aeruginosa*), *Escherichia coli* (*E. coli*), *Klebsiella pneumonia* (*K. pneumonia*). In particular, CXA-201 is a pharmaceutical composition useful for intravenous administration for the treatment of complicated intra-abdominal infections and/or complicated urinary tract infections, and is being evaluated for treatment of pneumonia.

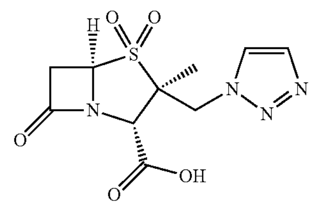
[0004] Ceftolozane is a cephalosporin antibacterial agent, also referred to as CXA-101, FR264205, or by chemical names such as (6R,7R)-3-[(5-amino-4-{[(2-aminoethyl)carbamoyl]amino}-1-methyl-1H-pyrazol-2-ium-2-yl)methyl]-7-({(2Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-[(1-carboxy-1-methylethoxy)imino]acetyl}amino)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate, and 7β-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(1-carboxy-1-methylethoxyimino)acetamido]-3-{3-amino-4-[3-(2-aminoethyl)ureido]-2-methyl-1-pyrazolio}methyl-3-cephem-4-carboxylate. The antibacterial activity of ceftolozane is believed to result from its interaction with penicillin binding proteins (PBPs) to inhibit the biosynthesis of the bacterial cell wall which acts to stop bacterial replication. Ceftolozane sulfate is a pharmaceutically acceptable ceftolozane salt of formula (I) that can be formulated for intravenous administration or infusion.

(I)



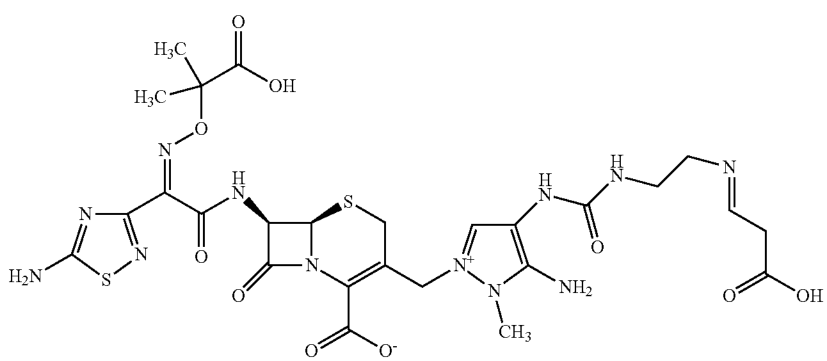
[0005] In CXA-201, ceftolozane is combined with the β-lactamase inhibitor ("BLI") tazobactam. Tazobactam is a BLI against Class A and some Class C β-lactamases, with well-established in vitro and in vivo efficacy in combination with active β-lactam antibiotics. Tazobactam can be combined with ceftolozane as a free acid tazobactam form of formula (II).

(II)



[0006] Pharmaceutical compositions comprising one or more drug substances can be prepared by lyophilization of a solution containing the drug substance(s). Lyophilization is a process of freeze-drying in which water is sublimed from a frozen solution of one or more solutes. Specific methods of lyophilization are described in Remington's Pharmaceutical Sciences, Chapter 84, page 1565, Eighteenth Edition, A. R. Gennaro, (Mack Publishing Co., Easton, Pa., 1990). It has now been found and reported herein that compositions formed by lyophilizing ceftolozane and tazobactam through co-lyophilization, (i.e., the ceftolozane and tazobactam were combined and lyophilized together in Example 3, as opposed to separately) resulted in the formation of significant amounts of an undesired by-product represented by formula (III) (See Example 5 and the results reported in Tables 5 and 6 in FIGS. **7**A and **7**B).

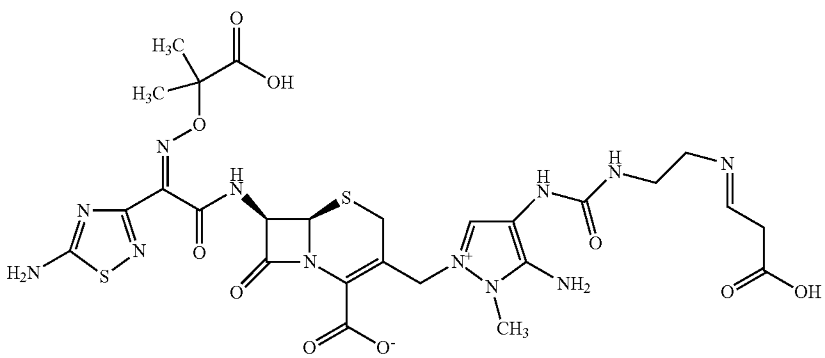
(III)



[0007] Therefore, there remains a need for compositions comprising ceftolozane and/or tazobactam with reduced or even undetectable amounts (e.g., less than about 0.03% by high performance liquid chromatography, or "HPLC") of the compound of formula (III) and methods for manufacturing these compositions.

SUMMARY

[0008] Applicants have discovered pharmaceutical compositions comprising ceftolozane and tazobactam with reduced and even undetectable amounts of the compound of Formula (III), and methods of manufacturing these compositions. The invention is based in part on the discovery that the formation of the compound represented by Formula (III) can be reduced if not completely suppressed by lyophilizing ceftolozane in the absence of tazobactam and then blending the lyophilized ceftolozane with a dry tazobactam composition, such as a tazobactam composition lyophilized in the absence of ceftolozane (See Example 6 and the results reported in Tables 8 and 9 in FIGS. 9A and 9B). Based on these results, pharmaceutical compositions comprising ceftolozane and tazobactam, and pharmaceutical compositions prepared using ceftolozane and tazobactam are provided herein. In particular, these pharmaceutical compositions can include ceftolozane and/or tazobactam with reduced or even undetectable amounts of a compound of formula (III).



(III)

[0009] In one embodiment, a pharmaceutical composition can include ceftolozane and tazobactam with less than 0.15%, 0.10%, 0.05% or 0.03% by weight; or from 0.03-0.05%, 0.03-0.1% or 0.03-0.15% by HPLC or even undetectable amounts of the compound of formula (III) (e.g., less than about 0.03% of the compound of Formula (III) measured by HPLC). These pharmaceutical compositions can be obtained by a process comprising the steps of (a) lyophilizing ceftolozane in the absence of tazobactam to obtain a lyophilized ceftolozane composition; and (b) combining the lyophilized ceftolozane with tazobactam under conditions suitable to obtain said pharmaceutical composition with the aforementioned purity levels. The combination of the lyophilized ceftolozane composition with tazobactam can include blending the lyophilized ceftolozane composition with lyophilized or crystalline tazobactam material.

[0010] In one aspect, provided herein is a pharmaceutical composition comprising a blend of separately lyophilized tazobactam and ceftolozane sulfate in an amount providing 1,000 mg of ceftolozane active per 500 mg of tazobactam active, further comprising less than 0.15%, 0.10%, 0.05% or 0.03% by weight; from 0.03-0.05%, 0.03-0.1% or 0.03-0.15% by HPLC; or even undetectable amounts (e.g., less than about 0.03% by HPLC) of a compound of formula (III) detectable at a retention time relative to ceftolozane of 1.22 by high performance liquid chromatography (HPLC) using a Develosil column ODS-UG-5; 5 micrometers; 250×4.6 mm, a mobile phase of sodium perchlorate buffer solution (pH 2.5)/CH_3CN 90:10 (v/v) at a 1.0 mL/min flow rate and oven temperature of 45° C. (hereinafter referred to as the "method of Example 2").

[0011] CXA-201 compositions comprising less than about 0.15%, 0.10%, 0.05% or 0.03% by weight; or from 0.03-0.05%, 0.03-0.1% or 0.03-0.15% by HPLC of the compound of formula (III) can be obtained by a process comprising the steps of: (a) forming a first aqueous solution comprising ceftolozane (e.g., in a pharmaceutically acceptable salt such as formula (I)), (b) lyophilizing the first aqueous solution to obtain a lyophilized ceftolozane composition, and (c) blending the lyophilized ceftolozane composition with a tazobactam composition (e.g., tazobactam acid lyophilized in the absence of ceftolozane) in an amount that provides a 2:1 weight ratio between the amount of ceftolozane active and tazobactam active.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] FIGS. 1A and 1B are chromatograms of CXA-101 ceftolozane drug substance obtained from the lyophilization process of Example 1. The chromatograms were obtained according to the analytical method described in Example 2.

[0013] FIG. 2 is a diagram of a lyophilization process for the ceftolozane obtained according to the process described in Example 1.

[0014] FIG. 3 is a table (Table 1) of peaks for the ceftolozane prepared by the lyophilization process in Example 1 obtained by HPLC according to the analytical method of Example 2.

[0015] FIG. 4A is a schematic showing a process for making the compound of formula (III) with ceftolozane and tazobactam.

[0016] FIG. 4B is a table (Table 2) showing a first composition that can be lyophilized to form a composition comprising the compound of formula (III).

[0017] FIG. 5 is a table (Table 3) showing in-process testing of blending samples of bulk drug product at five places.

[0018] FIG. 6 is a table (Table 4) of the composition of the formulation used to prepared the Co-Lyophilized Combo drug product used in Example 5.

[0019] FIG. 7A is a table (Table 5) of the impurity composition of the Co-Lyophilized Combo drug product at T_0 (time zero), T_1 (one month) and T_2 (three months) after being maintained at 25° C./60% relative humidity.

[0020] FIG. 7B is a table (Table 6) of the impurity composition of the Co-Lyophilized Combo drug product at T_0 (time zero), T_1 (one month) and T_2 (three months) after being maintained at 40° C./75% relative humidity.

[0021] FIG. 8 is a table (Table 7) of the composition of the formulation used to prepare the Blended Combination drug product used in Example 6.

[0022] FIG. 9A is a table (Table 8) of the impurity composition of the Blended Combination drug product at T_0 (time zero), T_1 (one month) and T_2 (three months) after being maintained at 25° C./60% relative humidity.

[0023] FIG. 9B is a table (Table 9) of the impurity composition of the Blended Combination drug product at T_0 (time zero), T_1 (one month) and T_2 (three months) after being maintained at 40° C./75% relative humidity.

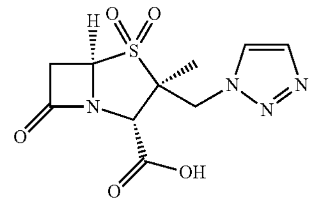
DETAILED DESCRIPTION

[0024] Pharmaceutical compositions comprising ceftolozane and tazobactam with reduced or even undetectable levels of the compound of formula (III) (e.g., including levels of compound of formula (III) that are not detectable by HPLC according to Example 2 and/or comprise less than 0.15%, 0.10%, 0.05% or 0.03% by weight; or from 0.03-0.05%, 0.03-0.1% or 0.03-0.15% by HPLC according to Example 2) can be obtained by blending a first composition comprising a therapeutically effective amount of ceftolozane in the absence of tazobactam with a second composition comprising a therapeutically effective amount of tazobactam in the absence of ceftolozane to form a blended pharmaceutical composition.

[0025] The (first) ceftolozane composition can be prepared in the absence of tazobactam by forming a first aqueous solution comprising ceftolozane sulfate and other components including excipients, stabilizers, pH adjusting additives (e.g., buffers) and the like. Non-limiting examples of these additives include sodium chloride, citric acid and L-arginine. For example, the use of sodium chloride results in greater stability; L-arginine is used to adjust the aqueous solution to a pH of 5-7 (e.g., to pH 6-7) and to increase the solubility of ceftolozane; and citric acid is used to prevent discoloration of the product, due to its ability to chelate metal ions. In one embodiment, the pH of the first aqueous solution is suitable for making an injectable product (e.g., a pH range of 5-7, including 6-7). Preferably, the first aqueous solution comprises about 125 mg-500 mg sodium chloride per 1,000 mg of ceftolozane active. The ceftolozane can be included as an amount of ceftolozane sulfate of formula (I) containing at least about 1,000 mg ceftolozane active. The (first) aqueous solution is then lyophilized to form a first lyophilized ceftolozane composition, which is combined with tazobactam, e.g., the lyophilized tazobactam (e.g., lyophilized tazobactam sodium) or crystalline tazobactam

[0026] The (second) tazobactam composition can be prepared in the absence of ceftolozane by forming a second solution comprising tazobactam. The tazobactam can be included in an amount providing about 500 mg of tazobactam active per 1,000 mg ceftolozane active (i.e., a 1:2 weight ratio of tazobactam active to ceftolozane active). Tazobactam is a β-lactamase inhibitor of the structure of formula (II) in its free acid form.

(II)



[0027] Unless otherwise indicated, tazobactam can be a free acid, a sodium salt, an arginine salt, or a hydrate or solvate thereof. In one embodiment, the tazobactam in the (second) tazobactam composition is tazobactam acid and the second composition further comprises sodium bicarbonate or sodium hydroxide. Lyophilizing tazobactam in the presence of sodium bicarbonate or sodium hydroxide forms a lyophilized tazobactam sodium, which can then be further blended with the (first) lyophilized ceftolozane composition.

[0028] Pharmaceutical compositions with reduced or undetectable amounts of the compound of formula (III) can be obtained by lyophilizing ceftolozane without formylacetic acid and/or tazobactam under conditions that prevent formation of the compound of formula (III) (e.g., Example 1 and 4). The presence of a compound of formula (III) can be detected by HPLC (e.g., Examples 2, 5 and 6). Specific methods of lyophilization are described in Example 1 and Remington's Pharmaceutical Sciences, Chapter 84, page 1565, Eighteenth Edition, A. R. Gennaro, (Mack Publishing Co., Easton, Pa., 1990). The formation of the compound of formula (III) can be avoided by preventing the reaction of ceftolozane and formylacetic acid. In one embodiment, the compound of formula (III) can be suppressed by separately lyophilizing ceftolozane sulfate and tazobactam in separate solutions, and then blending the lyophilized compositions to form a pharmaceutical composition.

[0029] In one aspect, antibiotic pharmaceutical compositions comprising ceftolozane and tazobactam with less than about 0.15%, 0.10%, 0.05% or 0.03% by weight; or from 0.03-0.05%, 0.03-0.1% or 0.03-0.15% by HPLC of the compound of formula (III) are obtained by a process comprising the steps of: (a) lyophilizing ceftolozane in the absence of tazobactam to obtain a lyophilized ceftolozane composition, and (b) blending the lyophilized ceftolozane composition with a composition comprising tazobactam under conditions suitable for attaining the aforementioned purity levels, e.g., by blending with crystalline tazobactam or lyophilized tazobactam.

[0030] In another aspect, antibiotic pharmaceutical compositions comprising ceftolozane and tazobactam and less than about 0.15%, 0.10%, 0.05% or 0.03% by weight; or from 0.03-0.05%, 0.03-0.1% or 0.03-0.15% by HPLC of the compound of formula (III) are obtained by a process comprising the steps of: (a) lyophilizing tazobactam in the absence of ceftolozane to obtain a lyophilized tazobactam composition, and (b) blending the lyophilized tazobactam composition with a composition comprising ceftolozane (e.g., lyophilized ceftolozane sulfate).

[0031] In a third aspect, antibiotic pharmaceutical compositions comprising ceftolozane and tazobactam and less than about 0.15%, 0.10%, 0.05% or 0.03% by weight; or from 0.03-0.05%, 0.03-0.1% or 0.03-0.15% by HPLC of the compound of formula (III) are obtained by a process comprising the steps of: (a) lyophilizing tazobactam in the absence of ceftolozane to obtain a lyophilized tazobactam composition, (b) lyophilizing ceftolozane in the absence of tazobactam to obtain a lyophilized ceftolozane composition, and (c) blending the lyophilized tazobactam composition with the lyophilized ceftolozane composition.

[0032] Pharmaceutical compositions comprising the compound of formula (III), ceftolozane and tazobactam can be formulated to treat infections by parenteral administration (including subcutaneous, intramuscular, and intravenous) administration. Pharmaceutical compositions may additionally comprise excipients, stabilizers, pH adjusting additives (e.g., buffers) and the like. Non-limiting examples of these additives include sodium chloride, citric acid and L-arginine. For example, the use of sodium chloride results in greater stability; L-arginine is used to adjust pH and to increase the solubility of ceftolozane; and citric acid is used to prevent discoloration of the product, due to its ability to chelate metal ions. In one particular embodiment, the pharmaceutical compositions described herein are formulated for administration by intravenous injection or infusion.

[0033] Other pharmaceutical antibiotic compositions can include ceftolozane sulfate and the compound of formula (III). For example, pharmaceutical compositions comprising 0.13%, 0.15%, 0.30%, 0.38%, 0.74% or 0.97% of the compound of formula (III) are herein. The pharmaceutical antibiotic compositions can be provided in a unit dosage form (e.g., in a vial). The unit dosage form can be dissolved with a pharmaceutically acceptable carrier, and then intravenously administered. The unit dosage form comprises 1000 mg of ceftolozane active and 500 mg tazobactam, typically 1000 mg ceftolozane active as ceftolozane sulfate and 500 mg of tazobactam active as tazobactam sodium, argininate or free acid. The unit dosage forms are commonly stored in vials.

[0034] In one aspect, provided herein is a unit dosage form container (e.g., a bag, vial or the like) containing a unit dosage form of a pharmaceutical composition formulated for parenteral administration for the treatment of complicated intra-abdominal infections or complicated urinary tract infections, the pharmaceutical composition comprising a therapeutically effective amount of ceftolozane sulfate and tazobactam in a ratio of 1,000 mg ceftolozane active per 500 mg of tazobactam active, the pharmaceutical composition obtained by a process comprising the steps of:

[0035] a. lyophilizing a first aqueous solution in the absence of tazobactam, the first aqueous solution comprising ceftolozane sulfate, 125 mg to 500 mg of sodium chloride per 1,000 mg of ceftolozane active, L-arginine and/or citric acid in an amount effective to adjust the pH of the first aqueous solution to 5-7 (e.g., 6-7) prior to lyophilization to obtain a first lyophilized ceftolozane composition,

[0036] b. lyophilizing a second solution in the absence of ceftolozane, the second solution comprising tazobactam being lyophilized to form a second lyophilized tazobactam composition; and

[0037] c. blending the first lyophilized ceftolozane composition and the second lyophilized tazobactam composition to obtain a blended pharmaceutical composition in the unit dosage form.

[0038] In one embodiment of the unit dosage form container, the tazobactam in the second solution is tazobactam acid, and wherein the tazobactam acid in the second solution is lyophilized in the presence of sodium bicarbonate or sodium hydroxide, thereby forming lyophilized tazobactam sodium in the second lyophilized tazobactam solution. A pharmaceutical composition can include ceftolozane sulfate and tazobactam in an amount providing 1,000 mg of ceftolozane active per 500 mg of tazobactam active, and 0.03% to 0.15% by HPLC of a compound of formula (III) detectable at a retention time relative to ceftolozane of 1.22 by high performance liquid chromatography using a Develosil column ODS-UG-5; 5 micrometers; 250×4.6 mm, a mobile phase of sodium perchlorate buffer solution (pH 2.5)/CH_3CN 90:10 (v/v) at a 1.0 mL/min flow rate and oven temperature of 45° C. Optionally, the pharmaceutical composition can further include 125 mg to 500 mg of sodium chloride per 1,000 mg of ceftolozane active, and L-arginine. The tazobactam in the composition can be tazobactam sodium.

[0039] The pharmaceutical compositions provided herein comprising ceftolozane sulfate and tazobactam in a ratio of 1,000 mg ceftolozane active per 500 mg of tazobactam active, can be obtained by a process comprising the steps of:

[0040] a. lyophilizing a first aqueous solution in the absence of tazobactam, the first aqueous solution comprising ceftolozane sulfate at a pH of 5-7 (e.g, 6-7) prior to lyophilization to obtain a first lyophilized ceftolozane composition,

[0041] b. blending the first lyophilized ceftolozane composition with tazobactam to obtain an antibacterial composition.

[0042] The pharmaceutical compositions can be administered for the treatment of infections, such as complicated intra-abdominal infections, complicated urinary tract infections (cUTIs) and pneumonia (e.g., community-acquired, hospital-acquired, etc). In one aspect, provided herein is a method for the treatment of bacterial infections in a mammal, comprising administering to said mammal a therapeutically effective amount of a pharmaceutical composition prepared according to the methods described herein. A method for the treatment of bacterial infections in a mammal can comprise administering to said mammal a therapeutically effective amount of a pharmaceutical composition comprising ceftolozane sulfate and sodium chloride.

[0043] Non-limiting examples of bacterial infections that can be treated by the methods of the invention include infections caused by: aerobic and facultative gram-positive microorganisms (e.g., *Staphylococcus aureus, Enterococcus faecalis, Staphylococcus epidermidis, Streptococcus agalactiae, Streptococcus pneumonia, Streptococcus pyogenes, Viridans* group *streptococci*), aerobic and facultative gram-negative microorganisms (e.g., *Acinetobacter baumanii, Escherichia coli, Haemophilus influenza, Klebsiella pneumonia, Pseudomonas aeruginosa, Citrobacter koseri, Moraxella catarrhalis, Morganella morganii, Neisseria gonorrhoeae, Proteus mirabilis, Proteus vulgaris, Serratia marcescens, Providencia stuartii, Providencia rettgeri, Salmonella enterica*), gram-positive anaerobes (*Clostridium perfringens*), and gram-negative anaerobes (e.g., *Bacteroides fragilis* group (e.g., *B. fragilis, B. ovatus, B. thetaiotaomicron*, and *B. vulgates*), *Bacteroides distasonis, Prevotella melaninogenica*).

[0044] In certain embodiments of the methods described herein, bacterial infection is associated with one or more of the following conditions: complicated intra-abdominal infections, complicated urinary tract infections (cUTIs) and pneumonia (e.g., community-acquired, or nosocomial pneumonia). Community-acquired pneumonia (moderate severity only) can include infections caused by piperacillin-resistant, beta-lactamase producing strains of *Haemophilus influenza*. Nosocomial pneumonia (moderate to severe) caused by piperacillin-resistant, beta-lactamase producing strains of *Staphylococcus aureus* and by *Acinetobacter baumanii, Haemophilus influenzae, Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*.

[0045] As used herein, "treating", "treat" or "treatment" describes the management and care of a patient for the purpose of combating a disease, condition, or disorder and includes the administration of a pharmaceutical composition of the present invention to alleviate the symptoms or complications of a disease, condition or disorder, or to reduce the extent of the disease, condition or disorder. The term "treat" can also include treatment of a cell in vitro or an animal model.

[0046] By a "therapeutically effective amount" of a compound of the invention is meant a sufficient amount of the compound to treat the disorder (e.g., bacterial infection). The specific therapeutically effective amount that is required for the treatment of any particular patient or organism (e.g., a mammal) will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound or composition employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts (see, for example, Goodman and Gilman's, "The Pharmacological Basis of Therapeutics", Tenth Edition, A. Gilman, J. Hardman and L. Limbird, eds., McGraw-Hill Press, 155-173, 2001, which is incorporated herein by reference in its entirety). The therapeutically effective amount for a given situation can be readily determined by routine experimentation and is within the skill and judgment of the ordinary clinician.

[0047] As used herein, the term "ceftolozane active" refers to active portion of a salt form of ceftolozane in the free base form of ceftolozane.

[0048] As used herein, the term "tazobactam active" refers to the active portion of a salt form of tazobactam in the tazobactam free acid form.

[0049] As used herein, "1,000 mg of ceftolozane as ceftolozane active" refers to an amount of ceftolozane sulfate effective to provide 1,000 mg of ceftolozane active. The amount of sodium chloride per gram of ceftolozane activity in a pharmaceutical composition containing ceftolozane sulfate and sodium chloride can be calculated using the relevant molecular weights of ceftolozane, ceftolozane sulfate, sodium chloride and sodium. As used herein, "500 mg of tazobactam as tazobactam active" refers to an amount of tazobactam sodium or tazbactam arginine effective to provide 500 mg of tazobactam active.

[0050] As used herein, references to an amount of a substance as "% of the compound of . . . " or "% by HPLC" (unless otherwise indicated) refer to the % of a compound detected by high performance liquid chromatography (HPLC) according to the method of Example 2.

ILLUSTRATIVE EXAMPLES OF SELECTED EMBODIMENTS OF THE INVENTION

Example 1

Manufacturing Procedure of Bulk (Tray) Lyophilized Ceftolozane

[0051] There are four main steps in the manufacture of CXA-101 bulk drug product: dissolution, sterile filtration, bulk lyophilization, and packaging into Sterbags®. These four main steps are composed of a total of 20 minor steps. The CXA-101 bulk drug product manufacturing process is presented below.

I. Dissolution

[0052] 1. The prescribed amount of water for injection ("WFI") is charged into the dissolution reactor.
[0053] 2. A prescribed amount of citric acid is added.
[0054] 3. The solution is cooled at 5° C. to 10° C.
[0055] 4. A prescribed amount of CXA-101 drug substance is added to the solution.
[0056] 5. A prescribed amount of L-arginine is slowly added to the solution.
[0057] 6. A check for complete dissolution is performed. Solution pH is verified to be in the target range of 6.5 to 7.0.
[0058] 7. A prescribed amount of sodium chloride is added to the solution.
[0059] 8. A check for complete dissolution is performed. Solution pH is verified to be in the target range of 6.0 to 7.0. If the pH is out of this range adjust with either L-Arginine or citric acid.
[0060] 9. WFI is added to bring the net weight to 124.4 kg and the solution is mixed well.
[0061] 10. Samples are withdrawn for testing of final pH.

II. Sterile Filtration

[0062] 11. The solution is passed through the filter (pore size 0.45 μm) followed by double filters (pore size 0.22 μm) onto a shelf on the Criofarma lyophilizer.
[0063] 12. The line is washed with WFI.
[0064] 13. The washing solution is passed from Step 12 through sterile filtration.

III. Bulk Lyophilization

[0065] 14. The washing solution is loaded onto a separate shelf in the lyophilizer (and later discarded).
[0066] 15. The solution is lyophilized until dry.
[0067] 16. The product shelf is cooled to 20° C.±5° C.
IV. Packaging into Sterbags®
[0068] 17. The lyophilized bulk drug product powder is milled.
[0069] 18. The milled powder is sieved.
[0070] 19. The sieved powder is blended for 30 minutes.
[0071] 20. The powder is then discharged into Sterbags®

Prefiltration and Sterile-Filtration

[0072] Filtrate the compounded solution with a sterile tilter-set which consists of a 0.2 um polyvinylidene fluoride membrane filter (Durapore®, Millipore) and a 0.1 urn polyvinylidene fluoride membrane filter (Durapore®, Millipore) connected in tandem. Confirm the integrity of each filter before and after the filtration. Take approximately 100 mL of the filtrate in order to check bioburden.

[0073] Filter the prefiltered compounded solution through a sterile filter-set which consists of a 0.2 um polyvinylidene fluoride membrane filter and a 0.1 urn polyvinylidene fluoride membrane filter connected in tandem, and introduce the final filtrate into an aseptic room. Confirm the integrity of each filter before and after the filtration.

Processing of Vial, Stopper and Flip-Off Cap

[0074] Wash a sufficient quantity of 28 mL vials with water for injection and sterilize the washed vials by a dry-heat sterilizer. Then transfer the sterilized vials into a Grade A area located in an aseptic room.

[0075] Wash a sufficient quantity of stoppers with, water for injection. Sterilize and dry the washed stoppers by steam sterilizer. Then transfer the sterilized stoppers into a Grade A area located in an aseptic room.

[0076] Sterilize a sufficient quantity of flip-off caps by steam sterilizer. Then transfer the sterilized flip-off caps into a Grade A or B area located in an aseptic room.

Filling and Partially Stoppering

[0077] Adjust the fill weight of the filtered compounded solution to 11.37 g (corresponds to 10 mL of the compounded solution), then start filling operation. Check the filled weight in sufficient frequency and confirm it is in target range (11.37 g±1%, 11.26 to 11.43 g). When deviation from the control range (11.37 g±2%, 11.14 to 11.59 g) is occurred, re-adjust the filling weight.

[0078] Immediately after a vial is filled, partially stopper the vial with a sterilized stopper. Load the filled and partially stoppered vials onto the shelves of a lyophilizer aseptically.

Lyophilization to Crimping, Visual Inspection, Labeling and Packaging

[0079] After all filled and partially stoppered vials are loaded into a lyophilizer, start the lyophilization program shown in FIG. **2**. Freeze the loaded vials at −40° C. and keep until all vials freeze. Forward the program to primary drying step (shelf temperature; −20° C., chamber pressure; 100 to 150 mTorr). Primary drying time should be determined by monitoring the product temperature. Forward the program to secondary drying step (shelf temperature; 30° C., chamber pressure; not more than 10 mTorr) after completion of the primary drying step. After all vials are dried completely, return the chamber pressure to atmospheric pressure with sterilized nitrogen. Then stopper vials completely.

[0080] Unload the lyophilized vials from the chamber and crimp with sterilized flip-off caps.

[0081] Subject all crimped vials to visual inspection and label and package all passed vials.

Example 2

Analytical HPLC Method

A. Operative Conditions

[0082]

Column	Develosil ODS-UG-5; 5 μm, 250 × 4.6 mm (Nomura Chemical, Japan)		
Mobile phase	Sodium Perchlorate Buffer Solution (PH 2.5)/ CH_3CN 90: 10 (vlv)		
Flow rate	1.0 mL/min		
Wavelength	254 nm		
Injection volume	10 μL		
Oven Temperature	45° C.		
Run Time	85 minutes		
Gradient Profile:	Time (min)	A %	B %
	0	75	25
	30	70	30
	60	0	100
	85	0	100
	85.1	75	25
	110	75	25

B. Mobile phase preparation.

[0083] Sodium Perchlorate Buffer Solution was made by dissolving 14.05 g of sodium perchlorate Monohydrate in 1000.0 mL of water followed by adjusting pH to 2.5 with diluted perchloric acid (1 in 20).

[0084] Mobile Phase was then made by mixing Sodium Perchlorate Buffer Solution (pH 2.5) and acetonitrile in the ratio 90:10 (v/v).

[0085] Sodium Acetate Buffer Solution pH 5.5 (Diluent) was made by dissolving 1.36 g of sodium acetate trihydrate in 1000.0 mL of water followed by adjusting to pH 5.5 with diluted acetic acid (1 in 10).

C. Sample Preparation.

[0086] Sample solution: dissolve 20.0 mg, exactly weighed, of Sample, in 20.0 mL of water (Prepare just before injection into HPLC system).

[0087] System Suitability Solution (1%): take 1.0 mL of the Sample Solution (use first sample if more are present) and transfer into a 100.0 mL volumetric flask, dilute with water to volume and mix.

D. HPLC Analysis Procedure

[0088] 1. Inject Blank (water)

2. Inject System Suitability Solution and check for tailing factor and theoretical plate number for CXA-101 peak:

[0089] The tailing factor must not be greater than 1.5

[0090] Theoretical plates number must not be less than 10000

3. Inject Sample Solution

[0091] 4. Inject System Suitability Solution and check for tailing factor and theoretical plate number for CXA-101 peak.

[0092] The tailing factor must not be greater than 1.5

[0093] Theoretical plates number must not be less than 10000

5. Identify the peaks of Related Substances in the Sample chromatogram based on the reference chromatogram reported in FIGS. **1**A and **1**B or, alternatively, on the basis of the RRT values reported in Table 1 (FIG. **3**)

E. Calculations

[0094] I. Report for each related substance its amount as expressed by area percent.

$$C_i = \frac{A_i \times 100}{A_t + \sum A_i}$$

[0095] wherein:

[0096] C_i=Amount of related substance i in the Sample, area %

[0097] A_i=Peak area of related substance i in the Sample chromatogram

[0098] A_t=Area of CXA-101 peak in the Sample chromatogram

[0099] $A_t+\Sigma A_i$=Total peaks area in the Sample chromatogram

[0100] Consider as any Unspecified Impurity, each peak in the chromatogram except CXA-101, peaks from 1 to 11 and every peak present in the blank chromatogram and report the largest.

II. Report the total impurities content as expressed by the following formula:

$$C_T = \frac{A_i \times 100}{A_t + \sum A_i}$$

[0101] wherein:

[0102] C_T=total impurities content in the Sample, area %

[0103] A_r=area of CXA-101 peak in the sample chromatogram

[0104] ΣA_i=total peak areas of impurities in the sample chromatogram

Example 3

Manufacturing of Combination Product (Tazobactam and Ceftolozane) Comprising a Compound of Formula (III) by Co-Lyophilization

[0105] Compositions comprising the compound of formula (III) were prepared by the process shown in FIG. **4**A by (a) forming an aqueous solution comprising the components in Table 2 (FIG. **4**B), and (b) lyophilizing the aqueous solution. Sodium content was approximately 78 mg/g of tazobactam in drug product after lyophilization. Water was removed during the lyophilization process and is controlled at no more than 4% by HPLC.

Example 4

Manufacturing of Combination Product (Tazobactam and CXA-101) without HPLC-Detectable Amounts of the Compound of Formula (III) by Blending

Sterile Dry Blending of Bulk Lyophilized Ceftolozane and Bulk Lyophilized Tazobactam

[0106] The CXA-101 produced by Example 1 is blended with lyophilized tazobactam. A low energy drum blender that agitates the material by tumbling and also moving the bed up and down is used. A representative process of blending is described according to the table in FIG. **5**. The table in FIG. **5** shows in-process testing of blending samples of bulk drug product at five places. For CXA-101/tazobactam for injection, the blender was charged with 23.4 kg of CXA-101 bulk product, and 5.4 kg of tazobactam bulk product. Both the CXA-101 and tazobactam were individually lyophilized beforehand. The material was blended for 180 minutes. In-process tests of content assay for both CXA-101 and tazobactam were performed to assess the homogeneity using the samples of blend materials taken from three places. The RSD for each of CXA-101 and tazobactam content assay was no greater than 2% and the RSD for the ratio of CXA-101/tazobactam was no greater than 2.2%. (See Table 3 in FIG. **5**).

Example 5

Co-Lyophilization of Ceftolozane and Tazobactam Produces the Compound of Formula (III) (RRT 1.22)

[0107] The Co-Lyophilized Combo Drug Product was prepared as described above in Example 3. The formulation composition of the Co-Lyophilized Combo drug product is shown in FIG. **6** (Table 4). This sample was maintained at 25° C./RH=60% and 40° C./RH=75% after one month (T1) and three months (T2). Samples were analyzed using a HPLC method as described in Example 2. The data for analysis of the samples by HPLC is shown in the tables in FIG. **7**A (Table 5: Stability data of Co-Lyo Combo Drug Product at 25° C.) and FIG. **7**B (Table 6: Stability data Co-Lyo Combo Drug Product at 40° C.). The presence of the compound of Formula (III) was identified has having a retention time of about 1.22 as measured by HPLC (see Example 2). RRT=1.22 was observed in co-lyophilized drug product. The compound of formula (III) is believed to be formed by a reaction between ceftolozane and formylacetic acid, which was a degradation product of tazobactam. The amount of the compound of formula (III) in a composition comprising ceftolozane and tazobactam can be increased over time at 25° C. and at 40° C.

Example 6

Assessment of Blend Combination Drug Product

A. Preparation of Blend Combination Drug Product

[0108] The blend drug product was prepared, as described above in Example 4, on lab scale by use of a small blender. The composition of the blend drug product is shown in Table 7, FIG. **8**. The CXA-101 was obtained by lyophilization of ceftolozane sulfate in the absence of tazobactam, and the tazobactam sodium material was obtained by lyophilization of tazobactam prior to blending of the ceftolozane and tazobactam components.

B. Stress Test

[0109] This sample was put into stability study. The following Tables 8 (FIG. **9**A) and 9 (FIG. **9**B) are representative examples that summarizes the results at 25° C./RH=60% and 40° C./RH=75% after one month (T1) and three months (T2). Samples were analyzed using a HPLC method as described in Example 2.

C. Conclusion

[0110] The data at both 25° C. and at 40° C. have shown that the blending process inhibits formation of amounts of the impurity RRT=1.22 to below the detection limit of the HPLC method of Example 2.

Example 7

Preferred Pharmaceutical Composition Comprising Ceftolozane and Tazobactam

[0111] Pharmaceutical compositions comprising ceftolozane and tazobactam with less than 0.15% (measured by HPLC according to Example 2) of the compound of formula (III) can be obtained as described herein.

TABLE 10

Excipients Used in Ceftolozane composition					
Component	Function	Amount, mg/Vial	Concentration in Infusion Solution, %	Rationale for Inclusion	Inactive Ingredients Database (IID) Range
Citric acid	Chelating agent	21	0.02	Used to prevent discoloration and degradation	0.0025 to 50%
Sodium Chloride	Stabilizing agent	487	0.49	Used as a stabilizing agent for ceftolozane sulfate	0.187 to 45%
L-arginine	Alkalizing agent	600[i)] Q.S. for pH adjustment	0.60	Used to adjust ceftolozane solution pH	0.29 to 88%

[i)]L-arginine is added as needed to achieve pH 6.5 ± 0.5; 600 mg per vial is considered a representative total amount.

TABLE 11

Unit Compositions of Ceftolozane/Tazobactam for Injection, 1000 mg/500 mg			
Component		Function	Nominal Compositionmg per Vial
Ceftolozane composition[1)]	Ceftolozane Sulfate	Active	1147
	Citric Acid, Anhydrous	Chelating Agent	21
	Sodium Chloride	Stabilizing Agent	487
	L-Arginine	Alkalizing Agent	600[2)] Q.S. for pH adjustment
Tazobactam Sodium[3)]		Active	537
Nitrogen		Processing Aid[ii)]	Q.S.
Total Weight			2792

[1)]Actual amount of Ceftolozane composition will vary based on the measured potency. Ceftolozane sulfate, 1147 mg, corresponds to 1000 mg ceftolozane free base.
[2)]L-arginine is added as needed to achieve pH 6.5 ± 0.5; 600 mg per vial is considered a representative total amount.
[3)]Actual weight of tazobactam sodium will vary based on the measured potency. Tazobactam sodium 537 mg, corresponds to 500 mg tazobactam free acid
4) Nitrogen blanket is applied after powders are dispensed to the vial and prior to insertion of stopper.

[0112] A first aqueous solution comprising the ingredients in the Ceftolozane composition in Table 11 is lyophilized in the absence of tazobactam to provide the lyophilized Ceftolozane composition. The first aqueous solution comprises ceftolozane sulfate and the specific excipients in the preferred compositions, in an amount per unit dosage form provided by the quantities and functions as provided in Table 10. All excipients are compendial and typical for sterile pharmaceutical dosage forms, requiring no additional treatment prior to use in the formulation. The excipients are used in levels within the range established in other FDA approved products as described in the Inactive Ingredients Database (IID). A second solution comprising tazobactam acid and sodium bicarbonate is lyophilized in the absence of ceftolozane to obtain the Tazobactam Sodium Composition in Table 11. Subsequently, the lyophilized Tazobactam Sodium Composition is dry blended with the lyophilized Ceftolozane composition comprising tazobactam sodium and ceftolozane sulfate in a weight ratio providing 500 mg of tazobactam acid equivalent per 1,000 mg of ceftolozane active equivalent.

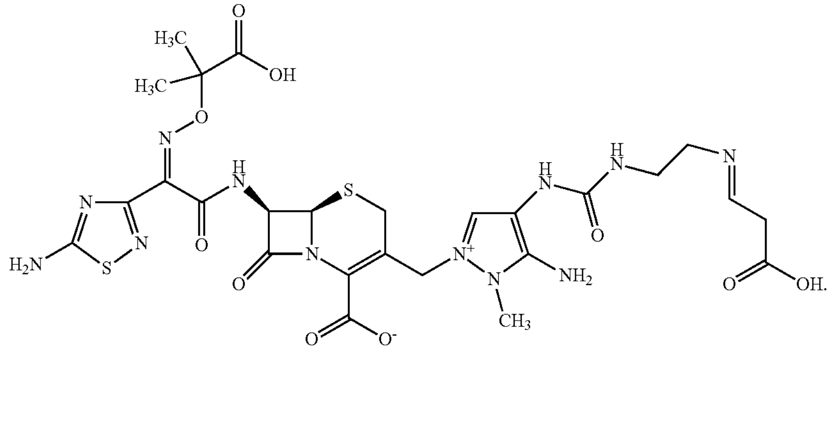
What is claimed is:

1. An antibacterial pharmaceutical composition comprising ceftolozane and tazobactam in a ratio of 1,000 mg ceftolozane active per 500 mg of tazobactam active, the pharmaceutical composition obtained by a process comprising the steps of

a. lyophilizing a first aqueous solution in the absence of tazobactam, the first aqueous solution comprising ceftolozane prior to lyophilization to obtain a first lyophilized ceftolozane composition,

b. blending the first lyophilized ceftolozane composition with tazobactam to obtain an antibacterial composition comprising less than 0.13% by HPLC of a compound of formula (III) detectable at a retention time relative to ceftolozane of 1.22 by high performance liquid chromatography using a Develosil column ODS-UG-5; 5 micrometers; 250×4.6 mm, a mobile phase of sodium perchlorate buffer solution (pH 2.5)/CH_3CN 90:10 (v/v) at a 1.0 mL/min flow rate and oven temperature of 45° C.

(III)



2. The antibacterial composition of claim 1, comprising less than 0.03% of the compound of formula (III) detected by HPLC.

3. The antibacterial composition of claim 1, wherein the first aqueous solution further comprises L-arginine in an amount effective to adjust the pH of the first aqueous solution to 6-7 prior to lyophilization to obtain a first lyophilized ceftolozane composition.

4. The antibacterial composition of claim 1, wherein the antibacterial pharmaceutical composition is obtained by a process further comprising the steps of

a. lyophilizing a second solution comprising tazobactam in the absence of ceftolozane to form a second lyophilized tazobactam composition; and

b. blending the first lyophilized ceftolozane composition and the second lyophilized tazobactam composition to obtain the antibacterial composition.

5. The antibacterial composition of claim 4, wherein the tazobactam in the second solution is tazobactam acid, and wherein the tazobactam acid in the second solution is lyophilized in the presence of sodium bicarbonate to form the second lyophilized tazobactam solution.

6. The antibacterial composition of claim 4, wherein the first aqueous solution comprises L-arginine in an amount effective to provide a pH of about 6-7.

7. The antibacterial composition of claim 4, wherein the first aqueous solution comprises 125 mg to 500 mg of sodium chloride per 1,000 mg of ceftolozane active.

8. The antibacterial composition of claim 7, wherein the first aqueous solution further comprises citric acid.

9. The antibacterial composition of claim 7, wherein the first aqueous solution consists of ceftolozane sulfate, citric acid, sodium chloride, L-arginine, and water.

10. A unit dosage form of a pharmaceutical composition formulated for parenteral administration for the treatment of a complicated intra-abdominal infection or a complicated urinary tract infection, the pharmaceutical composition comprising ceftolozane and tazobactam in a ratio of 1,000 mg ceftolozane active per 500 mg of tazobactam active, the pharmaceutical composition obtained by a process comprising the steps of

a. lyophilizing a first aqueous solution in the absence of tazobactam, the first aqueous solution comprising ceftolozane, 125 mg to 500 mg of sodium chloride per 1,000 mg of ceftolozane active, at a pH of 6-7 prior to lyophilization to obtain a first lyophilized ceftolozane composition,

b. lyophilizing a second solution comprising tazobactam in the absence of ceftolozane to form a second lyophilized tazobactam composition; and

c. blending the first lyophilized ceftolozane composition and the second lyophilized tazobactam composition to obtain the antibacterial composition.

11. The unit dosage form of claim 10, wherein the first aqueous solution consists of ceftolozane sulfate, citric acid, sodium chloride, L-arginine, and water.

12. The unit dosage form of claim 10, wherein the tazobactam in the second solution is tazobactam acid, and wherein the tazobactam acid in the second solution is lyophilized in the presence of sodium bicarbonate to form the second lyophilized tazobactam solution.

13. The unit dosage form of claim 10, wherein the first aqueous solution comprises 125 mg to 500 mg of sodium chloride per 1,000 mg of ceftolozane active.

14. The unit dosage form of claim 13, wherein the first aqueous solution further comprises citric acid.

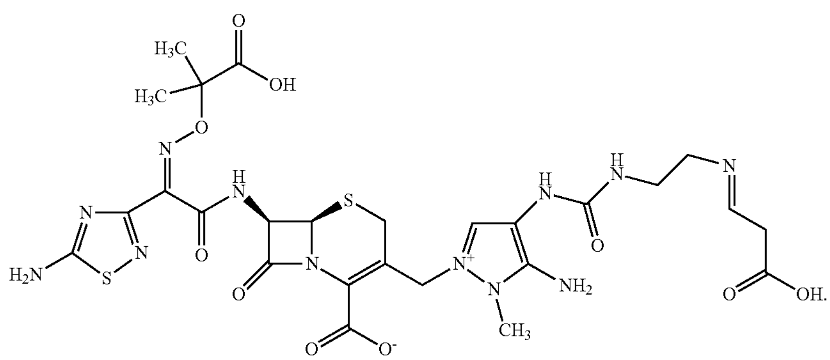
15. The unit dosage form of claim 14, wherein the first aqueous solution consists of ceftolozane sulfate, citric acid, sodium chloride, L-arginine, and water.

16. The unit dosage form of claim 10, comprising a total of 1,000 mg of ceftolozane active.

17. The unit dosage form of claim 16, comprising a total of 500 mg of tazobactam active.

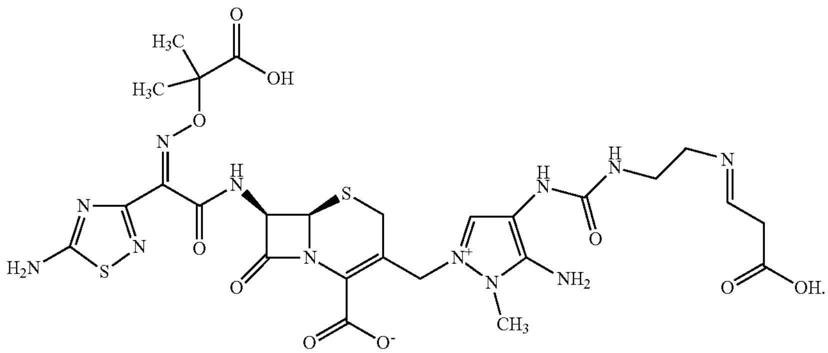
18. The unit dosage form of claim 17, comprising a total of not more than 0.03% by HPLC of a compound of formula (III) detectable at a retention time relative to ceftolozane of 1.22 by high performance liquid chromatography using a Develosil column ODS-UG-5; 5 micrometers; 250×4.6 mm, a mobile phase of sodium perchlorate buffer solution (pH 2.5)/CH_3CN 90:10 (v/v) at a 1.0 mL/min flow rate and oven temperature of 45° C.

(III)



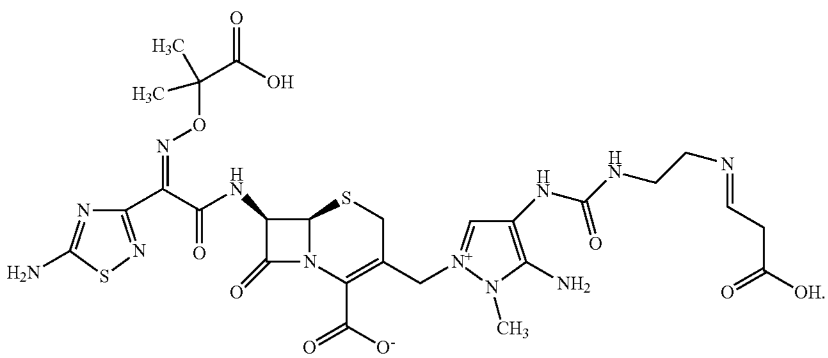
19. The unit dosage form of claim 15, comprising a total of 1,000 mg of ceftolozane active and a total of 500 mg of tazobactam active.

20. The unit dosage form of claim 19, comprising a total of not more than 0.03% by HPLC of a compound of formula (III) detectable at a retention time relative to ceftolozane of 1.22 by high performance liquid chromatography using a Develosil column ODS-UG-5; 5 micrometers; 250×4.6 mm, a mobile phase of sodium perchlorate buffer solution (pH 2.5)/CH_3CN 90:10 (v/v) at a 1.0 mL/min flow rate and oven temperature of 45° C.



(III)

21. A composition comprising lyophilized ceftolozane and tazobactam in a ratio of 1,000 mg ceftolozane active per 500 mg of tazobactam active, and less than 0.13% by HPLC of a compound of formula (III) detectable at a retention time relative to ceftolozane of 1.22 by high performance liquid chromatography using a Develosil column ODS-UG-5; 5 micrometers; 250×4.6 mm, a mobile phase of sodium perchlorate buffer solution (pH 2.5)/CH_3CN 90:10 (v/v) at a 1.0 mL/min flow rate and oven temperature of 45° C.

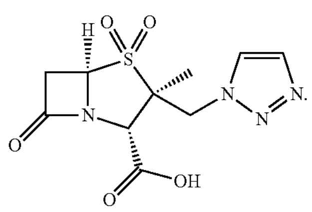


(III)

22. The antibacterial composition of claim **1**, wherein the tazobactam active comprises tazobactam sodium.

23. The antibacterial composition of claim **1**, wherein the tazobactam active comprises crystalline tazobactam.

24. The antibacterial composition of claim **1**, wherein the tazobactam active comprises a compound of formula (II) or a pharmaceutically acceptable salt thereof



(II)

25. The antibacterial composition of claim **1**, wherein the ceftolozane active comprises ceftolozane sulfate.

26. The unit dosage form of claim **10**, wherein the unit dosage form is obtained by a process further comprising dissolving the antibacterial composition comprising the ceftolozane and the tazobactam with a pharmaceutically acceptable carrier to obtain the pharmaceutical composition in a formulation for intravenous administration.

27. The unit dosage form of claim **26**, wherein the ceftolozane comprises ceftolozane sulfate.

28. The unit dosage form of claim **26**, wherein the tazobactam comprises tazobactam sodium.

29. The unit dosage form of claim **10**, wherein the unit dosage form is a vial or a bag.

30. The composition of claim **21**, wherein the composition comprises an amount of a pharmaceutically acceptable salt of ceftolozane providing a total of 1,000 mg of ceftolozane active.

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