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DIRECCIÓN DE NUEVAS CREACIONES

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Superintendencia de Industria y Comercio



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Tipo aplicación: Documentos Independientes

Re.: Expediente No. 16-100.057

Solicitud de Patente de Invención titulada: "FORMAS SÓLIDAS DE
CEFTOLOZANO".

Solicitante: MERCK SHARP & DOHME CORP

Nuestra Ref.: P2016/000040

MEMORIAL DE ALCANCE

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad en referencia, me permito informar que por fallas constantes en la plataforma SIPI, la respuesta a la oposición presentada por el doctor Tito Noé Parra Murillo, actuando como apoderado de la sociedad Laboratorios Franco Colombiano S.A.S. LAFRANCOL S.A.S, fue presentada como documentos independientes el día de ayer 2 de enero de 2017 ya que tras varios intentos de cargar la respuesta como debe ser, no fue posible.

De acuerdo a lo anterior, me permito enviar copia de la respuesta a la oposición anteriormente mencionada, así como también sus documentos adjuntos y pantallazo de la confirmación de los documentos cargados exitosamente en el expediente.

Atentamente,

CARLOS R. OLARTE

C.C. No. 79.782.747 de Bogotá

T.P. 74.295

Superintendencia de Industria y Comercio



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Anexos: Lo anteriormente mencionado

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIRECCIÓN DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Re.: Expediente No. 16-100.057

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Solicitante: MERCK SHARP & DOHME CORP

Nuestra Ref.: P2016/000040

RESPUESTA A LA OPOSICIÓN NOTIFICADA MEDIANTE OFICIO No 7285,

NOTIFICADO EL 5 DE JULIO DE 2017

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad solicitante, me permito manifestar lo siguiente, dentro del plazo de prórroga previsto en el Artículo 43 de la Decisión 486, ante la oposición interpuesta por el doctor Tito Noé Parra Murillo, actuando como apoderado de la sociedad Laboratorios Franco Colombiano S.A.S. LAFRANCOL S.A.S.

1. En primer lugar, con el ánimo de brindar mayor claridad a la materia reivindicada, me permito presentar un **Capítulo Reivindicatorio Modificado**, que reemplaza en su totalidad al Capítulo Reivindicatorio presentado el 26 de septiembre de 2016 en respuesta al examen de forma.

Así entonces, el Capítulo Reivindicatorio Modificado adjunto contiene los siguientes cambios:

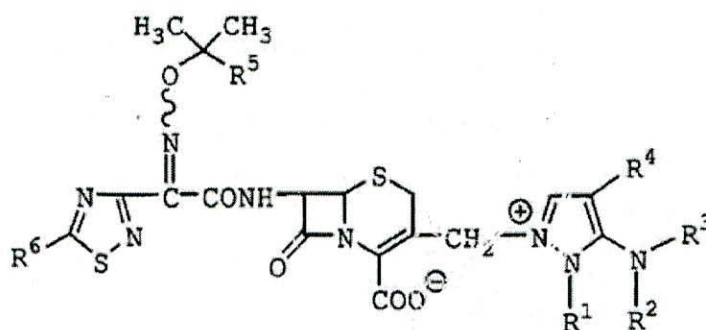
- se eliminan las Reivindicaciones 1 a 21 y 23;
- las nuevas Reivindicaciones 1 a 9, 12, 14 a 16, 19 a 22 y 26 a 30 corresponden a las antiguas Reivindicaciones 22 a 31, 33 a 35, 38 a 46, respectivamente;

- en la nueva Reivindicación 8 se sustituye el término "251" por "25.1";
- se adicionan las nuevas Reivindicaciones 10, 11 y 23 a 25 que tienen soporte en las páginas 17, 21, 22 y 43 del Capítulo Descriptivo;
- las nuevas Reivindicaciones 13 y 17 corresponden a la antiguas Reivindicaciones 31 y 36, en donde se adiciona en el ítem a. "*que produce un patrón de difracción de rayos X en polvo (XRPD) que tiene difracciones en ángulos ($2\theta \pm 0.2$) de 4.4, 8.8, 11.0, 14.9 y 17.7,*" y "*designada como Forma 2*", respectivamente, que tiene soporte en la página 3 del Capítulo Descriptivo;
- la nueva Reivindicación 18 corresponde a la antigua Reivindicación 37, en donde se adiciona "*o una sal farmacéuticamente aceptable de la misma*" que tiene soporte en la página 5 del Capítulo descriptivo;
- las dependencias de las reivindicaciones se adecuaron de acuerdo a la nueva numeración.

Valga anotar que las modificaciones efectuadas en el Capítulo Reivindicatorio cumplen a cabalidad con lo estipulado en el Artículo 34 de la Decisión 486, ya que éstas de ninguna manera implican una ampliación de la protección correspondiente a la divulgación contenida en la solicitud original. Éstas por el contrario corresponden a una limitación de la materia reclamada.

2. a- El Opositor sostiene que las patentes WO2004/039814 (D1), WO2013/063275 (D2), WO2013/036783 (D3) y US5254545 (D4) afecta el nivel inventivo de la presente invención.

El Opositor argumenta que D1 describe un compuesto de formula (I)



(I)

o una sal farmacéuticamente aceptable del mismo, tales como, hidrocloruro, hidrobromuro, sulfato, hidrógeno sulfato, sal de fosfato, etc. Particularmente, el ejemplo 7 de D1 describe una sal de ácido sulfúrico liofilizada de 7 $[\beta]$ -[(Z)-2-(5-amino-1,2, 4-tiadizol-3-il)-2-(1-carboxi-1-metiletoxiimino) acetamido]-3-{3-amino-4[3-(2-aminoetil)ureido]-2-metil-1-pirazolio) metil-3-cefem-4-carboxilato como un polvo amorfo. Posteriormente, se realizó un procedimiento de siembra para producir 7 $[\beta]$ -[(Z)-2-(5-amino-1,2, 4-tiadizol-3-il)-2-(1-carboxi-1-metiletoxiimino) acetamido]-3-{3-amino-4[3-(2-aminoetil)ureido]-2-metil-1-pirazolio)metil-3-cefem-4-carboxilato sulfato de hidrógeno cristalino. El análisis de difracción de rayos X (XRDP) de dicho cristal comprende los siguientes picos ($2\theta \pm 0.2$): 8.0, 12.7, 13.8, 16.1, 18.9, 20.4, 21.5, 22.4, 23.3, 24.0, 25.5, 26.7, 27.9, 28.5 y 31.3.

En cuanto a D2, el Opositor señala que describe un envase de vidrio farmacéutico resistente a la deslaminación particularmente adecuado para composiciones farmacéuticas que comprenden un ingrediente farmacéuticamente activo seleccionado del grupo que consiste en sulfato de ceftolozano, tazobactam sódico, ceftarolina fosamil, hilacidina y fosfato de tedizolid. Adicionalmente, D2 describe una combinación que consiste en CXA-101 (ceftolozano) y tazobactam.

D3 describe un método para tratar una infección intrapulmonar que comprende la etapa de administrar una composición farmacéutica que comprende ceftolozano y tazobactam.

Finalmente, respecto a D4, el Opositor señala que D4 describe una preparación que contiene 7 β -{2-(5-amino-1,2,4-tiadiazol-3-il)-(Z)-2-fluorometoxiiminoacetamido}-3-{E}-3-(carbamoilmetil etilmetilamonio)-1-propen-1-il}-3-cefem-4-carboxilato de etilo, o una sal farmacéuticamente aceptable del mismo y de 0.1 a 1.3 partes en peso de lactosa, de 0.01 a 0.065 partes en peso de arginina o un clorhidrato del mismo o cloruro de sodio. Las sales farmacéuticamente aceptables descritas en D4 son sales de adición de ácido tales como clorhidrato, sulfato, citrato y tartrato. Adicionalmente, D4 se refiere a una inyección liofilizada como una modalidad preferida.

De acuerdo con la interpretación anterior de D1 a D4, el Opositor concluye que las formas sólidas de ceftolozano son obvias, y por lo tanto, carecen de nivel inventivo.

b- i) En primer lugar, de nuevo me permito llamar la atención sobre las modificaciones realizadas en el Capítulo Reivindicatorio Modificado adjunto como se menciona en el primer punto del presente memorial, en donde se eliminan las Reivindicaciones 1 a 21 y 23. De esta manera, las nuevas Reivindicaciones 1 a 9, 12, 14 a

16, 19 a 22 y 26 a 30 corresponden a las antiguas Reivindicaciones 22 a 31, 33 a 35, 38 a 46, respectivamente. De hecho, vale la pena mencionar que el Capítulo Reivindicatorio Modificado adjunto corresponde al mismo que fue concedido en Estados Unidos (US8,906,898).

Asimismo, se adicionan las nuevas Reivindicaciones 10, 11 y 23 a 25 y las nuevas Reivindicaciones 13 y 17 corresponden a las antiguas Reivindicaciones 31 y 36, en donde se adiciona en el ítem a. *"que produce un patrón de difracción de rayos X en polvo (XRPD) que tiene difracciones en ángulos ($2\theta \pm 0.2$) de 4.4, 8.8, 11.0, 14.9 y 17.7,"* y *"designada como Forma 2"*, respectivamente. Además, la nueva Reivindicación 18 corresponde a la antigua Reivindicación 37, en donde se adiciona *"o una sal farmacéuticamente aceptable de la misma"*.

Adicionalmente, cabe resaltar que la nueva Reivindicación 1 ahora reclama *"una forma sólida de sulfato de ceftolozano que produce un patrón de difracción de rayos X de polvo (XRPD) que tiene difracciones en ángulos ($2\theta \pm 0.2$) de 4.4, 8.8, 11.0, 14.9, y 17.7."*

ii) Vale la pena señalar que las nuevas reivindicaciones de la presente invención están dirigidas a una forma sólida 2 de sulfato de ceftolozano que produce un patrón de difracción de rayos X de polvo (XRPD) que tiene difracciones en ángulos ($2\theta \pm 0.2$) de 4.4, 8.8, 11.0, 14.9, y 17.7 y composiciones farmacéuticas liofilizadas de los mismos.

Ahora bien, respecto al arte previo, es importante resaltar que D1 describe un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, un proceso para preparar un compuesto de la fórmula (I), y una composición que comprende un compuesto de la fórmula (I) en mezcla con un vehículo farmacéuticamente aceptable. En particular, en la página 44 y 45 de D1 se revelan los picos del cristal de sulfato de ceftolozano, en donde los picos característicos de difracción de rayos X son: 8.0, 12.7, 13.8, 16.1, 18.9, 20.4, 21.5, 22.4, 23.3, 24.0, 25.5, 26.7, 27.9, 28.5 y 31.3. Sin embargo, comparando el patrón de difracción de rayos X de polvo que caracteriza el cristal en D1 y el reclamado en la presente invención, son claramente diferentes, puesto que no tienen el mismo comportamiento ante la difracción de rayos X, por lo tanto para una persona medianamente versada en la materia es totalmente claro que el cristal reclamado en D1 no tiene la misma estructura que el cristal reclamado en la presente invención.

En cuanto a D2, describe la identificación de un recipiente farmacéutico formado y una composición de vidrio que exhibe una propensión reducida a la deslaminación, es decir, una

propensión reducida a desprender partículas de vidrio. Como resultado, los recipientes descritos son particularmente adecuados para el almacenamiento de composiciones farmacéuticas y, específicamente, una solución farmacéutica que comprende un ingrediente farmacéuticamente activo. En otras palabras, D2 se relaciona con un producto farmacéutico que comprende una composición de vidrio y opcionalmente un antibiótico tal como ceftolozano o tazobactam. Sin embargo, el objetivo divulgado en D2 y la presente invención es diferente, debido a que la invención reclama un cristal específico de sulfato de ceftolozano definido por su patrón de difracción de rayos X y no requiere una composición de vidrio en su estructura.

Por su parte, D3 se refiere al tratamiento de la infección bacteriana intrapulmonar que incluye el tratamiento de infecciones pulmonares por neumonía nosocomial con composiciones farmacéuticas que contienen la cerfalosporina y ceftolozano. Por lo tanto, D3 describe una composición que comprende ceftolozano y tazobactam para el tratamiento de dichas infecciones, no obstante, no describe un cristal de sulfato de ceftolozano con el patrón de difracción de rayos X específico que se reclama en la presente invención.

Por último, D4 describe una preparación que contiene un medicamento de cefalosporina. La preparación comprende un derivado de cefalosporina representado por la fórmula (I) y conocido como 7β -{2-(5-amino-1,2,4-tiadiazol-3-il)-(Z)-2-fluorometoxiiminoacetamido}-3-{E)-3-(carbamoilmetil etilmetilamonio)-1-propen-1-il}-3-cefem-4-carboxilato, o una de sus sales farmacéuticamente aceptables, o el derivado de cefalosporina representado por la fórmula (I) o una sal farmacéuticamente aceptable del mismo. Sin embargo, D4 no menciona el ceftolozano y mucho menos menciona un cristal con las características estructurales aquí reclamadas, que en este caso sería la cefalosporinas cristalizadas.

Así, es claro que nada en D1-D4 enseña las características estructurales del cristal reclamado en la presente invención. No hay enseñanza o sugerencia alguna en dichos documentos que guíen a la persona medianamente versada en la materia a desarrollar específicamente el objeto de la Reivindicación 1. Por el contrario, dicha persona, siguiendo las enseñanzas y sugerencias de D1-D4 se vería motivada a desarrollar productos con características estructurales completamente diferentes de los aquí reclamados, como por ejemplo, recipientes de vidrio o compuestos con otro tipo de configuración química y cristalina.

iii) Ahora bien, me permito llamar la atención sobre algunos ejemplos de la presente invención, específicamente los Ejemplos 3, 8 y 13 del Capítulo Descriptivo.

En el Ejemplo 3 se realiza una prueba comparativa de estabilidad, en donde se evalúa la pureza del sulfato de ceftolozano en diferentes sistemas de disolvente, evidenciando una alta pureza al formar el cristal en diferentes sistemas como lo son isopropanol/agua y etanol/agua, además se evalúa la estabilidad en dichos sistemas de disolventes puesto que se realizan pruebas en diferentes tiempos, las pruebas se llevan a cabo a los días 0, 3 y 6, en el que se evidencia que el día 0 se obtienen para cada sistema porcentajes de pureza de 96.74% y 96.84%, y además la estabilidad se evidencia puesto que a pesar que el tiempo se aumenta de 3 o 6 días, la pureza del cristal solo disminuye en un rango de 9 a 15 %, lo cual se considera bajo.

Adicionalmente, el Ejemplo 8 describe la liofilización de formas sólidas de Cefrolozano, en donde después de hacer diversos experimentos se concluye que los ciclos de liofilización preferidos para producir composiciones liofilizadas de ceftolozano a partir de una solución que comprende la Forma 2 sólida de sulfato de ceftolozano tienen una o más de las siguientes características: (1) no más de 150 mg de concentración de base libre de ceftolozano/g de solución a granel, (2) no más de 3 cm de profundidad de relleno, (3) parámetros de ciclo incluyendo congelación a al menos -40 a -45 °C, (4) secar a no más de 40 °C, y (4) secado de una o de varias etapas y establecimiento de la presión de cámara durante el inicio de secado primario a no más de 400 µbar.

Por último, el Ejemplo 13 de la presente invención se refiere a la higroscopicidad de la Forma 2 de sulfato de ceftolozan, en el que el sulfato de ceftolozano mostró adsorción continua de agua a través del ciclo con la absorción total de 23% a 30% de humedad relativa indicando que el sulfato de ceftolozano es higroscópico.

Por todo lo anterior, como ya he resaltado, una persona medianamente versada en la materia no habría encontrado sugerencia o motivación alguna en los documentos citados para desarrollar un cristal de sulfato de ceftolozano, o cualquier composición que lo comprenda, y que además este caracterizado por un patrón de difracción de rayos X de polvo (XRPD), picos de desplazamiento Raman, una endoterma de calorimetría diferencial de barrido (DSC) o un análisis termogravimétrico (TGA) reclamado en la presente invención, sin necesidad de acudir a experimentación adicional, puesto el cristal reclamado actualmente tienen un gran número de diferencias estructurales con respecto a D1, que el Opositor señala en la objeción por falta de nivel inventivo. De hecho, se requieren múltiples cambios estructurales para llegar al cristal reclamado actualmente. Estos cambios no son divulgados por las enseñanzas generales o los ejemplos de D1, o cualquier combinación de D1 y D2 a D4. Respetuosamente me permito

señalar que la forma sólida de la presente invención es inventiva respecto a D1 solo o en combinación con D2 a D4.

Así las cosas, y a la luz de las evidentes diferencias encontradas entre la materia reclamada en la solicitud frente al arte previo, vale la pena señalar que de acuerdo con el (Manual Andino de Patentes) MAP, para que pueda negarse la existencia de nivel inventivo, es necesario, no solamente que la combinación de las enseñanzas pueda hacerse, sino también que exista una sugerencia o razón tal, que lleve al técnico con conocimientos medios a combinar las enseñanzas de los documentos¹. Además, el MAP también establece que las invenciones en el campo de la química (farmacéutica) tienen nivel inventivo cuando la materia reclamada tiene una **estructura inesperada** (no derivable por la persona medianamente versada en la materia) **o** cuando presentan un **efecto técnico inesperado o mejorado impredecible del arte previo**². De manera similar, la Guía de la SIC establece que, para que una invención no resulte inventiva *“el conjunto de enseñanzas del estado de la técnica lo llevarían (a la persona medianamente versada en la materia) de forma inmediata a la solución propuesta por la solicitud. **Si se requiere de pasos adicionales o de corroboración o de superar obstáculos revelados por las propias enseñanzas entonces el estado de la técnica no revela la solución al problema**”*³ (subrayado y énfasis fuera del texto). Lo cual no sucede en el presente caso, toda vez que los cristales que se reclaman en la presente solicitud no pudieron haber sido predichos con éxito a partir de los documentos que menciona el Opositor.

3. Finalmente, me permito informar que para el concepto inventivo comprendido en la presente solicitud, ha sido otorgado hasta el momento el privilegio de patente en Australia, Estados Unidos (US8,906,898) y Nueva Zelanda.

Si bien es cierto que las concesiones de patentes en oficinas de otros países no son vinculantes en el sentido que obliguen a la SIC a tomar una decisión en el mismo sentido, considero que dichas concesiones sugieren el cumplimiento de los requisitos de patentabilidad de la materia reivindicada, ya que los criterios de evaluación y estudio aplicados para concluir la aceptación de dichas patentes resultan equivalentes a los que la SIC debe emplear.

¹ Manual Andino de Patentes, Sección 10.2.1 - Ejemplo 1.

² Manual Andino de Patentes, Sección 10.8.1.

³ Guía de la SIC, sección 2.13.2.

OLARTEMOURE

OLARTE MOURE & ASOCIADOS

Abogados - Attorneys

4. Por todo lo anterior, considero que las observaciones presentadas por el Opositor han sido superadas y solicito respetuosamente se proceda con el examen de fondo de la presente invención.

Atentamente,



CARLOS R. OLARTE

C.C. No. 79.782.747 de Bogotá

T.P. 74.295

Anexos:

- Capítulo Reivindicatorio Modificado
- Recibo de pago por modificación voluntaria
- Recibo de pago por 20 reivindicaciones adicionales
- Patente Estadounidense Concedida US 8,906,898

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CAPÍTULO REIVINDICATORIO MODIFICADO

(Modificaciones Voluntarias)

1. Forma sólida 2 de sulfato de ceftolozano que produce un patrón de difracción de rayos X de polvo (XRPD) que tiene difracciones en ángulos ($2\theta \pm 0.2$) de 4.4, 8.8, 11.0, 14.9, y 17.7.
2. La forma sólida de sulfato de ceftolozano de la Reivindicación 1 que produce picos de desplazamiento Raman ($\pm 5\text{ cm}^{-1}$) en alrededor de 151 cm^{-1} , 684 cm^{-1} y 802 cm^{-1} .
3. La forma sólida de sulfato de ceftolozano de la Reivindicación 1 caracterizada por una endoterma de calorimetría diferencial de barrido (DSC) que tiene una mínima en alrededor de 105 grados C.
4. La forma sólida de sulfato de ceftolozano de la Reivindicación 1, caracterizada por un análisis termogravimétrico (TGA) con una pérdida de peso de alrededor de 6.8% entre 25-181 grados C.
5. La forma sólida de sulfato de ceftolozano de la Reivindicación 1, caracterizada por
 - a. una endoterma de calorimetría diferencial de barrido (DSC) que tiene una mínima en alrededor de 105 grados C;
 - b. un análisis termogravimétrico (TGA) con una pérdida de peso de alrededor de 6.8% entre 25-181 grados C; y
 - c. Picos de desplazamiento Raman ($\pm 5\text{ cm}^{-1}$) en 151 cm^{-1} , 684 cm^{-1} , 802 cm^{-1} , 1174 cm^{-1} y 2953 cm^{-1} .
6. Una composición farmacéutica que comprende la forma sólida de sulfato de ceftolozano designado como Forma 2 de sulfato de ceftolozano que produce un patrón de difracción de rayos X de polvo (XRPD) que tiene difracciones en los ángulos ($2\theta \pm 0.2$) de 4.4, 8.8, 11.0, 14.9, y 17.7.
7. La composición farmacéutica de la Reivindicación 6, en donde el sulfato de ceftolozano produce picos de desplazamiento Raman ($\pm 5\text{ cm}^{-1}$) a aproximadamente 151 cm^{-1} , 684 cm^{-1} , 802 cm^{-1} , 1174 cm^{-1} y 2953 cm^{-1} .
8. La composición farmacéutica de una cualquiera de la Reivindicación 7, que comprende además sulfato de ceftolozano en una forma sólida que produce un patrón de

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difracción de rayos X en polvo (XRPD) que tiene difracciones en ángulos ($2\theta \pm 0.2$) de 12.4, 16.4, 22.6, 25.1 y 28.0.

9. La composición farmacéutica de la Reivindicación 6, que comprende además tazobactam.

10. La composición farmacéutica de la Reivindicación 6, que comprende además un excipiente farmacéuticamente aceptable.

11. La composición farmacéutica de la Reivindicación 10, en donde el excipiente farmacéuticamente aceptable es seleccionado del grupo que consiste de: cloruro de sodio, L-arginina, ácido cítrico y mezclas de los mismos.

12. La composición farmacéutica de la Reivindicación 11, se caracteriza por uno o más de los siguientes:

- a. una endoterma de calorimetría diferencial de barrido (DSC) que tiene una mínima en alrededor de 105 grados C;
- b. un análisis termogravimétrico (TGA) con una pérdida de peso de alrededor de 6.8% entre 25-181 grados C; y
- c. Picos de desplazamiento Raman ($\pm 5\text{ cm}^{-1}$) en 151 cm^{-1} , 684 cm^{-1} , 802 cm^{-1} , 1174 cm^{-1} y 2953 cm^{-1} .

13. Una composición farmacéutica que comprende una composición liofilizada de ceftolozano obtenida por un procedimiento que comprende las etapas de:

- a. combinar el sulfato de ceftolozano en una forma sólida designada como Forma 2 de sulfato de ceftolozano que produce un patrón de difracción de rayos X en polvo (XRPD) que tiene difracciones en ángulos ($2\theta \pm 0.2$) de 4.4, 8.8, 11.0, 14.9 y 17.7, con agua, cloruro de sodio y L-arginina para formar una solución acuosa; y
- b. liofilizar la solución acuosa para formar la composición liofilizada de ceftolozano que comprende sulfato de ceftolozano.

14. La composición farmacéutica de la Reivindicación 13, en donde el ciclo de liofilización se caracteriza por una o más de las siguientes características:

- a. Concentración no mayor a 150 mg de base libre de ceftolozano /g de solución a granel,
- b. no más de 3 cm de profundidad de llenado,
- c. congelar a por lo menos $-40\text{ }^{\circ}\text{C}$ durante el ciclo de liofilización,

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- d. secar a no más de 40° C, y
 - e. secar en una o varias etapas y establecer la presión de cámara durante el inicio de secado primario en no más de 400 μ bar.
15. La composición farmacéutica de la Reivindicación 13, que comprende además tazobactam.
16. La composición farmacéutica de la Reivindicación 15, obtenida por un proceso que comprende además combinar la composición liofilizada de ceftolozano con tazobactam en una combinación de dosis fija que proporciona aproximadamente 500 mg de tazobactam activo por 1.000 mg de ceftolozano activo en la composición farmacéutica.
17. Una composición farmacéutica que comprende una composición liofilizada de ceftolozano obtenida por un procedimiento que comprende las etapas de:
- a. combinar el sulfato de ceftolozano en una forma sólida designada como Forma 2 que produce un patrón de difracción de rayos X de polvo (XRPD) que tiene difracciones en ángulos ($2\theta \pm 0.2$) de 4.4, 8.3, 11.0, 14.9, y 17.7 con agua para formar una solución acuosa; y
 - b. liofilizar la solución acuosa para formar la composición liofilizada de ceftolozano que comprende sulfato de ceftolozano.
18. La composición farmacéutica de la Reivindicación 17, en donde la solución acuosa en la etapa (b) comprende además tazobactam o una sal farmacéuticamente aceptable de la misma.
19. La composición farmacéutica de la Reivindicación 18, en donde la composición farmacéutica comprende tazobactam sódico.
20. La composición farmacéutica de la Reivindicación 17, en donde la solución acuosa en la etapa (b) se liofiliza en ausencia de tazobactam.
21. La composición farmacéutica de la Reivindicación 17, en donde la composición farmacéutica que comprende el sulfato de ceftolozano en una cantidad que proporciona aproximadamente 1000 mg de ceftolozano activo.
22. La composición farmacéutica de la Reivindicación 21, en donde la composición farmacéutica comprende además unos 500 mg de tazobactam activo.

23. La composición farmacéutica de la Reivindicación 17, en donde la composición farmacéutica comprende ceftolozano activo y tazobactam activo, y el sulfato de ceftolozano está presente en la composición en una cantidad que proporciona 1000 mg de ceftolozano activo por 500 mg de tazobactam activo.
24. La composición farmacéutica de la Reivindicación 17, en donde la composición farmacéutica comprende ceftolozano y compuesto inhibidor de beta-lactamasa.
25. La composición farmacéutica de la Reivindicación 17, en donde la composición farmacéutica comprende aproximadamente 1000 mg de ceftolozano activo y 500 mg de tazobactam activo.
26. La composición farmacéutica de la Reivindicación 17, que se obtiene por un proceso que comprende además combinar la composición liofilizada de ceftolozano con tazobactam en una combinación de dosis fija que proporciona aproximadamente 500 mg de tazobactam activo por 1.000 mg de ceftolozano activo en la composición farmacéutica.
27. La composición farmacéutica de la Reivindicación 26, en donde la composición farmacéutica comprende tazobactam sódico.
28. La composición farmacéutica de la Reivindicación 26, en donde la composición farmacéutica comprende tazobactam cristalino.
29. La composición farmacéutica de la Reivindicación 26, en donde la solución acuosa se liofiliza en la etapa (b) con un ciclo de liofilización que se caracteriza por una o más de las siguientes características:
- Concentración no mayor a 150 mg de base libre de ceftolozano /g de solución a granel,
 - no más de 3 cm de profundidad de llenado,
 - congelar a por lo menos -40 °C durante el ciclo de liofilización,
 - secar a no más de 40° C, y
 - secar en una o varias etapas y establecer la presión de cámara durante el inicio de secado primario en no más de 400 µbar.
30. La composición farmacéutica de la Reivindicación 26, caracterizada por una o más de las siguientes:
- una endoterma de calorimetría diferencial de barrido (DSC) que tiene una mínima en alrededor de 105 grados C;

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- b. un análisis termogravimétrico (TGA) con una pérdida de peso de alrededor de 6.8% entre 25-181 grados C; y
- c. Picos de desplazamiento Raman ($\pm 5 \text{ cm}^{-1}$) en 151 cm^{-1} , 684 cm^{-1} , 802 cm^{-1} , 1174 cm^{-1} y 2953 cm^{-1} .



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(12) **United States Patent**
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- (54) **SOLID FORMS OF CEFTOLOZANE**
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(58) **Field of Classification Search**

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(57) **ABSTRACT**

Novel solid forms of ceftolozane are described, as well as methods for the preparation and use of these solid forms.

30 Claims, 5 Drawing Sheets

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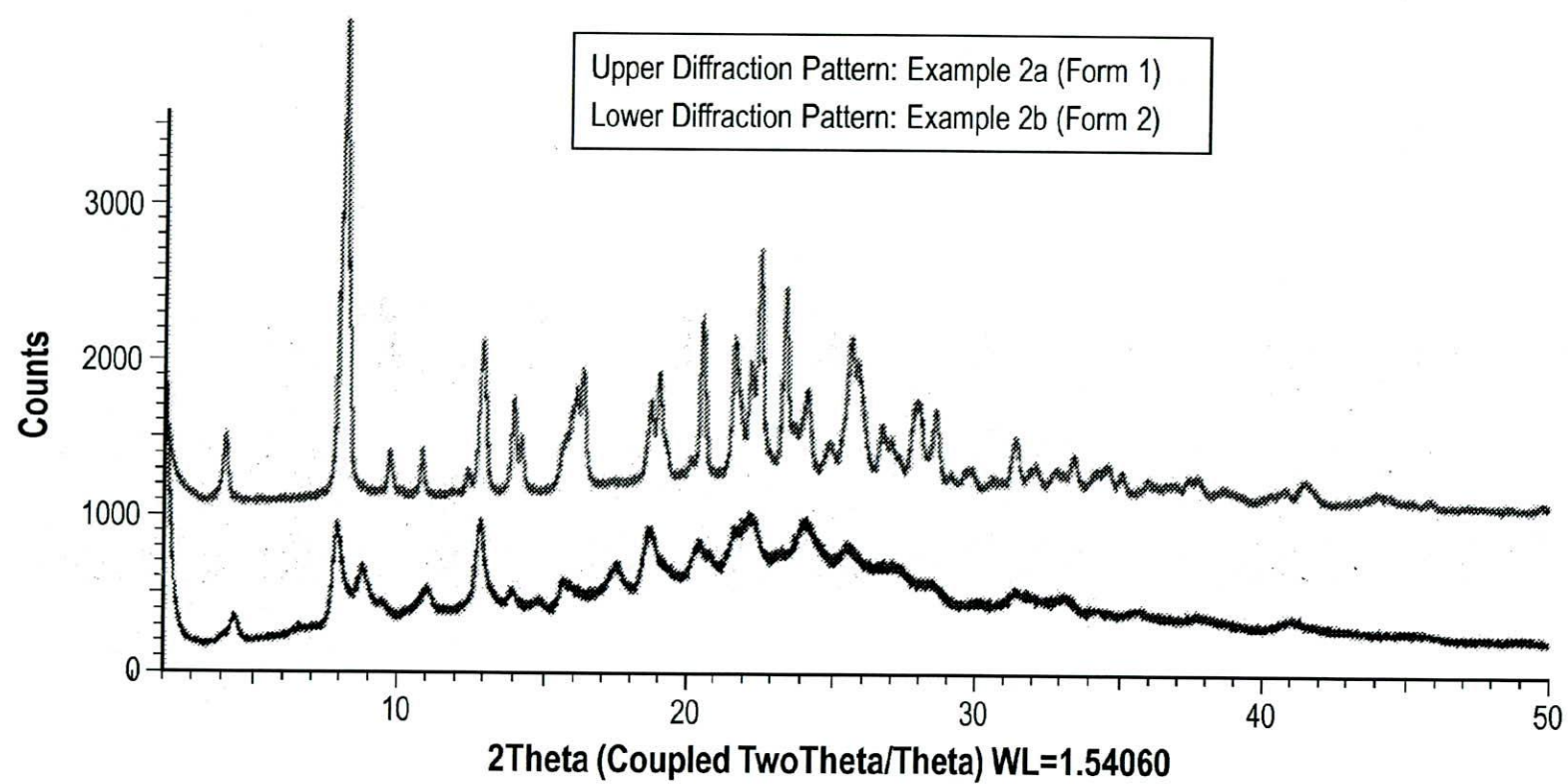
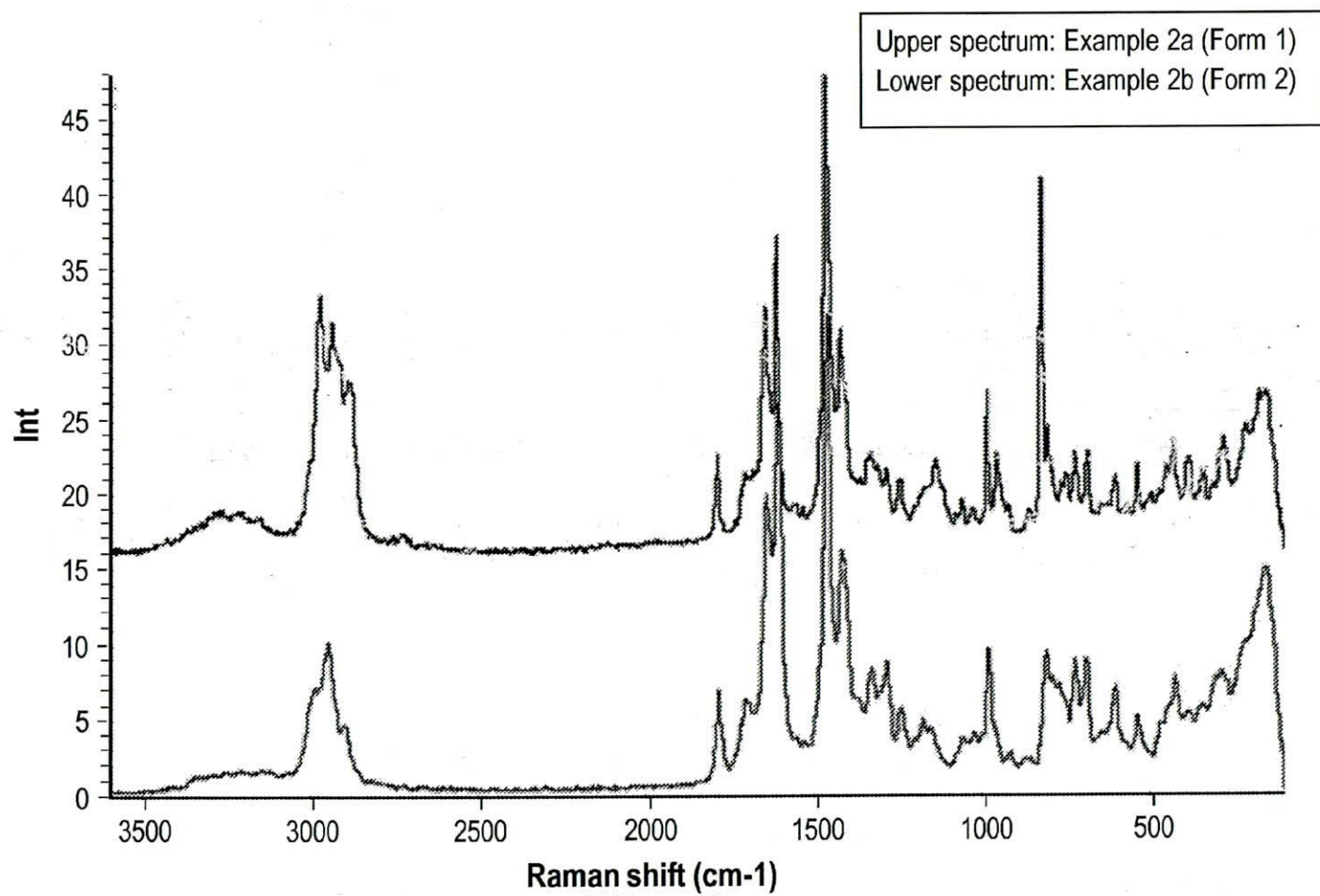
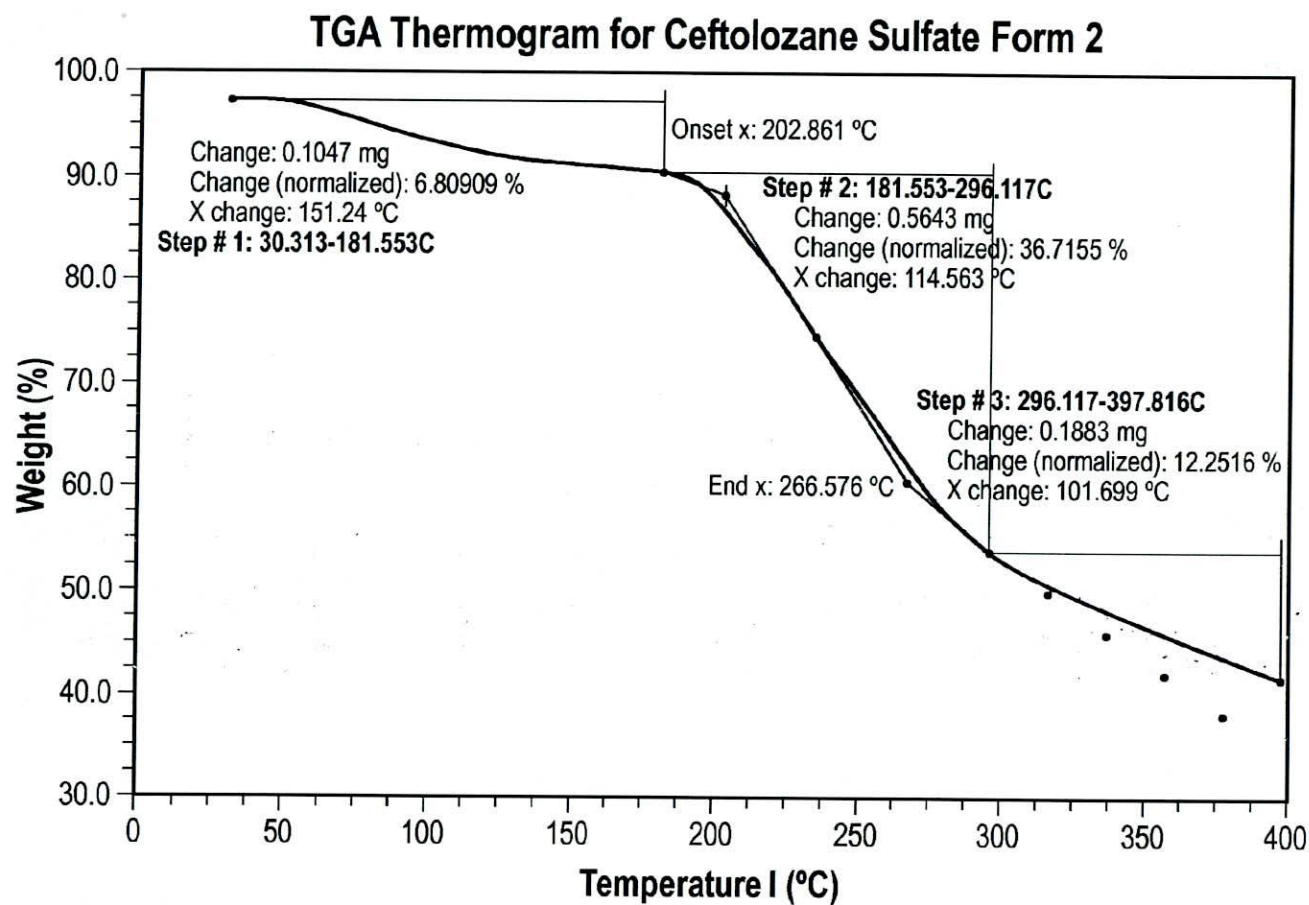
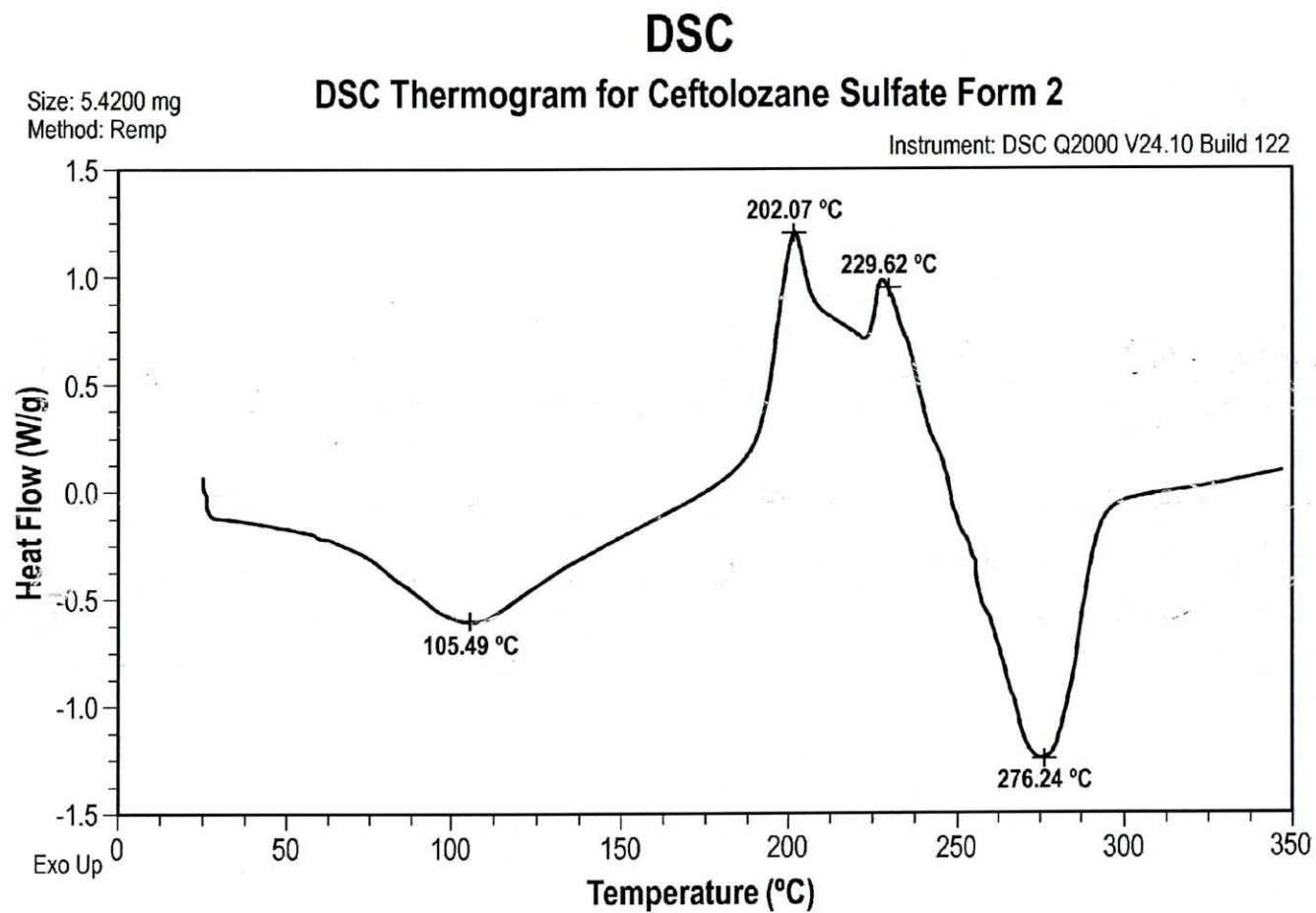
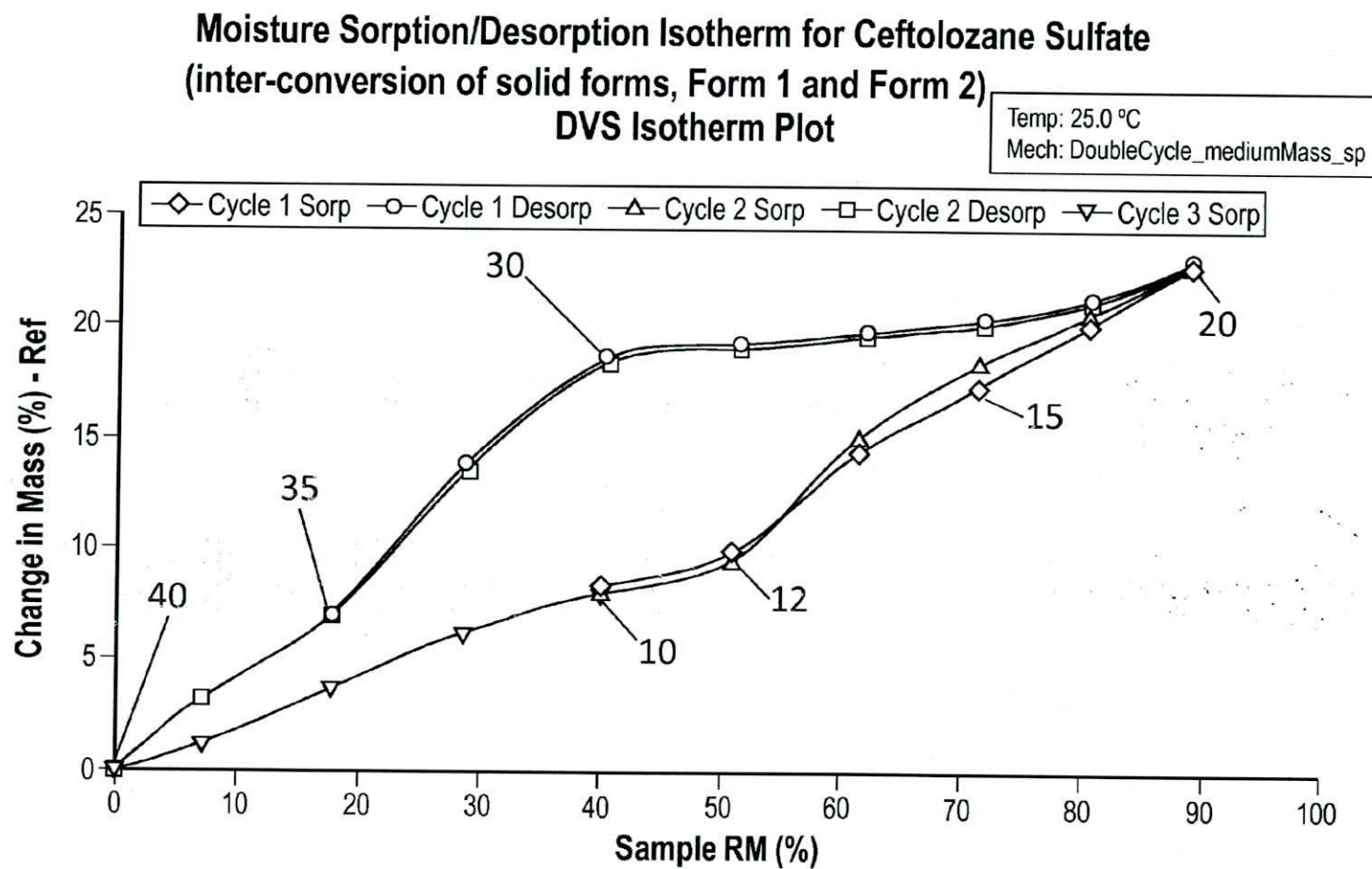


Fig. 1



**Fig. 3**

**Fig. 4**

**Fig. 5**

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SOLID FORMS OF CEFTOLOZANE

RELATED APPLICATIONS

This application claims priority to U.S. Provisional Patent Application No. 61/883,530, filed Sep. 27, 2013, which is incorporated herein in its entirety.

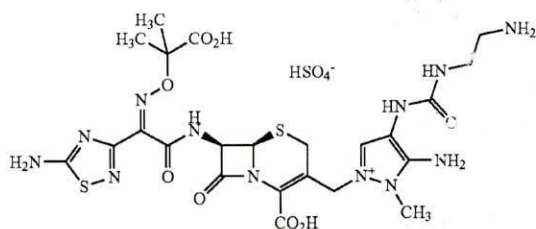
TECHNICAL FIELD

This disclosure relates to solid forms of ceftolozane.

BACKGROUND

The crystal state of a compound may be important when the compound is used for pharmaceutical purposes. Compared with an amorphous solid, the solid physical properties of a crystalline compound may change from one solid form to another, which may affect its suitability for pharmaceutical use. In addition, different solid forms of a crystalline compound can incorporate different types and/or different amounts of impurities. Different solid forms of a compound can also have different chemical stability upon exposure to heat and/or water over a period of time.

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-ylmethyl]-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-pyrazol-5-ylmethyl]-3-cephem-4-carboxylate. Ceftolozane sulfate is a pharmaceutically acceptable ceftolozane salt of formula (I) that can be formulated for intravenous administration or infusion.



U.S. Pat. No. 7,129,232 discloses ceftolozane hydrogen sulfate salt among other salts "with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt [e.g., sodium salt, potassium salt, etc.], an alkaline earth metal salt [e.g., calcium salt, magnesium salt, etc.], an ammonium salt; a salt with an organic base, for example, an organic amine salt [e.g., trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, ethanolanine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.]; an inorganic acid addition salt [e.g., hydrochloride, hydrobromide, sulfate, hydrogen sulfate, phosphate, etc.]; an organic carboxylic or sulfonic acid addition salt [e.g., formate, acetate, trifluoroacetate, maleate, tartrate, citrate, fumarate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.]; and a salt with a basic or acidic amino acid [e.g., arginine, aspartic acid,

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glutamic acid, etc.]. In addition, U.S. Pat. No. 7,129,232 discloses a crystal solid form of ceftolozane sulfate obtained by dissolving ceftolozane sulfate in a solution of water and ethanol, adding seed crystals, to obtain the crystal form described herein as (Comparative) Example 1. A synthesis of ceftolozane is also described in U.S. Pat. No. 7,129,232.

As reported herein, there remains a need for solid forms of ceftolozane having improved ceftolozane stability. For example, the purity of ceftolozane in an aqueous ethanol solution during precipitation according to the methods of U.S. Pat. No. 7,129,232 decreased from about 97% to about 68% during a 6-day stability test (See Example 3), as measured by high performance liquid chromatography (HPLC). Accordingly, there remains a need for solid forms of ceftolozane greater ceftolozane stability for use in drug substance and drug product development.

SUMMARY

Novel solid forms of ceftolozane (e.g., crystalline ceftolozane sulfate) disclosed herein include ceftolozane sulfate in Form 1 and Form 2, as well as compositions comprising a solid form of ceftolozane comprising at least one or more of ceftolozane sulfate Form 1 and ceftolozane sulfate Form 2. Novel compositions also include ceftolozane sulfate solid Form 1, ceftolozane sulfate solid Form 2 and/or crystalline and amorphous solid forms of ceftolozane. A novel ceftolozane solid Form 1 and a novel ceftolozane solid Form 2 of ceftolozane sulfate can both be identified by X-ray Powder Diffraction (XRPD), both having one or more characteristic diffractions at angles (2 theta±0.2) of 24.2 and 37.8. In addition, ceftolozane diffractions in both solid Form 1 and solid Form 2 can produce the Raman spectra comprising one or more of the following peaks (+/-5 cm⁻¹) at about 597 cm⁻¹, 716 cm⁻¹, and 1329 cm⁻¹. A preferred ceftolozane composition can include ceftolozane in one or more solid forms (e.g., solid Form 1 and/or solid Form 2) characterized by an XRPD pattern with diffractions at angles (2 theta±0.2) of 24.2 and 37.8, in addition to Raman spectra comprising one or more of the following peaks at about 597 cm⁻¹, 716 cm⁻¹, and 1329 cm⁻¹.

A novel ceftolozane solid Form 1 of ceftolozane sulfate can be identified by X-ray Powder Diffraction (XRPD), having one or more characteristic diffractions at angles (2 theta±0.2) of 12.4, 16.4, 22.6, 25.1, and 28.0. In addition, ceftolozane in solid Form 1 can produce the Raman spectra comprising one or more of the following peaks (+/-5 cm⁻¹) at 171 cm⁻¹, 743 cm⁻¹, 819 cm⁻¹, 1055 cm⁻¹, 2894 cm⁻¹, and 2976 cm⁻¹.

A novel ceftolozane solid Form 2 of ceftolozane sulfate can be identified by X-ray Powder Diffraction (XRPD), having one or more characteristic diffractions at angles (2 theta±0.2) of 4.4, 8.8, 11.0, 14.9, and 17.7. In addition, ceftolozane in solid Form 1 can produce the Raman spectra comprising one or more of the following peaks (+/-5 cm⁻¹) at 151 cm⁻¹, 684 cm⁻¹, 802 cm⁻¹, 1174 cm⁻¹, and 2953 cm⁻¹.

The applicants have also discovered that novel ceftolozane salt solid forms (e.g., Form 1 and Form 2 of ceftolozane sulfate) can also be obtained by maintaining a ceftolozane salt solid form under physical conditions effective to convert a ceftolozane salt in a first solid form into a ceftolozane salt in a second solid form. For example, performing a water sorption isotherm (e.g., FIG. 5) of ceftolozane sulfate in Form 1 showed a reversible transformation between ceftolozane sulfate in solid Form 1 and solid Form 2 as a function of relative humidity. The solid form of ceftolozane can be changed by maintaining the ceftolozane at certain relative humidity conditions (e.g., as described in the water sorption isotherm for

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ceftolozane sulfate in FIG. 5). Ceftolozane in solid Form 2 can be converted to ceftolozane in Form 1 by maintaining a sample at a relative humidity (RH) effective to convert ceftolozane in Form 2 to ceftolozane into Form 1 at a suitable temperature (e.g., RH of about 50% or higher at a temperature of about 20-25 degrees C., preferably at least about 70% RH at a temperature of about 25 degrees C.). Once formed in this manner, ceftolozane in solid Form 1 can be converted to ceftolozane sulfate in Form 2 by reducing the RH (e.g., RH of about 20-40%). The ceftolozane sulfate in Form 2 can be converted to a mixture of amorphous ceftolozane sulfate and Form 2 by reducing the RH to less than about 20%.

The ceftolozane solid forms (Form 1 and Form 2) can be obtained from a solution comprising isopropanol, or by maintaining a ceftolozane solid form under conditions effective to convert a first solid form into a second solid form (e.g., by maintaining ceftolozane sulfate in Form 1 under physical conditions effective to form ceftolozane sulfate in Form 2, or converting Form 2 under physical conditions effective to form ceftolozane sulfate of Form 1). An improved manufacturing method can include the steps of (a) combining ceftolozane sulfate with a molar excess of sulfuric acid (e.g., about 2.5 molar equivalents of sulfuric acid to ceftolozane) and isopropanol (e.g., about 20-40 volumes of isopropanol relative to the amount of ceftolozane active) under conditions effective to produce a ceftolozane solid form (e.g., ceftolozane sulfate Form 1), and (b) isolating the ceftolozane solid form (e.g., by filtering the ceftolozane solid form from a solution comprising the isopropanol).

The applicants have discovered novel methods of manufacturing ceftolozane sulfate solid forms that provide improved ceftolozane stability during manufacturing compared to the methods of manufacturing ceftolozane solid forms disclosed in U.S. Pat. No. 7,129,232 (see Comparative Example 1 herein). The improved manufacturing methods are based in part on the discovery that solid forms of ceftolozane sulfate obtained by certain processes comprising the use of isopropanol (e.g., as described in Example 2a) with ceftolozane provide improved ceftolozane stability in a liquid phase during manufacturing (compared to the manufacturing methods described in U.S. Pat. No. 7,129,232), as measured by a ceftolozane purity of about 82% after a 6-day ceftolozane stability test of Example 3 (compared to about 68% from ceftolozane solid forms disclosed in U.S. Pat. No. 7,129,232). The novel ceftolozane solid forms, including ceftolozane sulfate solid Form 1 and ceftolozane solid Form 2, can be obtained from an aqueous solution with isopropyl alcohol, even in the absence of ethanol. In contrast, U.S. Pat. No. 7,129,232 discloses a ceftolozane solid form obtained from an aqueous solution without isopropyl alcohol.

The manufacturing methods are useful for the manufacture of antibiotic compositions comprising ceftolozane in one or more solid forms suitable for treatment of infections. For example, a pharmaceutical composition comprising ceftolozane for parenteral administration can be obtained from ceftolozane sulfate in solid Form 1 and/or solid Form 2 by a process comprising the steps of: (a) forming a ceftolozane solution comprising ceftolozane sulfate in a solid Form 1 and/or solid Form 2, and (b) lyophilizing the ceftolozane solution to obtain a lyophilized ceftolozane composition. The lyophilized ceftolozane composition can be combined with tazobactam (or a pharmaceutically acceptable salt thereof) to obtain a CXA-201 pharmaceutical composition suitable for intravenous administration upon reconstitution.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 depicts two X-ray powder diffraction patterns of novel solid forms ceftolozane sulfate. The upper pattern cor-

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responds to the product of Example 2a. The lower pattern corresponds to the product of Example 2b.

FIG. 2 depicts two Raman spectra of novel solid forms of ceftolozane sulfate. The upper pattern corresponds to the product of Example 2a. The lower pattern corresponds to the product of Example 2b.

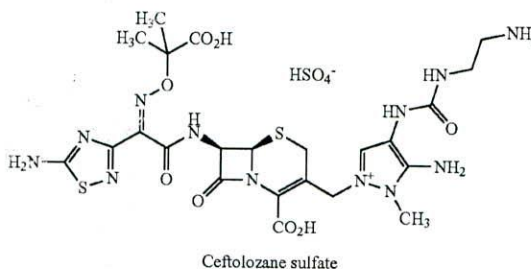
FIG. 3 is a thermogravimetric analysis (TGA) curve for ceftolozane sulfate in a solid form designated herein as Form 2.

FIG. 4 is a differential scanning calorimetry (DSC) thermograms for ceftolozane sulfate in a solid form designated herein as Form 2.

FIG. 5 is a moisture sorption/desorption isotherm for ceftolozane sulfate solid forms.

DETAILED DESCRIPTION

Ceftolozane can be prepared as a pharmaceutically acceptable salt in one or more solid forms. Ceftolozane is also known as CXA-101; CAS registry number 689293-68-3; (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; 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[[4-[[[(2-aminoethyl)amino]carbonyl]amino]-2,3-dihydro-3-imino-2-methyl-1H-pyrazol-1-yl]methyl]-7-[(2Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-[(1-carboxy-1-methylethoxy)imino]acetyl]amino]-8-oxo-, (6R,7R)—; and (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. Ceftolozane sulfate is an example of a pharmaceutically acceptable salt of ceftolozane. The structure of ceftolozane sulfate is shown below.



Ceftolozane sulfate is also referred to as: CAS registry number 936111-69-2; 1H-Pyrazolium, 5-amino-4-[[[(2-aminoethyl)amino]carbonyl]amino]-2-[[[(6R,7R)-7-[(2Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-[(1-carboxy-1-methylethoxy)imino]acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-, sulfate (1:1); and 5-amino-4-[[[(2-aminoethyl)carbamoyl]amino]-2-[[[(6R,7R)-7-[(2Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-[(1-carboxy-1-methylethoxy)imino]acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-1H-pyrazolium monosulfate.

Ceftolozane sulfate can occur in an amorphous solid form or in a crystalline solid form or in mixtures of solid forms. Crystalline solid forms of ceftolozane can exist in one or more unique solid forms, which can additionally comprise one or more equivalents of water or solvent (i.e., hydrates or solvates, respectively).

As disclosed herein, crystalline ceftolozane sulfate precipitated or crystallized from isopropanol/water has significantly better stability in a solution comprising isopropanol compared to the stability in a solution comprising ethanol, as used to prepare crystalline ceftolozane sulfate precipitated from ethanol/water, as previously described in U.S. Pat. No. 7,129,232 (see Example 3). Moreover, the crystalline forms precipitated or crystallized from isopropanol/water have distinct characteristic XRPD peaks (see Examples 1 and 2, and Tables 4 and 6) that are not observed in previously disclosed crystal forms of ceftolozane described in U.S. Pat. No. 7,129,232. Accordingly, provided herein are novel crystalline ceftolozane sulfate solid forms, pharmaceutical compositions thereof, and methods of preparing those crystalline ceftolozane sulfate solid forms and methods of use thereof.

Novel ceftolozane solid forms can be obtained from aqueous solutions comprising ceftolozane and isopropyl alcohol (herein, also called IPA, or isopropanol). As described in Example 2a, ceftolozane sulfate in solid Form 1 can be obtained by forming a ceftolozane solution comprising a ceftolozane salt, a strong acid and IPA and maintaining the solution under conditions effective to form a ceftolozane wet cake containing Form 1 of the ceftolozane salt. Preferably, the ceftolozane solution is an aqueous solution comprising ceftolozane and the strong acid (e.g., sulfuric acid) in an amount providing least 1 molar equivalent of the strong acid to the molar quantity of ceftolozane in the solution. In certain examples, the Form 1 of ceftolozane is obtained from a ceftolozane solution that is polish filtered and the temperature is adjusted and maintained throughout the entire salt formation and isolation process. An aqueous sulfuric acid (H_2SO_4) solution can be charged to the batch. Optionally, this can be followed by seeding with ceftolozane sulfate crystal. The batch is aged, followed by the addition of IPA over a period of time. After the IPA addition, the batch is agitated for an additional period, and then filtered. The wet cake of ceftolozane sulfate is washed with a solution of IPA and water.

The ceftolozane solution is preferably maintained at a temperature effective to provide a desired purity and yield of the ceftolozane in solid Form 1, such as 8-12 degrees C. In addition to the temperature (e.g., 8-12 degrees C., preferably about 10 degrees C.), and amount of strong acid (e.g., sulfuric acid in an amount providing 1-3 molar equivalents, and preferably 2.45-2.55 molar equivalents, relative to the molar amount of ceftolozane), the concentration of ceftolozane before salt formation (e.g., 75-85 g/L), seed amount (e.g., 0.1-1 w/w %) and aging time after seeding (e.g., 2-4 hours) are also parameters that can be adjusted to obtain ceftolozane in Form 1 solid form. Particularly preferred processes for making Form 1 ceftolozane sulfate solid form include maintaining an aqueous solution of ceftolozane sulfate, isopropyl alcohol and sulfuric acid at a temperature of 8-12 degrees C. Table 1 provides the exemplary range of values for various process parameters for the manufacturing of solid forms of ceftolozane sulfate, along with preferred ranges and target (most preferred) values for each process parameter.

TABLE 1

Process Parameters for the Formation and Isolation of Ceftolozane Sulfate Solid Forms			
Process Parameter	Exemplary Range	Preferred Range	Target Value
Ceftolozane concentration after final nanofiltration (g/L)	72 to 100	75 to 85	80
Sulfuric acid (equiv)	1.50 to 2.95	2.45 to 2.55	2.5
Seed amount (w/w %)	0.03 to 4.0	0.1 to 1.0	0.3
Aging time, after seeding (h)	1 to 5	2 to 4	3
IPA amount (vol)	20 to 40	29 to 31	30
IPA addition time (h)	0.5 to 8	6 to 7	6.5
Aging time, after IPA addition (h)	0 to 8	1 to 6	2
Temperature ($^{\circ}C$)	5 to 15	8 to 12	10
4:1 (v/v) IPA/water wash solution (vol)	≥ 2	≥ 2	4

Solid forms of ceftolozane can be obtained by methods comprising the step of combining ceftolozane sulfate and a solvent, such that a solution comprising ceftolozane sulfate is formed, and such that crystalline ceftolozane sulfate precipitates from the solution. Crystalline ceftolozane sulfate solid forms can be obtained from methods that include the steps of: (1) combining ceftolozane sulfate and a solvent, such that a solution of ceftolozane sulfate is formed; and (2) combining an antisolvent with the solution, wherein the antisolvent is miscible with the solvent and wherein ceftolozane sulfate is partially or completely insoluble in the antisolvent, such that crystalline ceftolozane sulfate precipitates or crystallizes from the solution.

A ceftolozane sulfate composition can be obtained by a process comprising the steps of: (a) forming a solution comprising water, 72-100 g/L ceftolozane active and 1.5-2.95 molar equivalents of sulfuric acid to ceftolozane; (b) combining the solution from step (a) with 20-40 volumes of isopropyl alcohol added to the solution over 0.5-8 hours to obtain solid ceftolozane sulfate; and (c) isolating the solid ceftolozane sulfate from the solution. The temperature of the solution can be about 0-20 degrees C., preferably 8-12 degrees C. (e.g. 10 degrees C.). Optionally, the process can further include adding a ceftolozane sulfate seed crystal, preferably in an amount of 0.03-4.0% w/w and allowing the seed crystal to age in the solution for about 1-5 hours. Optionally, the process can include allowing the solution to age for up to about 8 hours after adding the isopropyl alcohol.

In another aspect, methods of making crystalline ceftolozane sulfate can include the steps of: (1) combining ceftolozane freebase (i.e., the non-salt form of ceftolozane having a net formal charge of zero) and a solvent, such that a solution of ceftolozane freebase is formed; (2) combining an acid with the solution of ceftolozane free base (e.g., in an amount providing a molar equivalent or excess of the acid to the ceftolozane free base, and/or an amount effective to adjust the pH of the ceftolozane solution to about 1.5-2.0); and (3) allowing the crystalline ceftolozane sulfate to precipitate or crystallize from solution. In addition, the method can include adding an antisolvent (preferably isopropyl alcohol) in an amount effective to provide a desired rate or extent of precipitation and/or crystallization of the ceftolozane in the solution. Accordingly, step (3) may further comprise combining an antisolvent with the solution, wherein the antisolvent is miscible with the solvent and wherein ceftolozane sulfate is partially or completely insoluble in the antisolvent, such that crystalline ceftolozane sulfate precipitates or crystallizes from the solution. In some embodiments, the temperature of the solution is adjusted to 0-20 $^{\circ}$ C. In other embodiments, step (3) comprises the step of seeding the solution with one or

more crystals of cefotolozane sulfate. In some embodiments, the volume of antisolvent that is added to the solution is 20-40 volumes relative to the cefotolozane. In some embodiments, the temperature of the solution formed in step (1) is adjusted to 0-20° C. before proceeding to step (2). In one embodiment, the method of making crystalline cefotolozane sulfate can also include the step of: (4) drying the precipitated or crystallized crystalline cefotolozane sulfate. Drying may comprise techniques including, but not limited to, air-drying, exposure to vacuum, exposure to a neutral gas (e.g., nitrogen) flow and heating.

In an alternative embodiment, the acid (e.g., sulfuric acid) may first be combined with the solvent, and the resulting mixture then combined with cefotolozane. Alternatively, cefotolozane and the acid (e.g., sulfuric acid) may first be combined, and the resulting mixture then combined with the solvent. In one embodiment, the antisolvent is added to the solution of cefotolozane sulfate or freebase. In another embodiment, the solution of cefotolozane sulfate or freebase is added to the antisolvent. In certain embodiments, the solvent is selected from the group consisting of water and sulfuric acid. In certain embodiments, the antisolvent is selected from the group consisting of alcohols, ethers, esters, ketones, nitriles, amides, nitroalkanes, nitroarenes, substituted or unsubstituted aromatic solvents, substituted or unsubstituted aliphatic solvents and mixtures thereof. In certain embodiments, the antisolvent is selected from the group consisting of acetone, acetonitrile, 1-butanol, cyclohexane, dichloromethane, diisopropyl ether, dimethylformamide, dimethylsulfoxide, 1,4-dioxane, ethanol, ethyl acetate, heptanes, methanol, isopropyl acetate, methyl ethyl ketone, methyl isobutyl ketone, N-methyl-2-pyrrolidinone, nitromethane, isopropanol, tert-butylmethyl ether, tetrahydrofuran, toluene and mixtures thereof. In a preferred embodiment, the solvent is water. In another preferred embodiment, the antisolvent is isopropanol.

Also provided herein is a method of making crystalline cefotolozane sulfate, comprising one or more steps selected from the group consisting of: (1) combining cefotolozane freebase, sulfuric acid and water, such that an aqueous solution of cefotolozane sulfate is formed; and (2) combining isopropanol with the aqueous solution, such that crystalline cefotolozane sulfate precipitates or crystallizes from the solution. In another aspect, provided herein is a method of making crystalline cefotolozane sulfate, comprising: (1) combining cefotolozane freebase, sulfuric acid, and a solvent/antisolvent mixture, such that a solution of cefotolozane sulfate is formed; and (2) combining an antisolvent with the solution, wherein the antisolvent is miscible with the solvent and wherein cefotolozane sulfate is partially or completely insoluble in the antisolvent, such that crystalline cefotolozane sulfate precipitates or crystallizes from the solution. In another aspect, provided herein is a method of making crystalline cefotolozane sulfate comprising the steps of: a) dissolving cefotolozane sulfate in water to obtain a first solution of cefotolozane sulfate; b) combining the first solution of cefotolozane sulfate with isopropanol to afford a second solution of cefotolozane sulfate; c) crystallizing cefotolozane sulfate from the second solution to obtain crystalline cefotolozane sulfate. In another aspect, provided herein is crystalline cefotolozane sulfate produced according to any one of the preceding methods. In another aspect, provided herein is crystalline cefotolozane sulfate obtainable by any one of the preceding methods. The processes and methods described herein may also further comprise adding one or more seed crystals of crystalline cefotolozane sulfate.

As used herein, the term "precipitate" refers to the formation of a solid substance from a solution containing the same substance. A substance which precipitates from solution may be amorphous or crystalline. Precipitation may occur under a variety of conditions known to those of skill in the art, including the treatment of a solution of a solute (e.g., solute A in solvent B) with an antisolvent (i.e., a solvent that is miscible with solvent B, but does not dissolve solute A). Non-limiting examples of solvent/antisolvent pairs include water/isopropanol.

The solid forms of cefotolozane can be identified by various analytical techniques, such as X-ray powder diffraction (XRPD). Solid forms of cefotolozane sulfate in solid Form 1 and a novel cefotolozane solid Form 2 of cefotolozane sulfate can both be identified by XRPD both having one or more shared characteristic diffractions at angles ($2\theta \pm 0.2$) of 24.2 and 37.8. In addition, cefotolozane in both solid Form 1 and solid Form 2 can both produce the Raman spectra comprising one or more of the following peaks ($\pm 5\text{ cm}^{-1}$) at about 597 cm^{-1} , 716 cm^{-1} , and 1329 cm^{-1} . A preferred cefotolozane composition can include cefotolozane in one or more solid forms (e.g., solid Form 1 and/or solid Form 2) characterized by XRPD pattern with diffractions at angles ($2\theta \pm 0.2$) of 24.2 and 37.8, in addition to Raman spectra comprising one or more of the following peaks ($\pm 5\text{ cm}^{-1}$) at about 597 cm^{-1} , 716 cm^{-1} , and 1329 cm^{-1} . In addition, compositions comprising cefotolozane sulfate in solid Form 1 and/or solid Form 2 can be identified by XRPD patterns with diffractions at 2θ values ($2\theta \pm 0.2$) indicated in Table 4 (for Form 1) and/or Table 6 (for Form 2), respectively.

A novel cefotolozane solid Form 1 of cefotolozane sulfate can be identified by X-ray Powder Diffraction (XRPD), having one or more characteristic diffractions at angles ($2\theta \pm 0.2$) of 12.4, 16.4, 22.6, 25.1, and 28.0. In addition, cefotolozane in solid Form 1 can produce the Raman spectra comprising one or more of the following peaks ($\pm 5\text{ cm}^{-1}$) at 171 cm^{-1} , 743 cm^{-1} , 819 cm^{-1} , 1055 cm^{-1} , 2894 cm^{-1} , and 2976 cm^{-1} . In one embodiment, provided herein is crystalline cefotolozane sulfate Form 1 characterized by an X-ray powder diffraction pattern having peaks at substantially the same angles as the upper spectrum in FIG. 1. In another embodiment, the crystalline cefotolozane sulfate Form 1 is characterized by an X-ray powder diffraction pattern having one or more peaks at substantially the angles ($2\theta \pm 0.2$) as Table 4.

A novel cefotolozane solid Form 2 of cefotolozane sulfate can be identified by X-ray Powder Diffraction (XRPD), having one or more characteristic diffractions at angles ($2\theta \pm 0.2$) of 4.4, 8.8, 11.0, 14.9, and 17.7. In addition, cefotolozane in solid Form 1 can produce the Raman spectra comprising one or more of the following peaks ($\pm 5\text{ cm}^{-1}$) at 151 cm^{-1} , 684 cm^{-1} , 802 cm^{-1} , 1174 cm^{-1} , and 2953 cm^{-1} . In one embodiment, the crystalline cefotolozane sulfate Form 2 is characterized by an X-ray powder diffraction pattern having characteristic peaks at substantially the same angles as the lower spectrum in FIG. 1. In another embodiment, the crystalline cefotolozane sulfate Form 2 is characterized by an X-ray powder diffraction pattern having one or more peaks at substantially the same angles ($2\theta \pm 0.2$) as Table 6.

Crystalline forms of cefotolozane sulfate can also be characterized by their water content. In one embodiment, the crystalline cefotolozane sulfate comprises 11-27%, 12-26%, 13-25%, 14-24%, 15-23%, 16-22%, or 17-21% of water by weight. In a particular embodiment, the crystalline cefotolozane sulfate comprises 18-20% of water by weight. In another embodiment, the crystalline cefotolozane sulfate comprises

about 26.3% by weight of water. In a particular embodiment, the crystalline ceftolozane sulfate is ceftolozane sulfate decahydrate.

Crystalline forms of ceftolozane sulfate can also be defined by their water content. In one embodiment, crystalline ceftolozane sulfate comprises 4-10%, 5-9%, or 6-8% of water by weight. Form 1 of ceftolozane sulfate can include about 18-20% water. Form 2 of ceftolozane sulfate can include less than about 11% water, and preferably about 5-11% water, and most preferably about 7-8% water.

In another embodiment, the crystalline ceftolozane sulfate comprises about 7% of water by weight. In a particular embodiment, the crystalline ceftolozane sulfate is ceftolozane sulfate trihydrate.

In some embodiments, crystalline ceftolozane sulfate can be characterized by Raman spectroscopy. In a particular embodiment, the crystalline ceftolozane sulfate in Form 1 has a Raman spectrum substantially in accordance with the upper spectrum shown in FIG. 2. In another particular embodiment, the crystalline ceftolozane sulfate in Form 1 has a Raman spectrum with one or more peaks at substantially the same positions (± 5 cm⁻¹) as shown in Table 5. Ceftolozane solid Form 1 can produce Raman shift peaks comprising one or more of the certain peaks not observed in Form 1, at about (± 5 cm⁻¹) 171 cm⁻¹, 743 cm⁻¹, 819 cm⁻¹, 1055 cm⁻¹, 2894 cm⁻¹, and 2976 cm⁻¹.

In other embodiments, the crystalline ceftolozane sulfate in Form 2 has a Raman spectrum substantially in accordance with the lower spectrum shown in FIG. 2. In another particular embodiment, the crystalline ceftolozane sulfate in Form 2 has a Raman spectrum with one or more peaks at substantially the same positions (± 5 cm⁻¹) as shown in Table 7. Ceftolozane solid Form 2 can produce Raman shift peaks comprising one or more of the peaks at about (± 5 cm⁻¹) 151 cm⁻¹, 684 cm⁻¹, 802 cm⁻¹, 1174 cm⁻¹, and 2953 cm⁻¹.

Ceftolozane in solid Form 1 and solid Form 2 are both characterized by intense Raman shift peaks (± 5 cm⁻¹) at about 597 cm⁻¹, 716 cm⁻¹, and 1329 cm⁻¹. In addition, ceftolozane solid Form 1 and Form 2 can produce Raman shift peaks comprising one or more of the following peaks at indicated in both Table 5 and 7 (± 5 cm⁻¹).

In another aspect, provided herein is a composition comprising amorphous and crystalline solid forms of ceftolozane sulfate. In one embodiment, the composition comprises crystalline ceftolozane sulfate and amorphous ceftolozane sulfate, wherein the amorphous ceftolozane sulfate is present in an amount selected from the following ranges: 90-99%, 80-89%, 70-79%, 60-69%, 50-59%, 40-49%, 30-39%, 20-29%, 10-19%, 1-9% and 0-0.99%.

In some embodiments, the crystalline ceftolozane sulfate is a hydrate. In one embodiment, the crystalline ceftolozane sulfate is ceftolozane sulfate decahydrate. In a particular embodiment, the crystalline ceftolozane sulfate comprises 5-amino-4-[(2-aminoethyl)carbamoyl]amino}-2-[(6R, 7R)-7-[(2Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-[(1-carboxy-1-methylethoxy)imino]acetyl]amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-1H-pyrazolium monosulfate and water in a 1:10 molar ratio.

In another embodiment, the crystalline ceftolozane sulfate is ceftolozane sulfate trihydrate. In a particular embodiment, the ceftolozane sulfate comprises 5-amino-4-[(2-aminoethyl)carbamoyl]amino}-2-[(6R, 7R)-7-[(2Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-[(1-carboxy-1-methylethoxy)imino]acetyl]amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-1H-pyrazolium monosulfate and water in a 1:3 molar ratio.

Compared with previous crystalline forms of ceftolozane sulfate, certain novel crystalline forms of ceftolozane sulfate have advantageous properties. For example, these crystalline forms were found to be more chemically stable, which can be beneficial to the preparation of various drug formulations.

A pharmaceutical composition can comprise, and/or be obtained from, the solid form of ceftolozane sulfate designated as ceftolozane sulfate Form 2 that produces an X-ray powder diffraction (XRPD) pattern having diffractions at angles (2 theta $\pm$ 0.2) of 4.4, 8.8, 11.0, 14.9 and 17.7. The ceftolozane sulfate can produce Raman shift peaks (± 5 cm⁻¹) at about 151 cm⁻¹, 684 cm⁻¹, 802 cm⁻¹, 1174 cm⁻¹ and 2953 cm⁻¹.

A pharmaceutical composition can contain or be obtained from a solid form of ceftolozane characterized by one or more of the following: (a) the solid form of ceftolozane sulfate produces an XRPD pattern further comprising diffractions at angles (2 theta $\pm$ 0.2): 4.4, 8.8, 11.0, 14.9, and 17.7; (b) the solid form of ceftolozane sulfate of claim 1 that produces an XRPD pattern further comprising one or more additional diffractions at angles (2 theta $\pm$ 0.2) listed in Table 6; (c) the solid form of ceftolozane sulfate that produces Raman shift peaks at about (± 5 cm⁻¹) 151 cm⁻¹, 684 cm⁻¹, 802 cm⁻¹, 1174 cm⁻¹, and 2953 cm⁻¹; (d) the solid form of ceftolozane sulfate of claim 1 that produces one or more additional Raman shift peaks at values listed in Table 7; and any combination of one or more of characteristics (a)-(d).

A pharmaceutical composition can contain or be obtained from a lyophilized ceftolozane composition obtained by a process comprising the steps of: (a) combining ceftolozane sulfate in the solid form designated herein as ceftolozane sulfate in solid Form 2, with water, sodium chloride and L-arginine to form an aqueous solution; and (b) lyophilizing the aqueous solution to form the lyophilized composition comprising ceftolozane sulfate. The pharmaceutical composition obtained by such a method can include performing a lyophilization cycle characterized by one or more of the following characteristics: (a) not more than 150 mg ceftolozane free base/g bulk solution concentration, (b) no more than 3 cm fill depth, (c) freezing to at least -40°C. during the lyophilization cycle, (d) drying to no more than 40°C., and (e) single- or multi-step drying and setting chamber pressure during the start of primary drying at not more than 400 μ bar.

A ceftolozane sulfate composition can be obtained by a process comprising the steps of: (a) forming a solution comprising water, 72-100 g/L ceftolozane active and 1.5-2.95 molar equivalents of sulfuric acid to ceftolozane; (b) combining the solution from step (a) with 20-40 volumes of isopropyl alcohol added to the solution over 0.5-8 hours to obtain solid ceftolozane sulfate; and (c) isolating the solid ceftolozane sulfate composition from the solution.

Pharmaceutical compositions comprising ceftolozane and tazobactam can be obtained by blending a first composition comprising a therapeutically effective amount of ceftolozane with a second composition comprising a therapeutically effective amount of tazobactam to form a blended pharmaceutical composition. The pharmaceutical composition can comprise ceftolozane or a therapeutically effective salt thereof and tazobactam or a pharmaceutically effective salt thereof in an amount providing about 500 mg of tazobactam active per 1,000 mg of ceftolozane active. The pharmaceutical antibiotic composition preferably includes ceftolozane and tazobactam in a 2:1 weight ratio of ceftolozane active to tazobactam active ("CXA-201"), which displays antibacterial activity, including antibiotic activity against infections caused by many Gram-negative pathogens such as *Pseudomonas aeruginosa* (*P. aeruginosa*). 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.

Methods of treating an infection selected from the group consisting of: complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI), or hospital acquired/ventilator-associated bacterial pneumonia (HABP/VABP) are also provided herein. These methods can include administering to a patient an injectable pharmaceutical composition comprising ceftolozane in an injectable preparation prepared from a lyophilized composition obtained by a process comprising the steps of: (a) combining the ceftolozane sulfate in a solid form that produces an X-ray powder diffraction (XRPD) pattern having diffractions at angles ($2\theta \pm 0.2$) of 4.4, 8.8, 11.0, 14.9, and 17.7 with water to form an aqueous solution; and (b) lyophilizing the aqueous solution to form the lyophilized ceftolozane composition comprising ceftolozane sulfate.

Pharmaceutical compositions can be obtained by combining tazobactam (or a pharmaceutically acceptable salt thereof) in one or more solid forms with a ceftolozane composition comprising ceftolozane in one or more salts and/or solid forms. The ceftolozane in the pharmaceutical composition can be ceftolozane sulfate in one or more solid forms disclosed herein, including amorphous, Form 1, Form 2 and/or combinations thereof. The ceftolozane in the pharmaceutical composition can be obtained by a process comprising lyophilizing a solution of ceftolozane sulfate in solid Form 1, solid Form 2 and/or combinations thereof. For example, the ceftolozane in the pharmaceutical composition can be prepared in the absence of tazobactam by forming an aqueous solution comprising ceftolozane sulfate in solid Form 1, solid Form 2 and/or combinations thereof 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 of a ceftolozane stabilizing agent (such as 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 aqueous solution comprising ceftolozane (e.g., ceftolozane sulfate in Form 2, and/or other solid forms disclosed herein) 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.

The pharmaceutical composition can be obtained by combining the ceftolozane composition with a (second) tazobactam composition (e.g., preferably, but not necessarily, 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 beta-lactamase inhibitor in its free acid form. 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.

Pharmaceutical compositions can be obtained by lyophilization (e.g., lyophilizing an aqueous ceftolozane solution obtained by dissolving ceftolozane in Form 2 and/or Form 1 with other components such as a stabilizing agent, a chelating agent and/or an alkalizing agent). 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).

Pharmaceutical compositions comprising 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.

The pharmaceutical antibiotic compositions can be provided in a unit dosage form container (e.g., in a vial or bag, or the like). 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, arginate or free acid. The unit dosage forms are commonly stored in vials.

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, 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:

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,

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

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

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 composition.

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:

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;

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

As provided herein, ceftolozane can be stabilized in a pharmaceutical composition comprising ceftolozane and a stabilizing effective amount of a stabilizing agent selected from the group consisting of: sodium chloride, dextran 40, lactose, maltose, trehalose and sucrose. The pharmaceutical compositions provided herein are based in part on the surprising discovery that ceftolozane pharmaceutical compositions comprising these stabilizing agents demonstrate improved ceftolozane residual rates (e.g., % ceftolozane remaining after 3 days at 70 degrees C. as measured by HPLC) and/or chemical stability (e.g., lower reduction in ceftolozane purity measured by HPLC after 7 days at 60 degrees C. in a stability test) compared control samples comprising ceftolozane without a stabilizing agent.

Accordingly, preferred pharmaceutical antibiotic compositions can include ceftolozane sulfate and a stabilizing agent (e.g., 300 to 500 mg of a stabilizing agent per 1,000 mg ceftolozane active) in a lyophilized unit dosage form (e.g., powder in a container). The unit dosage form can be dissolved with a pharmaceutically acceptable carrier (e.g., 0.9% sodium chloride aqueous isotonic saline and/or water for injection), and then intravenously administered. In certain ceftolozane compositions, the stabilizing agent can be selected from the group consisting of: sodium chloride, lactose, maltose and dextran 40, and/or selected from the group consisting of: sodium chloride, trehalose and sucrose.

Ceftolozane pharmaceutical compositions comprising 125 to 500 mg (e.g., 480 to 500 mg) of sodium chloride per 1000 mg of ceftolozane active demonstrate improved ceftolozane purity and chemical stability compared to pharmaceutical compositions comprising ceftolozane with comparatively less sodium chloride. The disclosed ceftolozane pharmaceutical compositions comprise a stabilizing amount of sodium chloride (e.g., 125 to 500 mg of sodium chloride [more specifically, 480 to 500 mg] per 1000 mg of ceftolozane active). Certain preferred compositions demonstrate improved ceftolozane purity and chemical stability compared with pharmaceutical compositions comprising ceftolozane with comparatively less sodium chloride. For example, the disclosed pharmaceutical compositions typically comprise less than about 4% total impurity after being stored for seven days at 60 degrees C., as determined by HPLC. Alternatively, the disclosed pharmaceutical compositions comprise less than about 2% of the impurity represented by Peak 1 after being stored for seven days at 60° C., as determined by HPLC (refer to the HPLC method described in Table 10), where Peak 1 has a retention time relative to ceftolozane of approximately 0.15.

Another embodiment of the invention is a container 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 container can be obtained by a process comprising the steps of: a) lyophilizing an aqueous solution comprising 189 mg sodium from sodium chloride per 1000 mg ceftolozane active in the form of ceftolozane sulfate and further comprising citric acid, and L-arginine to obtain a lyophilized ceftolozane composition; and b) filling a

sufficient quantity of the lyophilized composition into a container to obtain a unit dosage form comprising a ceftolozane stabilizing effective amount of sodium from sodium chloride (e.g., 125-500 mg sodium chloride per 1 g ceftolozane active) and 1,000 mg of ceftolozane active in the form of ceftolozane sulfate. In one aspect, the pH of the aqueous solution is 6.0 to 7.0. In another aspect the pharmaceutical composition is formulated for parenteral administration by reconstituting the pharmaceutical composition in the container (e.g., with 10 mL of diluent such as water for injection or isotonic saline) followed by addition of the reconstituted pharmaceutical composition to a carrier for injection (e.g., about 100 mL of isotonic saline or other pharmaceutically acceptable carrier for intravenous administration). Optionally, the container is also filled with tazobactam (e.g., a lyophilized tazobactam such as tazobactam sodium). In yet another aspect, the pharmaceutical composition is a liquid composition comprising 487 mg sodium chloride per 1,000 mg of ceftolozane active and tazobactam in an amount providing about 500 mg tazobactam acid equivalent per 1,000 mg of ceftolozane active, formulated for parenteral administration and the pH of the aqueous solution is 5.0 to 7.0 and preferably about 6.0 to 7.0.

The pharmaceutical composition in the container can also be a Ceftolozane/Tazobactam for Injection Drug Product, 1000 mg/500 mg. It is presented as a combination of two sterile active powders in a single container intended for reconstitution and intravenous infusion. In one embodiment, the drug product is prepared by converting ceftolozane sulfate to a sterile composition as a powder with excipients citric acid, sodium chloride and L-arginine. This is can done by lyophilization, as described herein. Tazobactam sodium drug substance can be presented as a sterile powder without any excipients. The tazobactam sodium drug substance can be lyophilized, spray dried or provided as a crystalline material. The drug product is then prepared by aseptically filling the two powders (e.g., the two separately lyophilized drug powders) sequentially into a single container.

In an embodiment, the container of ceftolozane/tazobactam for injection contains approximately 2255 mg ceftolozane sterile composition powder that contains 1147 mg ceftolozane sulfate, which is equivalent to 1000 mg ceftolozane free base, as well as approximately 537 mg tazobactam sodium sterile drug substance, equivalent to 500 mg tazobactam free acid. At the time of administration, the container is reconstituted with 10 mL vehicle, sterile 5% Dextrose Injection USP, Water for Injection or 0.9% Sodium Chloride Injection USP, then the container contents further diluted in an infusion bag of 0.9% Sodium Chloride Injection USP or 5% Dextrose Injection USP, for administration.

Ceftolozane-containing pharmaceutically compositions can also include an amount of tazobactam in a pharmaceutically acceptable form providing 500 mg of tazobactam acid per 1,000 mg of ceftolozane active as a composition formulated for injection, or for reconstitution prior to parenteral administration. In one product presentation, ceftolozane/tazobactam can be provided in a single container comprising ceftolozane sulfate and tazobactam sodium, administered by reconstituting a container-unit dosage form container of solid ceftolozane/tazobactam to form a reconstituted injectable formulation. In one presentation (e.g., for treatment of certain urinary tract infections and/or certain intra-abdominal infections), each unit dosage form container of CXA-201 can contain 1000 mg of ceftolozane active (free base equivalent weight, e.g., provided as a pharmaceutically acceptable salt such as ceftolozane sulfate) and sterile tazobactam sodium at a quantity equivalent of 500 mg of tazobactam free acid, in a solid form. In another presentation (e.g., for treatment of

hospital acquired/ventilator-associated bacterial pneumonia (HABP/VABP)), a ceftolozane/tazobactam product can include a unit dosage form container providing 2,000 mg of ceftolozane active (e.g., as an equivalent amount of ceftolozane sulfate) and 1,000 mg of tazobactam acid (e.g., as an equivalent amount of tazobactam sodium). Ceftolozane/tazobactam compositions display potent antibacterial activity against various gram-negative infections such as, for example, complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI), or hospital acquired/ventilator-associated bacterial pneumonia (HABP/VABP).

Ceftolozane/tazobactam can be used for treating an infection selected from the group consisting of: urinary tract infections, and intra-abdominal infections. The methods of treatment can include intravenously administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition comprising ceftolozane sulfate and an amount of tazobactam providing about 500 mg of tazobactam active per 1,000 mg of ceftolozane active, the ceftolozane sulfate in the pharmaceutical composition obtained from a ceftolozane sulfate solid form obtained by a process comprising the steps of: (a) combining the ceftolozane sulfate in a solid form, designated as ceftolozane sulfate Form 2, with water, sodium chloride and L-arginine to form an aqueous solution; (b) lyophilizing the aqueous solution to form the lyophilized ceftolozane composition comprising ceftolozane sulfate; (c) combining the lyophilized ceftolozane composition with tazobactam to obtain the pharmaceutical composition; (d) reconstituting the pharmaceutical composition in a pharmaceutically acceptable diluent; and (e) intravenously administering the reconstituted pharmaceutical composition to the patient.

EXAMPLES

Instrumentation and Methods

Other than Comparative Example 1, and unless otherwise indicated, the following instrumentation and methods were used in the working Examples described herein. Comparative Example 1 is reported in U.S. Pat. No. 7,232,129.

X-ray Powder Diffraction (XRPD)

High Resolution X-ray Powder Diffraction experiments (Bruker, AXS D8 Advance) were performed on a Bruker D8 diffractometer using Cu K α radiation (40 kV, 40 mA), θ -2 θ goniometer, and primary & secondary soller slits (2.5°, a Ge monochromator and Lynxeye detector (opening angle of 2.948°). Certified Corundum standard (NIST 1976) was used to check the performance of the instrument. Data collection was performed by the Diffrac.Suite Measurement Center v2.2.47.1 and the data was analyzed and presented using Diffrac.EVA v2.0 or v3.0.

Samples were tested under ambient conditions. Approximately 500 mg of each sample was grinded for 3 minutes in a mortar and pestle. The sample was prepared by back-loading the triturated material into the sample holder and supporting it with a zero background silicon wafer. Once tightly packed, a flat surface was formed. When the sample was carefully flipped over, the appearance of the API in the sample holder appeared very similar to the appearance of the Corundum sample for NIST used to verify the performance of the instrument. The scan type of coupled TwoTheta/Theta was used for the data collection. The angular range was 2 to 50° 2 θ , and the step size was 0.001° 2 θ . Collection Time was 1 s for the each step. The goniometer radius was set at 280 mm. Sample rotation speed was 15 rpm, and the slit size was 0.1 mm.

Thermal Analysis

Thermo Gravimetric Analysis (TGA) experiments were performed on a TA Instruments Discovery Series TGA. The calibration for temperature was carried out using certified indium. Typically, 3-15 mg of a sample was flattened into sealed aluminum pans. Data was acquired for samples with and without a pinhole. For samples with a pinhole, once crimped and sealed, the auto-sampler punched the lid of the sample with its internal puncher right before analysis of the sample. Samples were heated at 20° C./min from 30° C. to 400° C. Dry nitrogen was purged into the system during the experiment at a rate of 50 ml/min. The software used to control the instrument was TRIOS Explorer Software v5.3.0.75. TRIOS software v2.40.1838 or v2.04.04563 was used for data analysis.

Differential Scanning calorimetry (DSC) experiments were performed on a TA Instruments Q2000 was used for collecting DSC data. The calibration for thermal capacity was carried out using sapphire and the calibration for energy and temperature was carried out using certified indium. Typically, 3-10 mg of a sample is flattened into sealed aluminum hermetic pans and the weight accurately recorded. Data was acquired for samples with a pinhole in the lid. Samples were heated at 10° C./min from 25° C. to 350° C. Dry nitrogen was purged into the system during the experiment at a rate of 50 ml/min. The software used to control the instrument is the Advantage for Q Series v2.9.0.396 and the Thermal Advantage v5.4.0. Data was analyzed using the Universal Analysis v4.5A software.

Gravimetric Dynamic Vapour Sorption

Gravimetric dynamic vapor sorption data (FIG. 5) was obtained using a SMS DVS Intrinsic moisture sorption analyzer, controlled by DVS Intrinsic Control software v1.0.0.30. The sample temperature was maintained at 25° C. by the instrument controls. The humidity was controlled by mixing streams of dry and wet nitrogen. The relative humidity was measured by a calibrated Rotronic probe, located near the sample. The weight change of the sample as a function of % RH was constantly monitored by the microbalance (accuracy ± 0.005 mg). Approximately 40 mg of sample was placed in a tared mesh stainless basket under ambient conditions. Weight reference was established at the start of an experiment. Moisture sorption isotherm parameters were described as below:

TABLE 2

Parameters	Values
Scan 1 Adsorption	40%-90%
Scan 2 Desorption/Adsorption	90%-0%/(0%-40%)
Interval (RH step increments)	10%
Number of Scans	4 (double cycle)
Flow rate for dry and wet N ₂	200 ml/min
Temperature	25° C.
Temperature Stability	0.2° C./min
Time out	6 hrs

Data analysis was undertaken in Microsoft Excel using DVS Analysis Suite v6.0. The sample was recovered after completion of the isotherm experiment for solid state characterization.

Spectroscopy Measurement

Raman spectra were acquired on a Fourier transform Raman 960 spectrometer (Thermo Nicolet) equipped with a germanium (Ge) detector. Wavelength verification was performed using sulfur and cyclohexane. Each sample was packed into a pellet and placed into a pellet holder accessory for analysis. Approximately 0.505 W of Nd:YVO₄ laser power (1064 nm excitation wavelength) was used to irradiate each sample. Peak lists were generated using OMNIC software v7.2a.

Solid Form Disclosed in U.S. Pat. No. 7,129,232

A solution of 7 β -[(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 (36 g) in water was purified by preparative HPLC utilizing ODS column. The eluate containing a desired product was concentrated to about 1.5 L in vacuo. The concentrate was adjusted to about pH 1 with concentrated hydrochloric acid and chromatographed on Diaion® HP-20 (6 L) eluting with 20% aqueous 2-propanol. The eluate was concentrated to about 800 ml in vacuo, and 2M sulfuric acid (17 ml) was added. The resulting solution was lyophilized to give a sulfuric acid salt as an amorphous powder (23.6 g).

The powder was dissolved in water (71 ml) and ethanol (57 ml). After addition of seed crystals (310 mg), which resulted in the precipitation of white solid, the mixture was stirred for 1 hour. A mixture of ethanol (47 ml) and water (37 ml) was added over 30 minutes, and ethanol (33 ml) was added over 20 minutes. Then the slurry was stirred for an additional 1.5 hour. The precipitate was collected by filtration, washed with ethanol/water (60 ml/20 ml) and ethanol (60 ml) and dried to give 7 β -[(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-carboxylic acid hydrogen sulfate as crystals (17.3 g).

IR(KBr) 3353, 3183, 1778, 1652, 1558, 1403, 1321, 1143, 1118, 997, 619 cm⁻¹

¹H-NMR (D₂O) δ 1.61 (6H, s), 3.10-3.55 (6H, m), 3.71 (3H, s), 5.02 and 5.23 (2H, ABq, J=16.7 Hz), 5.25 (1H, d, J=4.9 Hz), 5.87 (1H, d, J=4.9 Hz), 7.91 (1H, s)

ESI-MS: m/z=667 (M+H⁺)

TABLE 3

X-ray powder diffraction analysis (by Rigaku X-ray Diffraction system MultiFlex)	
2 θ	intensity
8.0	1286
12.7	585
13.8	423
16.1	618
18.9	520
20.4	748
21.5	667
22.4	1058
23.3	944
24.0	618
25.5	813
26.7	472
27.9	537
28.5	455
31.3	390

X-ray: Cu/40 kV/30 mA

Example 2a

Novel Solid Form of Cefotolozane Sulfate

To obtain cefotolozane sulfate in Form 1: cefotolozane (1 molar equivalent) was dissolved in water to afford a solution at a concentration of 80 g/L. An aqueous solution of sulfuric acid (20-98%, 2.5 molar equivalents) was added at 0-20° C. The resulting solution was seeded with cefotolozane sulfate (0.01 to 0.05% by weight relative to active cefotolozane) and

allowed to stir for 1-3 hours at 0-20° C. A precipitation was observed. Isopropanol (20-40 volumes relative to active cefotolozane) was added to result in a slurry at 0-20° C. After filtration, crystalline cefotolozane sulfate was obtained. The X-ray powder diffraction pattern of the crystalline cefotolozane sulfate Form 1 is depicted in FIG. 1 (upper diffraction pattern), and the corresponding data is summarized in Table 4. The Raman spectrum of the crystalline cefotolozane sulfate Form 1 is depicted in FIG. 2 (upper spectrum), and the corresponding data is summarized in Table 5.

TABLE 4

X-ray Powder Diffraction Patterns for Cefotolozane Sulfate Form 1 (Example 2a) Cefotolozane Sulfate Form 1	
Angle [°2 θ]	Intensity [cts]
4.061	629
8.126	3275
9.748	511
10.865	521
12.435	399
12.954	1225
14.016	867
14.284	613
16.177	937
16.413	1048
18.796	847
19.094	1024
20.200	484
20.596	1393
21.732	1260
22.278	1098
22.603	1816
23.490	1554
23.777	720
24.268	913
25.059	590
25.678	1261
25.929	1107
26.746	701
27.102	619
28.017	854
28.668	792
29.265	390
29.972	428
31.513	612
32.917	423
33.526	512
34.773	431
35.191	408
36.111	361
37.504	366
37.723	373
38.778	312
40.860	299
41.631	350
44.084	281
45.997	235

TABLE 5

Raman peaklist for cefotolozane sulfate Form 1 (Example 2a) Cefotolozane Sulfate Form 1	
Position (cm ⁻¹)	Intensity (Counts)
170.5	5.402
276.5	3.852
336.1	2.78
381.2	3.172
424	3.787
530.9	2.974
596.7	2.607
680.9	3.385

TABLE 5-continued

Raman peaklist for cefotolozane sulfate Form 1 (Example 2a) Cefotolozane Sulfate Form 1	
Position (cm ⁻¹)	Intensity (Counts)
716.2	3.408
742.8	2.64
798.8	4.282
818.7	12.666
951.9	3.307
980.9	5.46
1055.3	1.794
1135.1	3.121
1242	2.471
1285	2.835
1328.5	3.402
1418.7	7.494
1464.1	15.996
1607.7	10.642
1642.3	8.252
1786	3.322
2893.8	5.886
2940.8	7.789
2976.1	8.658
3265.8	1.5

Example 2b

Novel Solid Form of Cefotolozane Sulfate

To obtain cefotolozane sulfate in Form 2: The cefotolozane sulfate obtained as Form 1 in Example 2a was dried under vacuum and nitrogen bleed at 20-25° C. for 24-48 hours to afford crystalline cefotolozane sulfate (vacuum-dried). The X-ray powder diffraction pattern of the crystalline cefotolozane sulfate Form 2 is depicted in FIG. 1 (lower diffraction pattern), and the corresponding data is summarized in the Table 6.

TABLE 6

X-Ray Powder Diffraction Pattern of Cefotolozane Sulfate Form 2 (Example 2b) Cefotolozane Sulfate Form 2	
Angle [°2θ]	Intensity [cts]
4.400	348
7.900	950
8.827	700
9.381	466
11.000	536
12.861	981
13.980	534
14.913	479
15.753	610
17.673	711
18.749	923
20.488	858
21.692	924
22.178	1020
24.235	1000
25.678	842
27.180	708
28.593	587
31.482	546
33.277	508
34.397	438
35.789	428
37.767	403

The Raman spectrum of the crystalline cefotolozane sulfate Form 2 is depicted in FIG. 2 (lower spectrum), and the corresponding data is summarized in Table 7. Table 7 lists the Raman shift peaks for cefotolozane sulfate in solid Form 2.

TABLE 7

Raman peak list for cefotolozane sulfate form 2 (Example 2b) Cefotolozane Sulfate Form 2	
Position (cm ⁻¹)	Intensity (Counts)
151	11.618
282	6.341
418.1	6.139
530.2	4.005
596.8	5.656
683.7	7.226
716.2	6.968
802.3	7.45
976.9	7.505
1174.2	3.974
1237	4.582
1282.1	6.944
1328.1	6.577
1414.3	12.424
1458.5	25.508
1502.2	20.204
1637.5	15.561
1782	5.388
2552.8	7.588

The moisture sorption/desorption property of crystalline cefotolozane sulfate form 2 is depicted in FIG. 5. A reversible hysteresis associated with around 23% w/w water between 0% and 90% relative humidity (RH) was observed. The DVS isotherm in FIG. 5 is consistent with the presence of two crystalline forms that can be interconverted as function of relative humidity. The presence of cefotolozane sulfate solid Form 1 and cefotolozane sulfate solid Form 2 in the sample tested to obtain the DVS isotherm in FIG. 5 was confirmed by a variable humidity XRPD (VH-XRPD) measurement, based on the XRPD diffraction angles disclosed for Form 1 and Form 2 of cefotolozane sulfate (as disclosed herein). Referring to DVS the isotherm plot in FIG. 5, the lower curve corresponds to cefotolozane sulfate in solid Form 2, and the upper curve is corresponds to cefotolozane sulfate in solid Form 1. The Y-axis of the DVS plot is change in mass. The X-axis of DVS plot refers to the percent relative humidity (RH) of the sample. Reference point 10 in FIG. 5 is the starting point of Form 2 in DVS experiment. The lower portion of the curve in FIG. 5 was obtained by measuring the change in mass of a cefotolozane sulfate sample in solid Form 2 while increasing relative humidity (RH) in the sample, starting at reference point 10 of the lower curve from reference point 10 (Form 2) and moving toward reference point 20 (Form 1). Based on the data collected, the cefotolozane sulfate in the sample converted from Form 2 to Form 1 when the sample was exposed to conditions between 50% RH (reference point 12) and 70% RH (reference point 15). Referring again to the lower curve in FIG. 5, cefotolozane sulfate in Form 1 is present in the sample from 70% RH to reference point 20, where the sample is cefotolozane sulfate is in crystalline Form 1. Referring to the upper curve in FIG. 5, from reference point 20 to reference point 30, the cefotolozane sulfate in the sample material remains as solid Form 1. From reference point 30 to around 20% RH (reference point 35 on the upper curve), the crystalline form of cefotolozane sulfate in the material transforms from Form 1 to Form 2. As the relative humidity of the sample was dropped below about 20% on the upper curve between reference point 30 and reference point 40 (0% RH), the cefotolozane sulfate became more amorphous, with some residual Form 2 remaining at reference point 40. In summary, the cefotolozane sulfate in the sample was present as Form 2 at reference point 10 (40% RH), converted from Form 2 to Form

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1 between reference point 12 and reference point 15 on the lower curve, remained as solid Form 1 between reference point 20 and reference point 30 on the upper curve, converted from Form 1 to Form 2 between reference point 30 and reference point 35 on the upper curve, and remained as solid Form 2 from reference point 35 to reference point 40 (with formation of amorphous solid form in the sample). From reference point 40 to reference point 10 (lower curve), increasing the relative humidity of the partially crystalline Form 2 material resulted in material retaining some ceftolozane sulfate in Form 2 (partially crystalline).

Example 2d

Representative Example of Process to Manufacture Novel Solid Forms of Ceftolozane Sulfate

Using the process of steps 1-9 (below), active ceftolozane sulfate Form 2 was obtained as a white solid, with a weight assay of 76.2% (determined using HPLC method described with respect to parameters in Table 9 herein) and purity of 98.7% AUC using HPLC (determined using HPLC method discussed with respect to Table 10 herein). The ceftolozane sulfate solid Form 1 was produced by steps 1-8 in the procedure below, and further dried (step 9) to obtain ceftolozane sulfate Form 2. The materials used in the process below are summarized in Table 8a.

TABLE 8a

Step	Material	MW (g/mol)	Active (kg)	Amount (L)	Volume (L/kg)	Molar equiv.
1	Ceftolozane solution	666.7	55	650	N/A	1
2	50% (w/w) sulfuric acid	98.1	41	29	N/A	2.5
3	Ceftolozane sulfate seed	666.7	0.20	N/A	N/A	N/A
5	Isopropyl alcohol (IPA)	60.1	N/A	1653	30	N/A
8	IPA/Water (4:1)	N/A	N/A	221	4	N/A

- Polish filter (1 micrometer) the ceftolozane solution (85 g/L, 650 L) into a glass lined reactor and adjust the temperature to 8-12 degrees C., with a target temperature of about 10 degrees C. This temperature is maintained through step 6.
- Charge 50% (w/w) sulfuric acid (41 kg, 29 L, 2.5 equiv) to the solution in the reactor of step 1 over 10-30 minutes.
- (optional, but preferred step) Charge ceftolozane sulfate seed (200 g, 0.3% by weight) to the reactor and stir the solution. (Note: nucleation was observed upon seeding)
- Age the batch in the reactor for 3 hours.
- Charge isopropanol (IPA) (1650 L, 30 volumes) to the reactor at a uniform rate of 4-5 vol/hr. (6-7 hours addition time, target of 6.5 hours) (Note: if the rate of IPA addition is not uniform, the purity levels of the product may be adversely affected)
- Stir the batch in the reactor for 1-6 hours, target of 2 hours.
- Filter the resulting ceftolozane sulfate slurry from the reactor.
- Wash the ceftolozane slurry cake from step 7 with a solution of 4:1 IPA/water. (221 L, 4 volumes)
- Dry the solid from step 8 under vacuum using a dry nitrogen purge, with a nitrogen temperature of 15-35 degrees C., target temperature of about 25 degrees C. The drying process should be monitored by measuring for residual water and IPA levels in the cake. The drying process can be completed when the residual water content is less than

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about 8.5% and IPA levels are less than about 5000 ppm. Typically, drying is complete within 48 hours.

Example 3

Comparative Ceftolozane Solvent Stability Test

This stability study was to evaluate stability and purity of ceftolozane sulfate in different solvent systems.

Sample 1 was a solvent system used to prepare crystalline ceftolozane sulfate from a mixture of isopropanol and water, as described in Example 2b (in the absence of ethanol). Sample 2 was solvent system used to obtain crystalline ceftolozane sulfate prepared according to the procedure of U.S. Pat. No. 7,129,232, wherein the crystals were precipitated from a mixture of ethanol and water.

Sample 1 and sample 2 were maintained for 6 days (as described in Example 2a, with continuous stirring). The purity of ceftolozane in the samples in each solvent system was measured by HPLC at day 0, day 3, and day 6.

Surprisingly, the purity of ceftolozane sulfate in sample 1 was significantly higher than the purity of ceftolozane sulfate in sample 2 (see Table 8b).

TABLE 8b

The purity of ceftolozane in ceftolozane sulfate in different solvent systems used to obtain different solid forms

Sample	0	3 days	6 days
1	96.74%	87.39%	81.94%
2	96.84 %	87.97%	67.74%

Example 4

Determination of Water Content for Crystalline Ceftolozane

Water content of crystalline ceftolozane sulfate (prepared according to Example 2a as Form 1) was determined using a Mettler Toledo Karl Fischer volumetric titrator V30 that was connected to a Mettler Toledo Stromboli oven sample changer. AquaStar CombiTitrant 5 (EMD; Cat. No. 1.88065.1045; Lot No. 51096) was used as the titrant and the AquaStar Combi-Methanol (EMD; Cat. No. 1.88009.1045; Lot No. 53046) was used as the solvent. For data processing, the LabX software version 3.1.1.0 was employed.

The Hydranal Water Standard for KF-Oven (Fluka; Cat. No. 34693; Lot No. SZBB010AV) that is expected to contain 5% water was weighed accurately in duplicate at or very close to 200 mg. The crystalline ceftolozane sulfate (15-18 mg) was weighed accurately in triplicate in separate 20 mL Stromboli sample vials. The vials were sealed with aluminum seals and rubber caps. A blank vial was prepared by sealing an empty 20-mL Stromboli vial with the aluminum seal and the rubber cap. The blank vial was used to determine the background moisture in air inside the vial. All the vials were loaded onto the Stromboli oven sample changer. Weights of the water standard and the ceftolozane sulfate wet cake samples were entered in grams into the titrator program sequence. The water standard and the blank vial were equilibrated at 150° C. The crystalline ceftolozane sulfate samples were equilibrated at 130° C. Nitrogen flow at 40-50 mL/min was used to transport the moisture through the transfer tube into the titator vessel. Mixing time of 180 s was used and the data acquisition

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was programmed with a maximum start drift of 15 µg/min. At the end of the runs, the titrator software provided the water content in percent by weight. The KF titrator passed the accuracy test as the mean of the duplicate readings for the water standard was between the acceptance range of 4.80-5.20%. Water content results for crystalline cefotolozane sulfate derived from the triplicate weighings were recorded and the mean was reported. The water content determination follows the equation as described below. The software described above provided the result directly after factoring in the background moisture content without any need for manual computation.

A sample of crystalline cefotolozane sulfate prepared according to Example 1 was found to contain about 26.3% by weight of water.

Example 5

Determining Concentration of Cefotolozane

Standards and samples are prepared in 50 mM sodium perchlorate monohydrate, pH 4.00. A quantitation standard (Standard Solution 1) and check standard (Standard Solution 2) are both prepared at the target working concentration of 0.3 mg/mL taking into consideration the potency, as-is of the standard. The samples are prepared at the target active concentration of 0.3 mg/mL by preparing a sample at 0.04% (w/v).

TABLE 9

HPLC Conditions for Concentration Determination			
Column	Develosil ODS-UG-5, 5 µm, 250 mm x 4.6 mm, or Develosil ODS-UG-5, 5 µm, 10 mm x 4.0 mm, or		
Guard columns	40° C. ± 2° C.		
Column temperature	Gradient		
Mode	50 mM Sodium perchlorate monohydrate, pH 2.50		
Mobile phase A	90% Acetonitrile in water		
Mobile phase B			
Pump conditions	Time (min)	% A	% B
	0.0	89.5 ^a	10.5 ^a
	10.0	89.5 ^a	10.5 ^a
	15.0	20	80
	20.0	20	80
	20.1	89.5 ^a	10.5 ^a
	25.0	89.5 ^a	10.5 ^a
Flow rate	1.0 mL/minute		
Detection	UV at 254 nm		
Auto-sampler temperature	4° C. ± 2° C.		
Injection volume	10 µL		
Run time	25 minutes		

^aThe ratio of Mobile phase A to Mobile phase B may be adjusted to achieve the desired retention time, however the isocratic ratio of % A to % B must be identical for both isocratic intervals.

Standard Solution 1 is injected 6 times at the beginning of the analysis to establish system suitability and precision.

System suitability is determined using the first injection of Standard Solution 1. The tailing factor for the cefotolozane peak be 0.8 to 1.5 and the retention time for the cefotolozane peak should be 10.0 minutes ± 1.5 minutes. The binary pump setting at isocratic portions of the run (0.0 to 10.0 minutes and 20.1 to 25.0 minutes) may be adjusted to achieve the cefotolozane peak retention time.

Additional suitability of the run is determined by: % RSD of 6 Standard Solution 1 injections must be less than 1.0% The Standard Solution 2 recovery must be 100.0±1.0%.

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The retention time of Standard Solution 2 must be ±5% of the RT of the first injection of Standard solution 1.

The tailing factor of cefotolozane in Standard Solution 2 must be 0.8 to 1.5.

Each sample is prepared in duplicate and injected in singlet. The ratio of the response factor for the two preparations must be within 100.0±1.0%.

The mean cefotolozane potency, as is, is reported in µg/mg and calculated using the following equations:

$$\text{Potency, as-is (µg/mg)} = \frac{Ac \times Cstd \times 1000 \times Vc}{Astd \times Wc};$$

where:

- Ac=Cefotolozane peak area in sample chromatogram;
- Cstd=Cefotolozane Standard 1 concentration, mg/mL;
- Astd=Average peak area in 6 injection of standard 1;
- Wc=Sample weight, mg;
- Vc=Sample volume, mL;
- 1000=Conversion from mg to µg; and

$$\text{Mean Potency, as-is (µg/mg)} = \frac{(\text{Preparation 1} + \text{Preparation 2})}{2}$$

The mean cefotolozane assay, anhydrous and sulfuric acid free, is reported in % and calculated using the following equation:

$$\text{Mean Assay(\%)} = \text{Potency} \times 10 / (100 - \text{Water Content} - \text{Sulfuric Acid});$$

where:

- Potency=Mean Potency, as-is, µg/mg;
- Water Content=Mean water content, %; and
- Sulfuric Acid=Mean sulfuric acid content, %.

Example 6

Determining Water Content of Cefotolozane

Testing for water content is performed using a Stromboli oven and volumetric titrator in triplicate using separate weighing of 180 mg of cefotolozane sulfate. The test sample is extracted at 130° C., moisture is transferred to the titration vessel and titrated to the potentiometric end point. The percent moisture is calculated based on the weight of the sample, and the average of the three values is reported.

Example 7

Determination of the Purity of Cefotolozane Sulfate

Cefotolozane sulfate samples are prepared at a concentration of 1 mg/mL in diluent (50 mM sodium perchlorate monohydrate, pH 4.00). The system suitability standard (SST) is prepared at a concentration of 1 mg/mL of cefotolozane sulfate containing specified impurities in diluent (50 mM sodium perchlorate monohydrate, pH 4.00). Cefotolozane samples and SST are stored in a refrigerated autosampler tray at 4±2° C. and the samples are only stable for 5 hours at this condition. The HPLC conditions are listed in Table 10.

TABLE 10

HPLC Conditions for HPLC-RT, Related Substances, and Purity Method			
Column	Develosil ODS-UG-5, 5 μ m, 250 mm $\times$ 4.6 mm, or equivalent		
Guard columns	Develosil ODS-UG-5, 5 μ m, 10 mm $\times$ 4.0 mm, or equivalent		
Column temperature	45° C. $\pm$ 2° C.		
Mode	Gradient		
Mobile phase A	50 mM Sodium perchlorate monohydrate, pH 2.50		
Mobile phase B	63 mM Sodium perchlorate monohydrate, pH 2.50; ACN 80:20		
Pump conditions	Time (min)	% A	% B
	0.0	97.5	2.5
	3.0	73.0 ^a	27.0 ^a
	33.0	68.0 ^a	32.0 ^a
	63.0	0.0	100
	88.0	0.0	100
	88.1	97.5	2.5
	105.0	97.5	2.5
Flow rate	1.0 mL/minute		
Detection	UV at 254 nm		
Auto-sampler temperature	4° C. $\pm$ 2° C.		
Injection volume	10 μ L		
Run time	105 minutes		

^aThe ratio of mobile phase A to mobile phase B from 3 to 33 minutes may be adjusted to achieve the desired retention times.

At the beginning of each run, the diluent blank and SST are each injected in singlet. The system suitability is determined using the SST. The tailing factor for the ceftolozane peak should be between 0.8 and 1.5, and the retention time for the ceftolozane peak should be 24.0 minutes $\pm$ 1.0 minutes. The binary pump setting between 3.0 and 33.0 minutes may be adjusted to achieve the ceftolozane peak retention time.

Each sample is prepared in singlet and injected twice. Only impurities >LOD (0.008% Area) are integrated. The peak area percentage for each impurity >LOD is taken directly from the chromatogram. The mean % area of each peak is calculated and the absolute difference of any peak in the two replicates cannot be >0.030%. The purity and related substances are determined based on relative area % of each peak with respect to the total peak area of the sample. The total impurities are the sum of the individual impurities >LOD. The calculations are as follows:

$$\% \text{ Impurity (\% Area)} = \frac{\text{Area}_{\text{impurity}}}{\text{Area}_{\text{Total}}} \times 100\%;$$

where:

$\text{Area}_{\text{Impurity}}$ = Area of the Individual Impurity Peak, and

$\text{Area}_{\text{Total}}$ = Total Area of all peaks >LOD including Ceftolozane.

$$\text{Purity (\% Area)} = \frac{\text{Area}_{\text{Ceftolozane}}}{\text{Area}_{\text{Total}}} \times 100\%;$$

where:

$\text{Area}_{\text{Ceftolozane}}$ = Area of the Ceftolozane Peak; and

$\text{Area}_{\text{Total}}$ = Total Area of all peaks $\geq$ LOD including Ceftolozane.

$$\text{Total Impurities (\% Area)} = 100 - \text{Purity (\% Area)}.$$

Individual specified impurities equal to or above the limit of quantitation (LOQ) (0.027% Area) are reported. Individual unspecified impurities equal to or above 0.03% are also reported.

Example 8

Lyophilization of Ceftolozane Solid Forms

Sterile ceftolozane compositions suitable for combination with tazobactam to form a pharmaceutical composition are prepared as a lyophilized powder from the ceftolozane sulfate comprising solid Form 2 by compounding the drug substance with excipients into an aqueous solution, aseptically filtering the solution, lyophilizing the solution, then grinding, sieving and packaging the sterile lyophilized powder. The physical stability of the bulk solution at varying concentrations was examined and concentrations up to 150 mg ceftolozane free base/g solution were found suitable. All the registration batches were prepared using 150 mg/g ceftolozane concentration in the compounding solution and this concentration is proposed for commercial manufacturing. The resulting ceftolozane composition solubility was assessed in a concentration range proposed for manufacturing, in the presence of excipients intended for use in the ceftolozane formulation for use in the pharmaceutical composition. For each sample, the ratio of active to inactive ingredients was conserved. Samples were adjusted to pH 6.9, held at 2 to 8° C., and visually assessed for any precipitation. The results are reported in Table 11.

TABLE 11

Ceftolozane Precipitation Time as Function of Solution Concentration, 2 to 8° C.		
Ceftolozane Sulfate Concentration, mg/g	Ceftolozane Free Base Concentration, mg/g	Time to Precipitate
200	174	2 hours
189	165	<18 hours
178	156	>24 hours ¹⁾
172	150	>48 hours
149	130	>24 hours ^a

¹⁾Last observation was made at 24 hour; no sign of precipitation was noticed

Based on these observations, ceftolozane bulk solution with up to 150 mg ceftolozane free base/g solution can be held at 2 to 8° C. for up to 48 hours without affecting its solubility. The suitability of compounding to 150 mg ceftolozane free base/g solution at 10 $\pm$ 2.5° C. was confirmed during the manufacturing of batches on the laboratory, pilot and engineering scale. Refer to Table 12 for solution stability data. The purity data in Table 12 was generated using a modified version of the HPLC method that is described in Table 10. As part of the modification, the initial mobile phase composition comprised 75% mobile phase A and 25% mobile phase B. This composition was ramped to 70% mobile phase A and 30% mobile phase B in 30 minutes followed by a ramp to 100% mobile phase B over another 30 minutes. The 100% mobile phase B was then held constant for 25 minutes, after which the mobile phase composition was reverted back in 0.1 minutes to initial conditions of 75% mobile phase A and 25% mobile phase B. Column equilibration was performed at the initial mobile phase composition for up to 110 minutes, thereby giving a total HPLC run time of 110 minutes. The limit of quantification determined for the method with the conditions described above was 0.015% and therefore all individual specified impurities equal to or above 0.015% were reported.

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A compounding temperature of $10 \pm 2.5^\circ \text{C}$. was targeted to maintain ceftolozane purity. To confirm the compounding solution stability, a study was conducted in which ceftolozane was prepared according to the proposed commercial process and held at $10 \pm 2.5^\circ \text{C}$. for up to 2 days. The solution was sampled and tested for ceftolozane potency and purity/impurities. The results are provided in Table 12. The data indicated ceftolozane impurity profile was essentially unchanged from initial and none of the individual related substances increases more than 0.10%. Therefore, a 24 hour maximum hold time is proposed for the commercial process.

TABLE 12

Effect of Hold Time on Purity/Impurity Profile of Ceftolozane Bulk Solution					
Time from Compounding	t ₀	4 h	18 h	24 h	Day 2
Total Purity, %	98.7	98.8	98.6	98.6	98.7
Total Impurities, %	1.2	1.4	1.4	1.3	1.3

The ceftolozane bulk solution is rendered aseptic via sterilizing filtration. For routine commercial manufacturing, the compounded solution will be first filtered through a bioburden reduction filter, 0.45 μm , then sterile filtered through two 0.22 μm filters in sequence and the filter integrity of the 0.22 μm filters will be assessed during manufacturing.

Through a series of studies on both the pilot and commercial scale lyophilization equipment, the lyophilization process was developed and shown to be suitable: across a range of solution concentrations, at a variety of lyophilizer tray fill depths, following an array of lyophilization cycle parameters,

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However, on occasion, the collapse may be prevented by using primary drying temperatures that are dictated by the full melt temperature, vs. the glass transition temperature. Therefore, studies were performed to examine these two temperatures more closely, to determine which would be controlling to prevent collapse. A variety of lyophilization conditions and instrumentation have been shown to be robust across a range of lyophilization conditions. Therefore, the preferred lyophilization cycles for producing lyophilized ceftolozane compositions from a solution comprising ceftolozane sulfate solid Form 2 have one or more of the following characteristics: (1) not more than 150 mg ceftolozane free base/g bulk solution concentration, (2) no more than 3 cm fill depth, (3) cycle parameters including: freezing to at least -40 to -45°C ., (4) drying to no more than 40°C ., (4) single- or multi-step drying and setting chamber pressure during the start of primary drying at not more than 400 μ bar.

Example 9

Preferred Pharmaceutical Composition Comprising Ceftolozane and Tazobactam ("Representative Ceftolozane/Tazobactam Product")

Pharmaceutical compositions comprising ceftolozane and tazobactam can be obtained as described herein. A Representative Ceftolozane/Tazobactam Product is described in Table 14 below (ceftolozane and tazobactam for injection) as an injectable antibacterial combination product consisting of the cephalosporin antibacterial ceftolozane sulfate and the beta-lactamase inhibitor tazobactam sodium for intravenous administration.

TABLE 13

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 ⁰ Q.S. for pH adjustment	0.60	Used to adjust ceftolozane solution pH	0.29 to 88%

⁰L-arginine is added as needed to achieve pH $(.5 \pm 0.5)$; 600 mg per vial is considered a representative total amount.

in a number of lyophilizers, of both laboratory and commercial scale, and in two different commercial lyophilization suites.

In particular, six different lyophilizers (one pilot lyophilizer and five commercial lyophilizers from two separate commercial suites) have been used to make acceptable ceftolozane material using concentrations as high as 150 mg ceftolozane free base/g solution, fill depths from 1 to 3 cm, and different cycle parameters, including primary and/or secondary drying temperatures as high as 40°C . Based on these studies, freezing the product to at least -40 to -45°C . was considered an appropriate target. Primary drying temperatures are also typically set based on the glass transition temperature of the frozen bulk solution to minimize collapse.

TABLE 14

Unit Compositions of Ceftolozane/Tazobactam for Injection, 1000 mg/500 mg			
Component	Function	Nominal Composition mg per Vial	
Ceftolozane composition ¹⁾	Ceftolozane Sulfate (Solid Form 2)	Active	1147
	Citric Acid, Anhydrous	Chelating Agent	21
	Sodium Chloride	Stabilizing Agent	487

TABLE 14-continued

Unit Compositions of Cefotolozane/Tazobactam for Injection, 1000 mg/500 mg		
Component	Function	Nominal Composition mg per Vial
L-Arginine	Alkalinizing Agent	600 ²⁾
Tazobactam Sodium ³⁾	Active	Q.S. for pH adjustment 537
Nitrogen	Processing Aid ⁴⁾	Q.S.
Total Weight		2792

1) Actual amount of cefotolozane composition will vary based on the measured potency. Cefotolozane sulfate, 1147 mg, corresponds to 1000 mg cefotolozane 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.

A first aqueous solution comprising cefotolozane sulfate Form 2 and the ingredients in the cefotolozane composition in Table 13 is lyophilized in the absence of tazobactam to provide the lyophilized cefotolozane composition. The first aqueous solution comprises cefotolozane 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 14. 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 cefotolozane to obtain the Tazobactam Sodium Composition in Table 14. Subsequently, the lyophilized Tazobactam Sodium Composition is dry blended with the lyophilized Cefotolozane composition comprising tazobactam sodium and cefotolozane sulfate in a weight ratio providing 500 mg of tazobactam acid equivalent per 1,000 mg of cefotolozane active equivalent.

Example 10

Reconstitution of Cefotolozane/Tazobactam Preparation Prior To Administration to a Subject

The cefotolozane/tazobactam composition of Example 9 was reconstituted prior to intravenous (IV) administration. In accordance with one embodiment of the method of treatment, immediately prior to injection into a patient, a single vial, containing 1500 mg cefotolozane and tazobactam, was reconstituted with 20 mL 0.9% NaCl (normal saline) and diluted into a 80 mL bag of sterile water for injection for a total volume of 100 mL.

The cefotolozane and tazobactam composition was reconstituted in accordance with the procedure as follows:

Obtain 1 vial of cefotolozane/tazobactam unit dosage form, 1500 mg/vial. Record the site and subject number and time and date of preparation in the spaces provided on the vial label. Cefotolozane/tazobactam of Example 9 does not contain a bacteriostatic preservative. Aseptic technique must be followed in preparing the infusion solution.

Aseptically reconstitute a lyophilized vial of cefotolozane/tazobactam unit dosage form, 1500 mg with 10 mL water for injection or 0.9% Sodium Chloride for injection, USP (nor-

mal saline) and gently shake to dissolve. The final volume is approximately 11.4 mL. The resultant concentration is approximately 132 mg/mL.

Using aseptic technique, withdraw the entire contents (approximately 11.4 mL) of the reconstituted vial using a syringe and add it to an infusion bag containing 100 mL of 0.9% Sodium Chloride for Injection, USP (normal saline) or 5% Dextrose Injection, USP. Ensure the entire volume of the reconstituted vial is added to the infusion bag.

Gently swirl the contents of the IV bag to ensure complete mixing and dissolution of the drug. The final volume of diluted cefotolozane/tazobactam unit dosage form of Example 9 for infusion will be ~111 mL. The entire contents of the infusion bag of cefotolozane/tazobactam is administered to each subject. This means that the infusion line is flushed with sterile saline to completely administer the proper dose).

Inspect the infusion bag for excess air, visible contamination and leaks. The diluted solution should be clear.

Upon constitution with sterile water for injection or 0.9% sodium chloride (normal saline) injection, the cefotolozane/tazobactam solution in the vial may be held for 1-hour prior to transfer and dilution in the infusion bag.

Following dilution of the solution with normal saline or 5% dextrose, the cefotolozane/tazobactam solution obtained from the cefotolozane/tazobactam composition of Example 9 is stable for 24 hours when stored at room temperature or 10 days when stored under refrigeration at 2 to 8° C. (36 to 46° F.).

Example 11

Melting Point of Cefotolozane Sulfate Form 2

Melting point experiment was performed for cefotolozane sulfate form 2 using the SRS Optimelt melting point apparatus. SRS-certified vanillin and phenacetin were used to verify the system performance. The temperature scan from 100° C. to 400° C. was performed for cefotolozane sulfate. The material decomposed prior to melting. The decomposition, as indicated by the distinct change in color, appeared to commence at about 170° C.

Example 12

TGA and DSC of Cefotolozane Sulfate Form 2

Thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) thermograms are shown in FIG. 3 and FIG. 4, respectively. An initial weight loss of 6.8% observed in the TGA thermogram from initial temperature to 181° C. is consistent with the content of water and residual isopropanol present in cefotolozane sulfate, lot 440637 0004 2. Analysis of the thermogram beyond 181° C. indicated that cefotolozane sulfate likely undergoes degradation beyond this temperature. The DSC thermogram exhibited a broad endotherm with the minima at about 105.49° C. The subsequent exotherm in the thermogram is indicative of decomposition that is consistent with the observation in the melting point experiment.

Example 13

Hygroscopicity of Cefotolozane Sulfate Form 2

Hygroscopicity of cefotolozane sulfate, Form 2 was assessed using the SMS DVS Intrinsic moisture sorption analyzer equipped with a calibrated Rotronic probe. The tem-

perature was maintained at 25° C. and the material was exposed to relative humidity from 0 to 90%. Cefotolozane sulfate showed continuous adsorption of water through the cycle with total uptake of 23% at 90% relative humidity indicating that cefotolozane sulfate is hygroscopic.

What is claimed:

1. Solid Form 2 of cefotolozane sulfate that produces an X-ray powder diffraction (XRPD) pattern having diffractions at angles (2 theta±0.2) of 4.4, 8.8, 11.0, 14.9, and 17.7.

2. The solid form of cefotolozane sulfate of claim 1 that produces Raman shift peaks (±5 cm⁻¹) at about 151 cm⁻¹, 684 cm⁻¹, and 802 cm⁻¹.

3. The solid form of cefotolozane sulfate of claim 1 characterized by a differential scanning calorimetry (DSC) endotherm having a minima at about 105 degrees C.

4. The solid form of cefotolozane sulfate of claim 1, characterized by a thermogravimetric analysis (TGA) with a weight loss of about 6.8% between 25-181 degrees C.

5. The solid form of cefotolozane sulfate of claim 1, characterized by

a. a differential scanning calorimetry (DSC) endotherm having a minima at about 105 degrees C.;

b. a thermogravimetric analysis (TGA) with a weight loss of about 6.8% between 25-181 degrees C.; and

c. Raman shift peaks (±5 cm⁻¹) at 151 cm⁻¹, 684 cm⁻¹, 802 cm⁻¹, 1174 cm⁻¹, and 2953 cm⁻¹.

6. A pharmaceutical composition comprising the solid form of cefotolozane sulfate designated as cefotolozane sulfate Form 2 that produces an X-ray powder diffraction (XRPD) pattern having diffractions at angles (2 theta±0.2) of 4.4, 8.8, 11.0, 14.9, and 17.7.

7. The pharmaceutical composition of claim 6, wherein the cefotolozane sulfate produces Raman shift peaks (±5 cm⁻¹) at about 151 cm⁻¹, 684 cm⁻¹, 802 cm⁻¹, 1174 cm⁻¹, and 2953 cm⁻¹.

8. The pharmaceutical composition of claim 7, further comprising cefotolozane sulfate in a solid form that produces an X-ray powder diffraction (XRPD) pattern having diffractions at angles (2 theta±0.2) of 12.4, 16.4, 22.6, 25.1 and 28.0.

9. The pharmaceutical composition of claim 6, further comprising tazobactam.

10. The pharmaceutical composition of claim 6, further comprising a pharmaceutically acceptable excipient.

11. The pharmaceutical composition of claim 10, wherein the pharmaceutically acceptable excipient is selected from the group consisting of: sodium chloride, L-arginine, citric acid and mixtures thereof.

12. The pharmaceutical composition of claim 11, characterized by one or more of the following:

a. a differential scanning calorimetry (DSC) endotherm having a minima at about 105 degrees C.;

b. a thermogravimetric analysis (TGA) with a weight loss of about 6.8% between 25-181 degrees C.; and

c. Raman shift peaks (±5 cm⁻¹) at 151 cm⁻¹, 684 cm⁻¹, 802 cm⁻¹, 1174 cm⁻¹, and 2953 cm⁻¹.

13. A pharmaceutical composition comprising a lyophilized cefotolozane composition obtained by a process comprising the steps of:

a. combining the cefotolozane sulfate in a solid form designated as cefotolozane sulfate Form 2 that produces an X-ray powder diffraction (XRPD) pattern having diffractions at angles (2 theta±0.2) of 4.4, 8.8, 11.0, 14.9, and 17.7, with water, sodium chloride and L-arginine to form an aqueous solution; and

b. lyophilizing the aqueous solution to form the lyophilized cefotolozane composition comprising cefotolozane sulfate.

14. The pharmaceutical composition of claim 13, wherein the lyophilization cycle is characterized by one or more of the following characteristics:

a. not more than 150 mg cefotolozane free base/g bulk solution concentration,

b. no more than 3 cm fill depth,

c. freezing to at least -40° C. during the lyophilization cycle,

d. drying to no more than 40° C., and

e. single- or multi-step drying and setting chamber pressure during the start of primary drying at not more than 400μ bar.

15. The pharmaceutical composition of claim 13, further comprising tazobactam.

16. The pharmaceutical composition of claim 15, obtained by a process further comprising combining the lyophilized cefotolozane composition with tazobactam in a fixed dose combination providing about 500 mg of tazobactam active per 1,000 mg of cefotolozane active in the pharmaceutical composition.

17. A pharmaceutical composition comprising a lyophilized cefotolozane composition obtained by a process comprising the steps of:

a. combining the cefotolozane sulfate of solid Form 2 that produces an X-ray powder diffraction (XRPD) pattern having diffractions at angles (2 theta±0.2) of 4.4, 8.8, 11.0, 14.9, and 17.7 with water to form an aqueous solution; and

b. lyophilizing the aqueous solution to form the lyophilized cefotolozane composition comprising cefotolozane sulfate.

18. The pharmaceutical composition of claim 17, wherein the aqueous solution in step (b) further comprises tazobactam or a pharmaceutically acceptable salt thereof.

19. The pharmaceutical composition of claim 18, wherein the pharmaceutical composition comprises tazobactam sodium.

20. The pharmaceutical composition of claim 17, wherein the aqueous solution in step (b) is lyophilized in the absence of tazobactam.

21. The pharmaceutical composition of claim 17, wherein the pharmaceutical composition comprises the cefotolozane sulfate in an amount providing about 1,000 mg of cefotolozane active.

22. The pharmaceutical composition of claim 21, wherein the pharmaceutical composition further comprises about 500 mg of tazobactam active.

23. The pharmaceutical composition of claim 17, wherein the pharmaceutical composition comprises cefotolozane active and tazobactam active, and the cefotolozane sulfate is present in the pharmaceutical composition in an amount providing 1,000 mg of cefotolozane active per 500 mg of tazobactam active.

24. The pharmaceutical composition of claim 17, wherein the pharmaceutical composition comprises cefotolozane and a beta-lactamase inhibitor compound.

25. The pharmaceutical composition of claim 17, wherein the pharmaceutical composition comprises about 1,000 mg of cefotolozane active and 500 mg of tazobactam active.

26. The pharmaceutical composition of claim 17, obtained by a process further comprising combining the lyophilized cefotolozane composition with tazobactam in a fixed dose combination providing about 500 mg of tazobactam active per 1,000 mg of cefotolozane active in the pharmaceutical composition.

27. The pharmaceutical composition of claim 26, wherein the pharmaceutical composition comprises tazobactam sodium.

28. The pharmaceutical composition of claim 26, wherein the pharmaceutical composition comprises crystalline tazobactam.

29. The pharmaceutical composition of claim 28, wherein the aqueous solution is lyophilized in step (b) with a lyophilization cycle characterized by one or more of the following characteristics:

- a. not more than 150 mg ceftolozane free base/g bulk solution concentration,
- b. no more than 3 cm fill depth,
- c. freezing to at least -40°C . during the lyophilization cycle,
- d. drying to no more than 40°C ., and
- e. single- or multi-step drying and setting chamber pressure during the start of primary drying at not more than $400\mu\text{bar}$.

30. The pharmaceutical composition of claim 26, characterized by one or more of the following:

- a. a differential scanning calorimetry (DSC) endotherm having a minima at about 105°C ;
- b. a thermogravimetric analysis (TGA) with a weight loss of about 6.8% between 25 - 181°C .; and
- c. Raman shift peaks ($\pm 5\text{ cm}^{-1}$) at 151 cm^{-1} , 684 cm^{-1} , 802 cm^{-1} , 1174 cm^{-1} , and 2953 cm^{-1} .

* * * * *

 Tareas

 Búsqueda de tareas

256 Tarea(s)

Advertencia(s)

Los documentos independientes han sido subidos exitosamente para el expediente NC2017/0001492.

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