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Description

This invention relates to a novel, convenient and economic process for producing sodium cefoperazone. More particularly, it relates to the production of highly crystalline sodium cefoperazone.

Cefoperazone is a broad spectrum beta-lactam antibiotic usually administered parenterally as the sodium salt, which is provided by the available procedures (British Patent Specification 1,508,071) as an amorphous solid.

Amorphous compounds are, in general less desirable than are crystalline forms thereof, from the standpoint of preparation, storage and use. A crystalline compound is generally considerably more stable than an amorphous form of the compound, and resists decomposition and discoloration. For pharmaceutical use, it is much easier to prepare dosage forms from crystalline compounds than from those in amorphous form. Finally, amorphous compounds are frequently more hygroscopic than those in crystalline form.

A relatively simple, inexpensive process has now been discovered to obtain highly crystalline sodium cefoperazone essentially free of residual organic solvents, comprising the steps of combining a water/acetone/cefoperazone solution containing 1.0—1.5 parts of water by volume, 2.0—5.0 parts of acetone by volume, and 1 part of sodium cefoperazone by weight with sufficient acetone to provide a water/acetone solution containing from about 14% to 17% water v/v, at about 5 to 25°C with a preferred temperature of 18—25°C; adding sufficient acetone to the resulting slurry at said temperature to provide a water/acetone solution containing from about 3% to 5% water v/v, based on acetone level; and separating the resulting crystalline sodium cefoperazone.

The initial water/acetone/sodium cefoperazone solution may be prepared by combining appropriate amounts of a slurry of cefoperazone free acid in acetone with an aqueous solution containing about one equivalent of a base selected from sodium bicarbonate, sodium carbonate and sodium 2-ethyl hexanoate.

The highly crystalline product may be separated by filtration or centrifugation and dried under vacuum (0.1 to 10 mm Hg) at about 25°C.

Highly crystalline sodium cefoperazone may be prepared by the controlled staged addition of acetone to an initial water/acetone/sodium cefoperazone solution of the composition 1.0—1.5 parts of water by volume, 2.0—5.0 parts of acetone by volume, and 1 part of sodium cefoperazone by weight. The aforementioned initial sodium cefoperazone solution is preferably formed *in situ* by combining appropriate amounts of a slurry of cefoperazone free acid in acetone with an aqueous solution of about one equivalent of a basic sodium salt compound, selected from the group consisting of sodium bicarbonate, sodium carbonate, and sodium 2-ethylhexanoate.

Acetone is added to the initial aqueous acetone solution of sodium cefoperazone until the water content is reduced to 14—17% of the acetone volume at a temperature of 5—25°C, with a preferred temperature range of 18—25°C, producing a ratio of water/acetone/sodium cefoperazone solution of 1.0—1.5, parts of water by volume, 7.0—12.0 parts of acetone by volume, and 1 part of sodium cefoperazone by weight. The solution is then stirred until a haze develops, and stirring continued until a thick slurry has formed. Further acetone is then added, with stirring in the aforementioned temperature range until a final water content of 3—5% of the acetone level is obtained. The resulting crystals of sodium cefoperazone can be collected by conventional means, preferably by centrifugation or vacuum filtration and, if desired washed with available organic solvent, preferably 3% water/acetone solution, then with acetone or ethanol, and dried. The product is preferably dried at about 25—50°C, preferably under a vacuum of about 0.1 to 10 mm Hg, for about 1 to 20 hours.

The process of the present invention allows for the formation of highly crystalline sodium cefoperazone. By highly crystalline is meant a crystalline product that is substantially free of amorphous material. The process of the present invention also results in highly crystalline sodium cefoperazone which is essentially free of residual organic solvents, without requiring extraordinary drying conditions to reduce the amount of organic solvent to a range acceptable for human use.

Sodium cefoperazone is a broad spectrum antibiotic useful in treating bacterial infections in humans. The crystalline sodium cefoperazone produced by the process of this invention is used in the same manner as the amorphous product described in the art including British Patent Specifications 1,508,071 and U.S. Patent 4,087,424. The highly crystalline sodium cefoperazone produced by the present process is more stable, less subject to undesirable decomposition and more conveniently handled and incorporated in pharmaceutical dosage forms than the amorphous material.

The present invention is illustrated by the following examples. It will, however, be understood that the invention is not limited to the specific details and conditions of these examples.

Example I

10 g. of partially crystalline sodium cefoperazone was dissolved in 15 ml. of water at a temperature of 20—25°C. To the stirred solution 106 ml of acetone was added at a temperature of 20—25°C, resulting in a slight haze. (When 50 ml of the acetone had been added, the solution contained 1.5 parts by volume of water, 5 parts by volume of acetone and 1 part by weight of sodium cefoperazone. When all the acetone had been added, the solution comprised 15 ml water and 106 ml acetone, i.e., contained 14.2% (v/v) water based on acetone level.) The hazy solution was

stirred at 18—21°C until a thick slurry developed. After the thick slurry developed 325 ml of acetone was added over 2 hours. The final water content was measured at 3—4% of acetone content. Stirring was continued for 5 hours at 20—25°C, and the resulting crystals of sodium cefoperazone were collected by vacuum filtration, 8.9 g. yield.

Example II

A slurry of 25 g of cefoperazone free acid in 75 ml. acetone at 20—25°C was treated with a solution of 3.08 g. sodium bicarbonate in 37.5 ml. of water with stirring to adjust the pH to 6.5—6.8 at 20—25°C. The resulting solution (containing approximately 1.5 parts by volume of water, 3 parts by volume of acetone and 1 part by weight of sodium cefoperazone) was clarified and 170 ml. of acetone was added over a half hour at 20—25°C until a slight haze resulted. The hazy solution (now comprising 37.5 ml water and 245 ml acetone, i.e. containing 15.3% (v/v) water based on acetone level) was stirred at 20—25°C for about 2 hours until a thick slurry developed. 640 ml. of acetone was then added over 2 hours, maintaining the temperature of 20—25°C, (thus reducing the water content to 4.2% (v/v) based on acetone level). Stirring continued for 5 hours at 20—25°C and the crystals were collected by vacuum filtration, 21.5 g. yield.

Claims

1. A process for preparing crystalline sodium cefoperazone substantially free of amorphous material which comprises the steps of (a) combining a water/acetone/sodium cefoperazone solution containing 1—1.5 parts of water by volume, 2.0—5.0 parts of acetone by volume, and 1 part of sodium cefoperazone by weight with sufficient acetone to provide a water/acetone solution containing from about 14% to about 17% (v/v) water based on acetone level at a temperature of about 5—25°C; (b) adding sufficient acetone to the resulting slurry at said temperature to provide a water/acetone solution containing from about 3% to 5% water based on acetone level; and (c) separating the resulting crystalline sodium cefoperazone from said slurry.

2. The process of claim 1 wherein said temperature is 18—25°C.

3. The process of claim 1, wherein said water/acetone/sodium cefoperazone solution is formed *in situ* by combining a slurry of cefoperazone free acid in acetone with an aqueous solution containing about one equivalent of a base selected from the group consisting of sodium bicarbonate, sodium carbonate and sodium 2-ethylhexanoate.

Patentansprüche

1. Verfahren zum Herstellen von kristallinem

Natrium-Cefoperazon, das im wesentlichen frei von amorphem Material ist, welches die Schritte

(a) Vereinigen einer Wasser/Aceton-Natrium-Cefoperazon-Lösung mit einem Gehalt von 1—1,5 Volumenteilen Wasser, 2,0—5,0 Volumenteilen Aceton und 1 Gewichtsteil Natrium-Cefoperazon bei etwa 5 bis 25°C mit ausreichend Aceton, um eine Wasser/Aceton-Lösung mit einem Gehalt von etwa 14% bis etwa 17% Wasser (v/v), bezogen auf die Acetonmenge, zu ergeben,

(b) Hinzufügen von ausreichend Aceton zu der entstandenen Suspension bei der genannten Temperatur, um eine Wasser/Aceton-Lösung mit einem Gehalt von etwa 3% bis 5% Wasser, bezogen auf die Acetonmenge, zu ergeben, und

(c) Abtrennen des entstandenen kristallinen Natrium-Cefoperazons aus dieser Suspension umfaßt.

2. Verfahren nach Anspruch 1, worin die Temperatur 18—25°C beträgt.

3. Verfahren nach Anspruch 1, worin die Wasser/Aceton-Natrium-Cefoperazon-Lösung *in situ* durch Vereinigen einer Aufschlämmung von freier Cefoperazon-Säure in Aceton mit einer wäßrigen Lösung gebildet wird, die etwa ein Äquivalent einer Base, ausgewählt aus der Gruppe, die aus Natriumhydrogencarbonat, Natriumcarbonat und Natrium-2-ethylhexanoat besteht, enthält.

Revendications

1. Procédé de préparation de céfopérazone sodique cristalline substantiellement dépourvue de matériaux amorphes, qui consiste (a) à combiner une solution eau/acétone/céfopérazone sodique contenant 1—1,5 partie d'eau en volume, 2,0—5,0 parties d'acétone en volume, et 1 partie de céfopérazone sodique en poids avec suffisamment d'acétone pour donner une solution eau/acétone contenant d'environ 14% à environ 17% (v/v) d'eau par rapport à la concentration en acétone à une température d'environ 5—25°C; (b) à ajouter suffisamment d'acétone à la solution résultante à ladite température pour donner une solution eau/acétone contenant environ 3% à 5% d'eau par rapport à la concentration d'acétone; et (c) à séparer la céfopérazone sodique cristalline résultante de ladite bouillie.

2. Procédé selon la revendication 1, dans lequel ladite température est de 18—25°C.

3. Procédé selon la revendication 1, caractérisé en ce que ladite solution eau/acétone/céfopérazone sodique est formée *in situ* en combinant une bouillie de céfopérazone dépourvue d'acide dans de l'acétone avec une solution aqueuse contenant environ en équivalent d'une base choisie dans le groupe comprenant le bicarbonate de sodium, le carbonate de sodium et le 2-éthylhexanoate de sodium.

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stirred at 18—21°C until a thick slurry developed. After the thick slurry developed 325 ml of acetone was added over 2 hours. The final water content was measured at 3—4% of acetone content. Stirring was continued for 5 hours at 20—25°C, and the resulting crystals of sodium cefoperazone were collected by vacuum filtration, 8.9 g. yield.

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Claims

1. A process for preparing crystalline sodium cefoperazone substantially free of amorphous material which comprises the steps of (a) combining a water/acetone/sodium cefoperazone solution containing 1—1.5 parts of water by volume, 2.0—5.0 parts of acetone by volume, and 1 part of sodium cefoperazone by weight with sufficient acetone to provide a water/acetone solution containing from about 14% to about 17% (v/v) water based on acetone level at a temperature of about 5—25°C; (b) adding sufficient acetone to the resulting slurry at said temperature to provide a water/acetone solution containing from about 3% to 5% water based on acetone level; and (c) separating the resulting crystalline sodium cefoperazone from said slurry.

2. The process of claim 1 wherein said temperature is 18—25°C.

3. The process of claim 1, wherein said water/acetone/sodium cefoperazone solution is formed *in situ* by combining a slurry of cefoperazone free acid in acetone with an aqueous solution containing about one equivalent of a base selected from the group consisting of sodium bicarbonate, sodium carbonate and sodium 2-ethylhexanoate.

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(c) Abtrennen des entstandenen kristallinen Natrium-Cefoperazons aus dieser Suspension umfaßt.

2. Verfahren nach Anspruch 1, worin die Temperatur 18—25°C beträgt.

3. Verfahren nach Anspruch 1, worin die Wasser/Aceton-Natrium-Cefoperazon-Lösung *in situ* durch Vereinigen einer Aufschlämmung von freier Cefoperazon-Säure in Aceton mit einer wäßrigen Lösung gebildet wird, die etwa ein Äquivalent einer Base, ausgewählt aus der Gruppe, die aus Natriumhydrogencarbonat, Natriumcarbonat und Natrium-2-ethylhexanoat besteht, enthält.

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