EUROPEAN PATENT SPECIFICATION

(54) Process for converting loracarbef dihydrate to loracarbef monohydrate
Umwandlungsverfahren von Lorabef Dihydrate in Loracarbef Monohydrate
Procédé de conversion du dihydrate de loracarbef en monohydrate de loracarbef

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE

(30) Priority: 04.06.1993 US 71550

(43) Date of publication of application:

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• CHEMICAL ABSTRACTS, vol. 116, no. 22, 1 June 1992, Columbus, Ohio, US; abstract no. 221407d,
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• CHEMICAL ABSTRACTS, vol. 74, no. 4, 25 January 1971, Columbus, Ohio, US; abstract no. 16554x,

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This invention relates to a process for the preparation of crystalline loracarbef monohydrate. The \( \beta \)-lactam antibiotic of the formula (I)

\[
\text{NH}_2 \quad \text{O} \quad \text{N} \quad \text{H} \quad \text{O} \\
\text{C} \quad \text{C} \quad \text{N} \quad \text{H} \quad \text{C} \quad \text{H} \\
\text{Cl} \quad \text{COOH}
\]

is the potent orally active antibiotic known as loracarbef. The antibiotic is described, for example, by Hashimoto et al. in U.S. Patent No. 4,335,211, issued June 15, 1982.

The above compound is known in various forms, including the crystalline monohydrate form, which is disclosed in European Patent Publication 0,311,366 having a publication date of April 12, 1989. Other known solvate forms of the compound are disclosed in Eckrich et al. U.S. Patent No. 4,977,257. The crystalline dihydrate form of loracarbef is disclosed in European Patent Publication 0,369,686 having a publication date of May 23, 1990. As indicated in the EPO application, the crystalline monohydrate may be prepared by first suspending the dihydrate in water and effecting solution by the addition of acid followed by the adjustment of the pH with base, or by the addition of base followed by acid.

It has been determined that loracarbef crystalline monohydrate is a fine "hair-like" crystal which results in very slow filtration. In filtering the monohydrate, the crystals tend to form a mat on the filter medium which prevents or reduces the ability to de-water the filter cake, which increases the wash volume required. As loracarbef monohydrate is moderately soluble in water, (approximately 10 mg/ml), loss of yield results when such washes are increased. Total filtration time is of course increased as wash volume increases.

What is needed in light of the above difficulties is a process for preparing crystalline loracarbef monohydrate in a more efficient manner, that is, to avoid the requirement of filtering the crystalline monohydrate.

The invention provides a process for the preparation of the crystalline monohydrate form of the compound of formula (I)

\[
\text{NH}_2 \quad \text{O} \quad \text{N} \quad \text{H} \quad \text{O} \\
\text{C} \quad \text{C} \quad \text{N} \quad \text{H} \quad \text{C} \quad \text{H} \\
\text{Cl} \quad \text{COOH}
\]

which exposes the crystalline dihydrate form of a compound of formula (I) to a temperature between 50° to 65°C and a relative humidity between 60 to 100%.

Loracarbef dihydrate exists in a plate-like habit and consequently filters much more quickly than the crystalline monohydrate form of loracarbef. Experimentation has shown that this filtration may be 20 times as fast as the filtration of the monohydrate. Attempts have been made to convert dihydrate to monohydrate as a wet cake or dry solid using high temperatures alone. However, that procedure proved unsuccessful.

It was discovered that using a high relative humidity in combination with high temperatures produced a solid state
conversion from dihydrate to monohydrate. This discovery provided a process to avoid isolation of the monohydrate through filtration, as the monohydrate may be isolated through forming the easily filtered dihydrate, which then may undergo the solid state conversion to the monohydrate. Also, there is no need to crystallize the monohydrate from solution using acid or base, as described previously.

The solid state conversion from dihydrate to monohydrate takes place in an environment of both elevated temperature, from 50° to 65°C, and at high relative humidities, from 60 to 100%. While other forms of loracarbef were used in such a process, it has been found that the dihydrate form surprisingly converts exclusively to the monohydrate. Other solvate forms such as the bis(DMF)solvate and the ethanolate, which were exposed to various combinations of temperatures and relative humidities converted to nonmonohydrate forms or a mixture of forms. Therefore, the invention also provides for a conversion of the dihydrate crystal form exclusively to the monohydrate crystal form.

The dihydrate can be prepared through means known in the art, such as taught in the European Patent Publication 369,666, previously referenced. The dihydrate may be in the form of a wet cake or a dry powder. The dihydrate is placed in an uncovered container, and thereafter placed in a humidity cabinet having a relative humidity of 60-100%, at a temperature of 50° to 65°C. A preferred humidity range is between 80 to 90%, and a preferred temperature range is between 50° to 60°C. The dihydrate is left at these conditions for several hours, and it is noted that in some experiments the conversion to the monohydrate at a temperature of 60°C and relative humidity of 90% occurred in under 8 hours. The conversion can be monitored via microscopic observation and when the material appears microscopically to have converted to the monohydrate, samples may be taken and sent for Karl Fischer and X-ray diffraction pattern assays for confirmation of composition. It is believed that the conversion is a solid to solid transformation, rather than a dissolution followed by a recrystallization. This is surprising as there is a net loss of water in a wet environment.

Microscopically, the crystals could be seen changing from plates of dihydrate to the needles of monohydrate during the conversion. The Karl Fischer values changed from 9% to 5%, coinciding with the change from dihydrate to monohydrate. The X-ray diffraction patterns of the resulting materials had a pattern identical to that of the monohydrate reference pattern. Also, no new peaks are observed, so the dihydrate is shown to convert exclusively to monohydrate.

**EXPERIMENTAL SECTION**

**Example 1**

Loracarbef dihydrate (5g, starting KF=9.3%), was placed in a petri dish and then placed in humidity cabinet at 60% relative humidity and 20°C. It was left at that setting for 24 hours, and monitored via microscopic observations. No changes were seen, so that temperature was increased by 10°, and again left for 24 hours. This process was repeated until the temperature reached 60°C. No monohydrate growth took place until the temperature reached 50°C, and at 60°C much more monohydrate was visible. The X-ray patterns showed that at 50°C, mostly dihydrate remained, but at 60°C, the patterns showed primarily monohydrate with a trace of dihydrate left. The KF assays showed a decrease in water content after the material was held at 60°C.

**Example 2**

Loracarbef dihydrate (3g) was placed in a petri dish, and the open container placed in a humidity cabinet at 60°C, and 80% relative humidity. After 2 hours the material looked largely like monohydrate as seen through the microscope. The X-ray pattern confirmed the conversion, showing mostly monohydrate with a small amount of dihydrate remaining.

**Example 3**

Loracarbef dihydrate (5g, starting KF=8.7%), was placed in a petri dish and then placed in a humidity cabinet at 60°C and 80% relative humidity. Conversion was monitored via microscopic observation and after 72 hours the material appeared to be primarily monohydrate. The product had a KF=5.5%, the amount of total related substances was 0.51%, and the potency was 96.5%. The X-ray pattern confirmed the material to be monohydrate.

**Example 4**

A 500 ml one neck glass Parr Bottle was equipped with a rubber stopper, and two concentric tubes. The tubes provided a path to supply and remove nitrogen saturated with water vapor to the inside of the bottle. The end of each tube was sealed, and a hole was drilled in the tubing wall; this provided volume for a water trap if any water vapor were to condense in these lines. Loracarbef dihydrate (approximately 0.75 grams) was spread evenly on the bottom of the Parr Bottle, and the bottle was tightly stoppered. The Parr Bottle was then submerged in a 4 liter Resin Flask filled with water. The resin flask was equipped with a heating mantle and temperature controller, set to 65°C. In addition, dry nitrogen was sparged into the water through a sintered metal frit at a controlled rate of 100 sccm/min; this provided a nitrogen
stream saturated with water vapor at the temperature of the water and submerged Parr Bottle. The resin flask and Parr bottle tubing were sealed and connected so that the 100 sccm/min of nitrogen had to vent by sweeping through the Parr bottle. The dihydrate loaded into the Par bottle assayed at 8.9 wt% H₂O by KF titration. Visual observation with an optical microscope indicated a plate crystal habit characteristic of the dihydrate crystal form. After exposing the dihydrate to 65°C with 100 sccm/min of nitrogen saturated with water vapor (100% relative humidity) for 70 hours, the material in the Parr bottle was removed. Visual observation with an optical microscope indicated a needle crystal habit characteristic of the monohydrate crystal form. The KF titration indicated the crystals were 5.5 wt% H₂O.

Claims

1. A process for the preparation of the crystalline monohydrate form of the compound of formula (I)

\[
\text{NH}_2\text{CCHC\text{N}}\text{HOCOCl}
\]

which exposes the crystalline dihydrate form of the compound of formula (I) to a temperature of between 50°C to 65°C and a relative humidity of between 60 to 100%.

2. The process as recited in Claim 1 wherein said relative humidity is between 80 to 90%.

3. The process as recited in Claim 2 wherein said temperature is between 50°C to 60°C.

Patentansprüche

1. Verfahren zur Herstellung der Form des kristallinen Monohydrats der Verbindung der Formel (I)

\[
\text{NH}_2\text{CCHC\text{N}}\text{HOCOCl}
\]

dadurch gekennzeichnet, daß die Form des kristallinen Dihydrats der Verbindung der Formel (I) einer Temperatur zwischen 50°C und 65°C und einer relativen Feuchtigkeit zwischen 60% und 100% ausgesetzt wird.

2. Verfahren nach Anspruch 1, worin die relative Feuchtigkeit zwischen 80% und 90% beträgt.

3. Verfahren nach Anspruch 2, worin die Temperatur zwischen 50°C und 60°C beträgt.
Revendications

1. Procédé de préparation de la forme monohydrate cristalline du composé répondant à la formule (I)

\[
\text{\begin{center}
\includegraphics[width=0.5\textwidth]{image}
\end{center}}
\]

(I)

qui expose la forme dihydrate cristalline d'un composé répondant à la formule (I) à une température entre 50 ° et 65 °C et à une humidité relative entre 60 et 100 %.

2. Procédé selon la revendication 1, dans lequel ladite humidité relative se situe entre 80 et 90 %.

3. Procédé selon la revendication 2, dans lequel ladite température se situe entre 50 ° et 60 °C.