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(54) Title: GANCICLOVIR SODIUM SALT IN CRYSTALLINE FORM

(57) Abstract: Anhydrous ganciclovir sodium salt and a process for its preparation.



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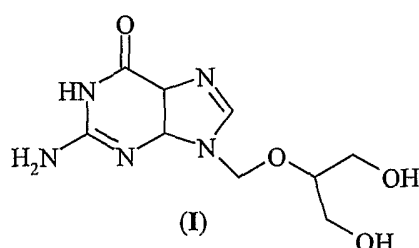
GANCICLOVIR SODIUM SALT IN CRYSTALLINE FORM

FIELD OF THE INVENTION

The present invention relates to ganciclovir, in particular a crystalline form of the corresponding sodium salt, and to a process for its preparation.

TECHNOLOGICAL BACKGROUND

5 Ganciclovir [9-(1,3-dihydroxy-2-propoxymethyl)guanine] (I)



is one of the most important nucleoside analogues having selective anti-herpes activity, commonly used in therapy in the form of the corresponding sodium salt.

US 4,355,032 (example 2) discloses the preparation of lyophilised ganciclovir sodium salt, whereas CN 1,342,651 discloses the preparation of ganciclovir sodium salt dihydrate. Both forms are, however, instable, as they easily adsorb humidity from the environment.

15 Therefore it would be advantageous to provide ganciclovir sodium salt in a stable form.

DISCLOSURE OF THE INVENTION

The present invention relates to anhydrous crystalline ganciclovir sodium salt, preferably anhydrous crystalline ganciclovir sodium salt characterized by the X ray diffraction spectrum reported in the enclosed Figure.

The compound of the invention can be prepared starting both from ganciclovir and amorphous ganciclovir sodium salt.

CONFIRMATION COPY

In the first case, two alternative processes can be followed.

In the first process, a ganciclovir suspension in ethanol is added with an equimolar amount of sodium hydroxide aqueous solution. 200 ml of ethanol per 100 g of ganciclovir are preferably used, and the concentration of the sodium hydroxide solution preferably ranges from 15 to 18% (w/v). The mixture is refluxed until complete salification of the product, then is diluted with ethanol (1500 ml per 100 g of starting ganciclovir) and approx. half the solvent is distilled off under atmospheric pressure to obtain anhydrous ganciclovir sodium salt.

In the second process, a ganciclovir suspension in water is added with an equimolar amount of sodium hydroxide aqueous solution. 100 ml of water per 100 g of ganciclovir are preferably used, and the concentration of the sodium hydroxide solution preferably ranges from 15 to 18% (w/v). The resulting solution is added with ethanol, preferably 700 ml per 100 g of starting ganciclovir; the precipitated solid is filtered and suspended in ethanol, preferably using 500 ml of ethanol per 100 g of starting ganciclovir. After refluxing for about two hours, the mixture is left to cool to room temperature, filtered again and dried to obtain anhydrous ganciclovir sodium salt.

When starting from amorphous ganciclovir sodium salt, this is suspended in ethanol, preferably 500 ml of ethanol per 100 g of ganciclovir and refluxed for two hours. Afterwards the mixture is left to cool, the solid is filtered and dried to obtain anhydrous ganciclovir sodium salt.

The anhydrous crystalline ganciclovir sodium salt according to the present invention can be used for the preparation of pharmaceutical compositions, which can be prepared with conventional excipients and techniques, such as those reported in Remington's Pharmaceutical Sciences Handbook, XVII Ed., Mack Pub., N.Y., U.S.A.

The invention will be further illustrated by some examples.

EXAMPLES

Example 1 - Preparation of anhydrous crystalline ganciclovir sodium salt from ganciclovir

A suspension of ganciclovir (100 g) in ethanol (200 ml) is added with a
5 15.7% (100 ml) sodium hydroxide solution. The resulting solution is refluxed,
diluted with ethanol (1500 ml), and approx. 900 ml of solvent are distilled off
under approx. atmospheric pressure. After cooling, the crystalline solid is
filtered and dried at 60°C under vacuum to constant weight.

102 g of anhydrous crystalline ganciclovir sodium salt are obtained
10 (water content according to Karl-Fisher < 1%).

Example 2 - Preparation of anhydrous crystalline ganciclovir sodium salt from ganciclovir

A suspension of ganciclovir (100 g) in water (100 ml) is added with a
15.7% (100 ml) sodium hydroxide solution. The resulting solution is diluted
15 with ethanol (700 ml), to precipitate a solid which is filtered and suspended in
ethanol (500 ml). The suspension is refluxed for 2 hours, then cooled, the
crystalline solid is filtered and dried at 60°C under vacuum to constant weight.
98 g of anhydrous crystalline ganciclovir sodium salt are obtained, which is
the same as that obtained in Example 1.

Example 3 - Preparation of anhydrous crystalline ganciclovir sodium salt from amorphous ganciclovir sodium salt

A suspension of amorphous ganciclovir sodium salt (100 g) in ethanol
(500 ml) is refluxed for 2 hours, then cooled to room temperature, filtered and
dried at 60°C under vacuum to constant weight. 99 g of anhydrous crystalline
25 ganciclovir sodium salt are obtained, which is the same as that obtained in
Example 1.

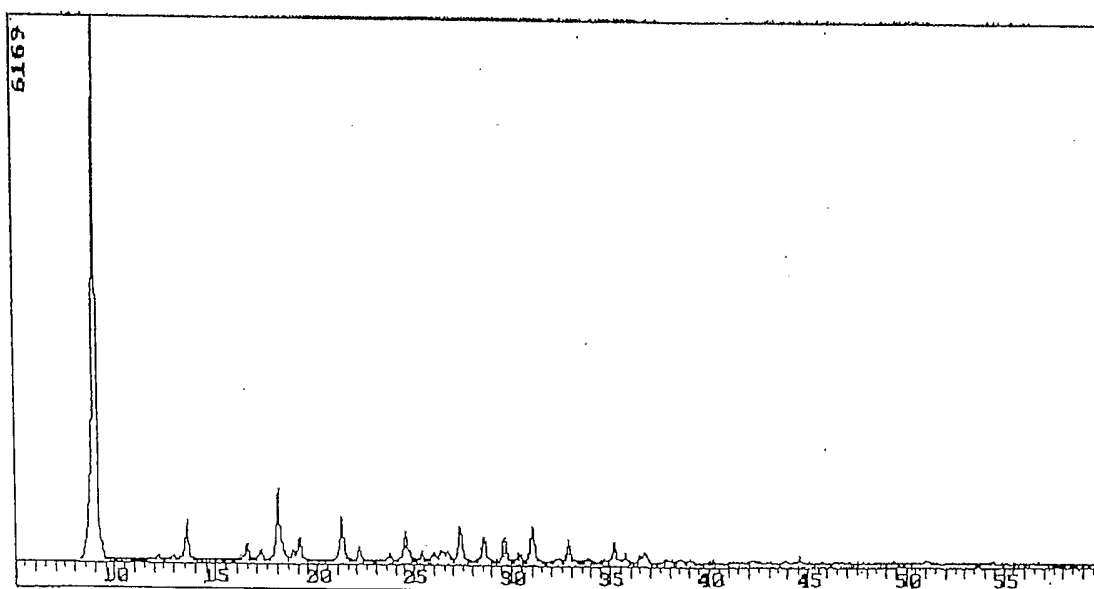
CLAIMS

1. Anhydrous crystalline ganciclovir sodium salt.
2. Anhydrous crystalline ganciclovir sodium salt characterized by the X-
5 ray diffraction spectrum reported in the annexed Figure.
3. A process for the preparation of anhydrous crystalline ganciclovir sodium salt comprising:
 - adding an equimolar amount of sodium hydroxide aqueous solution to a suspension of ganciclovir in ethanol;
 - 10 • heating to complete salification of the product;
 - cooling and diluting the mixture with ethanol;
 - concentrating the mixture by distilling off the ethanol under atmospheric pressure;
 - filtering and drying the product.
- 15 4. A process for the preparation of anhydrous crystalline ganciclovir sodium salt comprising:
 - adding an equimolar amount of sodium hydroxide aqueous solution to a ganciclovir aqueous suspension;
 - adding ethanol;
 - 20 • filtering the precipitate;
 - suspending the precipitate in ethanol and heating to reflux;
 - cooling the mixture and filtering the product.
5. A process for the preparation of anhydrous crystalline ganciclovir sodium salt comprising:
 - 25 • heating an ethanol suspension of amorphous ganciclovir sodium salt;
 - filtering and drying the product.
6. Anhydrous crystalline ganciclovir sodium salt obtainable according to the process of any one of claims 3 - 5.

7. The use of the anhydrous crystalline ganciclovir sodium salt of any one of claims 1, 2 or 6 for the preparation of pharmaceutical compositions.
8. Pharmaceutical compositions containing anhydrous crystalline ganciclovir sodium salt of any one of claims 1, 2 or 6 in admixture with
5 suitable excipients and/or carriers.

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FIGURE



INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D473/00 A61K31/52

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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

EPO-Internal, WPI Data, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	DATABASE WPI Section Ch, Week 200253 Derwent Publications Ltd., London, GB; Class B02, AN 2002-491195 XP002300299 & CN 1 342 651 A (LIU W) 3 April 2002 (2002-04-03) cited in the application abstract -----	1-8
Y	US 4 642 346 A (CHAN TAI W ET AL) 10 February 1987 (1987-02-10) examples ----- -/-	1-8

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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