Available online at www.sciencedirect.com
ScienceDirect
International Journal of Pharmaceutics 323 (2006) 101–109
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Investigations on the polymorphism and pseudopolymorphism of triamcinolone diacetate

Viktor Suitchmezian, Inke Jeß, Christian Näther*

Institut für Anorganische Chemie der Christian-Albrechts-Universität zu Kiel, Olshausenstrasse 40, D-24098 Kiel, Germany

Received 28 January 2006; received in revised form 5 May 2006; accepted 24 May 2006
Available online 2 June 2006

Abstract

The glucocorticoide triamcinolone diacetate was investigated for polymorphism. Crystallization experiments in different solvents performed at room-temperature reveal that in most cases solvates has formed (form B) which are isotypic and which crystallize in the orthorhombic space group $P2_12_12_1$. In their crystal structure channels are formed in which the solvent molecules are located. In some other solvents the commercial available form A is the thermodynamic most stable form. On heating form A using differential scanning calorimetry (DSC) the compound melts at a peak temperature of 136 °C without any further polymorphic transformation. If the solvents are removed at higher temperatures using simultaneous differential thermoanalysis and thermogravimetry coupled to mass spectroscopy (DTA–TG–MS) the remaining residues are amorphous against X-rays because the compound melts directly after desolvation. If the desolvation process is investigated by DSC measurements the same is observed for most solvents but in some cases different peaks for desolvation and melting are observed. In this case a new modification can be isolated after removing the solvent (form C). If the solvent are removed in vacuum or by storage at room-temperature always the commercial available form A is obtained, whereas desolvation experiments at 80 °C indicate the formation of a further polymorphic modification (form D).

Keywords: Triamcinolone diacetate; Polymorphism; Pseudopolymorphism; Solvates; Crystal structures; Thermoanalytical investigations

1. Introduction

Polymorphism, which is defined as the ability of a compound to exist in more than one crystalline modification is a widespread phenomenon (Bernstein, 1987; Bernstein et al., 1999; Desiraju, 1989; Dunitz, 1995; Dunitz and Bernstein, 1995; Näther et al., 1996, 2002) and is of special interest in pharmaceutical chemistry (Bernstein, 1984; Brittain, 1999, 2000; Chemburkar, 2000; Morris et al., 2001; Bechtlov et al., 2001; Vippagunta et al., 2001). In this area several aspects are of importance. Before new drugs are offered to the market there are several requests by the authority which includes also investigations for polymorphism. Moreover, also information on the influence of the corresponding phase onto the chemical, biological or physical properties of a drug has to be investigated. Furthermore different modifications can be patented separately if they have some advantages in therapy compared to other forms.

In this context also pseudopolymorphism is of importance which is found if molecules contain additional solvent (Bechtlov et al., 2001). However, because the chemical composition of these solvates are clearly different they would be much better described as molecular adducts or co-crystals. If pseudopolymorphs are formed it has to be investigated in detail which modification is formed during desolvation (Bechtlov et al., 2001).

In our own work we are interested in the polymorphism and pseudopolymorphism of glucocorticoids like, e.g. triamcinolone, its acetonide and diacetate. This interest originates from collaboration with one company that sterilizes such compounds by sterile filtration. In this method the drug is dissolved in a given solvent, filtered off and afterwards the solvent is evaporated. This method can lead to different polymorphic and pseudopolymorphic modifications and it has to be investigated that only that phase is formed which is used in therapy. During these investigations we have found a new polymorphic form for the acetonide and we have proven that the commercial available form of this drug is a hydrate which contains a small amount of water needed for the stability of this material (Näther and Jeß, 2006). Starting from these findings we have investigated triamcinolone diac-

* Corresponding author. Tel.: +49 431 880 2092; fax: +49 431 880 1520.
E-mail address: cnaether@ac.uni-kiel.de (C. Näther).

0378-5173/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2006.05.055

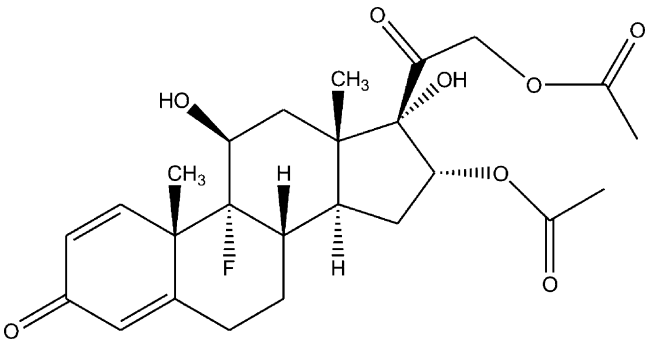

Diagram 1.

etate (Diagram 1) (Florey, 1972) for polymorphism. This drug is a synthetic glucocorticoid used primly in the treatment of adrenocortical and rheumatic disorders (Sieh, 1982).

Even if this drug is used for several decades in therapy there are only minor investigations on the polymorphism and pseudopolymorphism reported in literature. From IR investigations it was concluded that triamcinolone diacetate occurs in two different forms. One of these forms should contain about 4.5% moisture (Bernstein et al., 1956, 1959; Florey, 1972). Melting point measurements shows a wide area of melting temperatures depending on the solvent used for crystallization (Bernstein et al., 1956, 1959; Thoma et al., 1957; Florey, 1972). The same is observed in DTA measurements but a complicated behavior was observed which was interpreted as the occurrence of different solvates (Beancone and Ferrari, 1966; Florey, 1972; Jacobson, 1972). From DTA–TG measurements there are hints that a hydrate exist (Beancone and Ferrari, 1966; Florey, 1972). According to X-ray powder measurements triamcinolone diacetate should exist in two different forms. Polymorph I was obtained by crystallization in chloroform, methylene chloride, acetone or acetone/petroleum ether and benzene/petroleum ether, whereas polymorph II has been obtained from acetone and from acetone/petroleum ether under different conditions. No crystal structures of the pure triamcinolone diacetate or of solvates are available in the Cambridge Structure Database (CSD) (Allen & Kennard, 1993). However, up to now there are no definite investigations if triamcinolone diacetate occurs in different polymorphic or pseudopolymorphic modifications. Therefore, we have investigated this drug. Here we report on our results.

2. Materials and methods

2.1. Crystal structure determination

All data were measured at 170 K using a STOE IPDS-1 imaging plate diffraction system. Structure solutions were performed with direct methods using SHELXS-97 (Sheldrick, 1997). The structure refinements were performed against F^2 using SHELXL-97 (Sheldrick, 1997). All non-hydrogen atoms were refined using anisotropic displacement parameters. The C–H hydrogen atoms were positioned with idealized geometry (some of the methyl H atoms were allowed to rotate but not tip) and refined with isotropic displacement parameters ($U_{iso}(C) = 1.2 \times U_{eq}(C_{methin/methylene/olefinic}) = 1.5 \times U_{eq}(C_{methyl})$) using a riding model with $C–H_{methin} = 1.00$ Å, $C–H_{olefinic} = 0.95$ Å $C–H_{methylene} = 0.99$ Å and $C–H_{methyl} = 0.98$ Å. The O–H hydrogen atoms were located in difference maps but positioned with idealized geometry allowed to rotate but not tip with isotropic displacement parameter using a riding model with O–H = 0.84 Å. Because no heavy elements are present the absolute structure and absolute configuration cannot be determined. Therefore, Friedel equivalents were merged and the absolute configuration was assigned based on the known absolute configuration of the starting material. Some of the atoms of the 2-butanone as well as the O–H hydrogen atom of the 2-butanol are disordered and were refined using a split model. Crystal data and results of the structure refinement are found in Table 1.

Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 612095, ethyl alcohol solvate), (CCDC 612091, 1-propanol solvate), (CCDC 612096, 2-propanol solvate), (CCDC 612090, 1-butanol solvate), (CCDC 612092, 2-butanol solvate), (CCDC 612094, acetone solvate), (CCDC 612093, 2-butanone solvate) and (CCDC 612097, methyl acetate solvate). Copies may be obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1E2, UK (fax: +44 01223/336-033, e-mail: deposit@chemcrys.cam.ac.uk).

2.2. X-ray powder diffraction experiments

X-ray powder diffraction experiments were performed using a STOE STADI P transmission powder diffractometer with an fixed 45° PSD (position sensitive detector) using Cu Kα radiation (λ = 1.540598 Å) and a graphite monochromator. The samples were rotated during measurement and the measuring time was optimized in order to have at least 10.000 counts above background. The solvent free samples were light grinded in a mortar and about 5 mg were prepared using transmission foil. The solvates prepared by stirring crystalline suspensions were not grinded, because the particle size is appropriate for direct powder measurements. All data were analyzed using WinXPOW from STOE & CIE (1999).

2.3. Differential thermal analysis, thermogravimetry and mass spectroscopy

DTA–TG measurements were performed in Al_2O_3 crucibles using a STA-409CD thermobalance from Netzsch. Several measurements under nitrogen atmosphere (purity 5.0) with different heating rates were performed. For MS measurements this instrument is equipped with Skimmer coupling and a quadrupole mass spectrometer from Balzers. The MS measurements were performed in analog and in trend scan mode, in Al_2O_3 crucibles under a nitrogen atmosphere (purity 5.0) using heating rates of 4 °C/min. All measurements were performed with a flow rate of 75 ml/min and were corrected for buoyancy and current effects. The instrument was calibrated using standard reference materials.