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

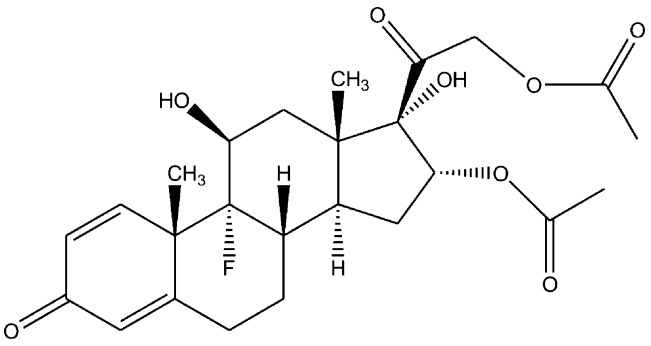

Diagram 1.

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.

Table 1
Crystal data and results of the structure refinement for the solvates of form B

Solvent	Ethyl alcohol	1-Propanol	2-Propanol	1-Butanol	2-Butanol	Acetone	2-Butanone	Methyl acetate
Empirical formula	$C_{27}H_{37}FO_9$	$C_{28}H_{39}FO_9$	$C_{28}H_{39}FO_9$	$C_{29}H_{41}FO_9$	$C_{29}H_{41}FO_9$	$C_{28}H_{37}FO_9$	$C_{29}H_{39}FO_9$	$C_{28}H_{37}FO_{10}$
MW ($g\,mol^{-1}$)	524.57	538.59	538.59	552.62	552.62	536.58	550.60	552.58
Crystal color	Colorless	Colorless	Colorless	Colorless	Colorless	Colorless	Colorless	Colorless
Crystal size (mm^3)	$0.4 \times 0.15 \times 0.15$	$0.25 \times 0.1 \times 0.07$	$0.2 \times 0.1 \times 0.08$	$0.3 \times 0.12 \times 0.12$	$0.25 \times 0.1 \times 0.08$	$0.35 \times 0.14 \times 0.1$	$0.3 \times 0.14 \times 0.12$	$0.26 \times 0.1 \times 0.07$
Crystal system	Orthorhombic	Orthorhombic	Orthorhombic	Orthorhombic	Orthorhombic	Orthorhombic	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
a (Å)	7.9284(4)	8.0908(4)	8.2429(4)	8.1108(4)	8.2610(4)	8.1027(4)	8.3278(4)	8.1663(4)
b (Å)	14.3916(8)	14.3685(8)	14.4422(8)	14.3357(9)	14.7423(9)	14.4364(10)	14.8022(11)	14.3429(7)
c (Å)	23.8158(12)	23.9119(17)	23.438(2)	24.1983(15)	23.3821(12)	23.5353(12)	22.8334(12)	23.5647(16)
V ($Å^3$)	2717.4(2)	2779.8(3)	2790.2(3)	2813.6(3)	2847.62	2753.0(3)	2814.7(3)	2760.1(3)
Temperature (K)	170(2)	170(2)	170(2)	170(2)	170(2)	170(2)	170(2)	170(2)
Z	4	4	4	4	4	4	4	4
$D_{calculated}$ ($g\,cm^{-3}$)	1.282	1.287	1.282	1.305	1.289	1.295	1.299	1.330
$F(0\,0\,0)$	1120	1152	1152	1184	1184	1144	1176	1176
θ-range	2.83–28.06°	2.66–28.00°	2.62–28.01°	2.65–28.10°	2.76–28.08°	2.66–28.05°	2.25–28.06°	2.64–28.05°
$h/k/l$ ranges	$-9 \le h \le 10$ $-19 \le k \le 19$ $-31 \le l \le 18$	$-10 \le h \le 10$ $-18 \le k \le 18$ $-31 \le l \le 22$	$-9 \le h \le 10$ $-18 \le k \le 18$ $-20 \le l \le 30$	$-8 \le h \le 10$ $-18 \le k \le 18$ $-31 \le l \le 32$	$-10 \le h \le 8$ $-19 \le k \le 19$ $-30 \le l \le 30$	$-10 \le h \le 10$ $-19 \le k \le 19$ $-31 \le l \le 30$	$-9 \le h \le 10$ $-19 \le k \le 12$ $-30 \le l \le 30$	$-10 \le h \le 10$ $-18 \le k \le 18$ $-31 \le l \le 31$
μ (Mo Kα) (mm^{-1})	0.100	0.099	0.099	0.100	0.099	0.100	0.100	0.105
Measured reflexes	0.0449	14611	11237	19613	18338	18806	13413	26861
$R_{int.}$	0.0445	0.0818	0.0445	0.0409	0.0550	0.0481	0.0609	0.0645
Independent reflections	3617	3763	3728	3836	3858	3656	3767	3748
Reflections with $I > 2\sigma(I)$	2999	2771	2853	3380	3244	3092	2935	3263
Refined parameters	340	349	349	358	395	350	377	357
R_1 ($I > 2\sigma(I)$)	0.0407	0.0516	0.0448	0.0380	0.0406	0.0378	0.0434	0.0392
wR_2 (all data)	0.1046	0.1267	0.1120	0.1002	0.1078	0.0976	0.1082	0.1043
GooF	1.028	1.005	1.019	1.020	1.027	1.029	1.005	1.029
Min./max. res. (Einstein $Å^{-3}$)	0.239 and −0.260	0.450 and −0.291	0.246 and −0.198	0.230 and −0.198	0.225 and −0.195	0.220 and −0.202	0.261 and −0.202	0.505 and −0.218

2.4. DSC investigations

DSC investigations were performed with the DSC 204/1/F from Netzsch. The measurements were performed in Al pans with heating rates of 3 °C/min. The instrument was calibrated using standard reference materials.

2.5. Chemicals

Triamcinolone diacetate is commercial available and were received from HPP pharmaceuticals. All solvents used for the crystallization experiments were of analytical grade.

2.6. Preparation of the solvates

All solvates were prepared by stirring suspensions of triamcinolone diacetate in the corresponding solvent for about 1 week. The homogeneity of all samples was checked by comparing the experimental pattern with those calculated from single crystal structure analysis. The single crystals were prepared by slow cooling of saturated solutions of triamcinolone diacetate in the corresponding solvent.

3. Results and discussion

3.1. DSC investigations

In the beginning commercial available triamcinolone diacetate (form A) was investigated by differential scanning calorimety (DSC). On heating only one endothermic signal is observed at $T_p = 136$ °C which corresponds to the melting of this compound (Fig. 1). On cooling no crystallization peak is observed and if the solidified melt is investigated by X-ray powder diffractometry it can be shown that the residue is amorphous against X-rays. IR and Raman investigations prove that no decomposition takes place. From these investigations there is no hint for a polymorphic transformation before melting.

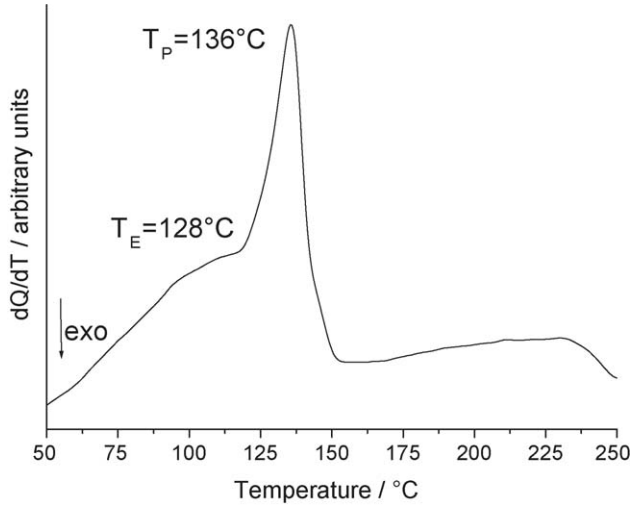

Fig. 1. DSC curve of commercial available triamcinolone diacetate (form A) T_E = extrapolated onset temperature and T_P = peak temperature.

Table 2
Results of the crystallization experiments on triamcinolone diacetate

Solvent	Form
Methyl isobutyl ketone	A
Methyl alcohol	A
Heptane	A
tert-Butyl methyl ether	A
Acetone/H_2O = 90/10	A
Water	A
150 mM NaCl solution	A
2-Butanone	B
Methyl acetate	B
1-Butanol	B
Tetrahydrofuran	B
Toluene	A
Ethyl alcohol/H_2O = 90/10	A
Carbon tetrachloride	A
Cyclohexane	A
Ethyl acetate	A
1 M hydrochloric acid	A
Acetone	B
1-Propanol	B
Isopropyl alcohol	B
2-Butanol	B
Ethyl alcohol	B

3.2. Crystallization experiments

To investigate which form is the most stable at room-temperature we stirred crystalline suspensions of commercial available triamcinolone diacetate in different solvents for three months and investigated the residues by X-ray powder diffraction (Table 2). Altogether, two different forms were detected. In methyl isobutyl ketone, toluene, *n*-heptane, methyl alcohol, carbon tetrachloride, cyclohexane and water form A is found which corresponds to that form which is commercial available and which is used in therapy. In most other solvents a second form B occurs (Table 2). For this form all X-ray powder patterns are similar indicating that all forms are isotypic. In addition, investigations on the stability of these forms show that they decompose on storage indicating for the formation of solvates.

To investigate all compounds by X-ray single crystal structure analysis we performed crystallization experiments under different conditions. In those solvents in which form A is formed we received only bundles of very small needles, to small for structure analysis. In contrast, form B crystallizes in long discrete needles up to 2 mm suitable for single crystal X-ray diffraction (Fig. 2). The morphologies of these crystals are similar in all solvents investigated.

3.3. Crystal structures

All compounds of form B represent monosolvates which crystallizes in the primitive orthorhombic space group $P2_12_12_1$ with $Z = 4$ formula units in the unit cell and all atoms in general positions (Fig. 3, bottom). The compounds are isotypic to the previously reported chloroform solvate (Suitchmezian et al., 2006). All geometric parameters are in agreement with literature data and the conformation in all structures is comparable.

Fig. 2. Microscopic images of crystals of form B obtained from acetone as a representative.

Table 3
Bond lengths (Å) and bond angles (°) of intermolecular O–H···O hydrogen bonding between the triamcinolone diacetate molecules ($1 = $-x + 1$, $y + 1/2$, $-z + 3/2$; $2 = $x + 1/2$, $-y + 3/2$, $-z + 1$)

Solvents	O2–H1O2···O8_$1; D = O2, A = O8			O3–H1O3···O1_$2; D = O3, A = O1		
	H···A (Å)	D···A (Å)	∠(DHA) (°)	H···A (Å)	D···A (Å)	∠(DHA) (°)
2-Butanone	1.965	2.776(3)	162.05	1.949	2.744(3)	157.44
1-Butanol	1.953	2.788(2)	172.87	1.941	2.729(2)	155.87
Acetone	1.933	2.764(2)	170.25	1.942	2.726(2)	154.94
Ethyl alcohol	1.929	2.752(3)	166.08	1.938	2.724(3)	155.27
2-Butanol	1.963	2.775(3)	162.09	1.952	2.730(2)	153.48
n-Propanol	1.952	2.776(4)	166.48	1.939	2.722(3)	154.68
Isopropyl alcohol	1.941	2.758(3)	164.07	1.930	2.717(3)	155.57
Methyl acetate	1.955	2.783(2)	168.57	1.955	2.743(2)	157.82

In the crystal the molecules are connected via intermolecular O–H···O hydrogen bonding between the hydroxyl group O3 and the carbonyl oxygen atom O1 as well as between the hydroxyl group O2 and the carbonyl group O8 into a three-dimensional hydrogen bonded network (Fig. 3, bottom and Tables 3 and 4). From this arrangement channels are formed witch elongate in the direction of the crystallographic *a*-axis (Fig. 3, bottom). Within these channels the solvent molecules are located. Those solvents which contain hydroxyl groups are connected via additional O–H···O hydrogen bonding between the hydroxyl group O9 and the carbonyl oxygen atom O4 to the triamcinolone diacetate molecules, like, e.g. the ethyl alcohol solvate.

Table 4
Bond lengths (Å) and bond angles (°) of intermolecular O–H···O hydrogen bonds between triamcinolone diacetate and the solvent molecules ($3 = $-x + 1$, y-1/2, $-z + 3/2$)

Solvent	O9–H1O9···O4_$3; D = O9, A = O9		
	H···A (Å)	D···A (Å)	∠(DHA) (°)
1-Butanol	2.015	2.836(2)	165.60
Ethyl alcohol	2.062	2.889(3)	168.43
2-Butanol	2.013 2.135	2.811(10) 2.963(13)	158.40 (a) 168.92 (b)
n-Propanol	2.069	2.860(4)	156.73
Isopropyl alcohol	2.088	2.891(4)	159.69

For 2-butanol two hydrogen bonds are found (a) and (b) because of disorder of the oxygen atom O9. There are two conformational possibilities for this oxygen atom.

The channel volume in all solvates is about 20% of the unit cell volume. As expected we found that bigger solvent molecules need more space than smaller molecules. If the channel volume of isomeric solvent molecules like, e.g. 1- and 2-butanol is compared to each other then the branched molecules needs more space than the linear one. Interestingly, the channel volume for those solvents which are connected by O–H···O hydrogen bonding to the triamcinolone diacetate molecules is larger than for those without hydrogen bonding.

3.4. DTA–TG–MS measurements

In the following we investigated the desolvation process for all solvates in detail using DTA–TG–MS measurements. Fig. 4 shows these curves for the solvate with isopropyl alcohol as a representative. On heating all solvates decompose in two different mass steps. From the MS trend scan curves it is obvious that in the first step the solvents are emitted and in the second step the solvent free form decomposes. In most cases the emission of the solvent is accompanied with a very broad endothermic peak in the DTA curve, whereas in a few cases two different very weak endothermic peaks are observed which cannot be resolved successfully.

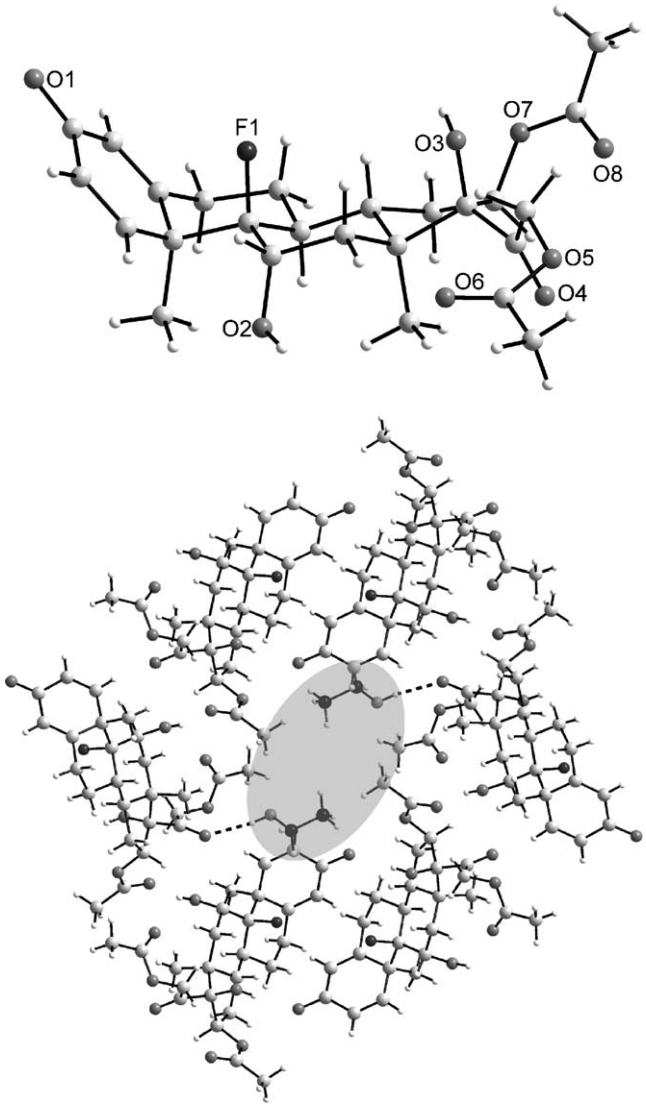

Fig. 3. Crystal structure of the ethyl alcohol solvate as a representative for form B with labeling (top) and with view in the direction of the crystallographic *a*-axis (bottom; only O–H· · ·O hydrogen bonding to the solvent molecule is shown as a dashed line; the ethanol molecule is differently colored).

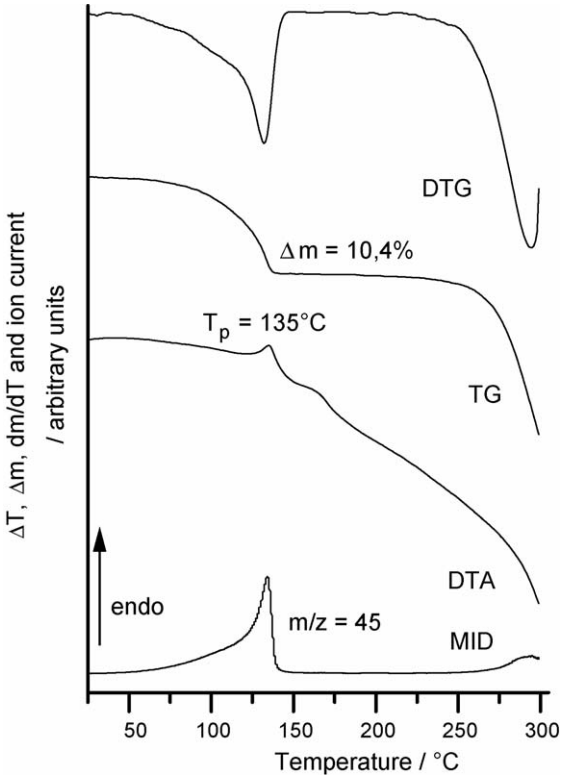

Fig. 4. DTA-, DTG-, TG- and MS trend scan curve for the isopropyl alcohol solvate as a representative (Al_2O_3 crucible; nitrogen atmosphere; heating rate: 4 °C/min; given are the mass change in % and the peak temperatures T_p in °C; the theoretical mass loss for one isopropyl alcohol molecule is 11.2%).

To investigate which modification has formed during desolvation all TG measurements were repeated, stopped after the first mass loss and the residues obtained were investigated by X-ray powder diffraction. These investigations show that all samples are amorphous against X-rays. Obviously, under these conditions the desolvation and melting of the samples occur simultaneously.

3.5. DSC measurements

From the DTA–TG–MS curves it is obvious that the desolvation and melting cannot be resolved. Therefore, the decomposition reaction was investigated using DSC measurements. In these experiments closed Al pans with a small hole are used and therefore, the reaction takes place in part under a self-produced atmosphere leading to an improvement in the resolution. In these experiments for all solvates of form B two different types of DSC curves are observed. The first type of curves is found nearly for all solvents which are connected by O–H· · ·O hydrogen bonding to the triamcinolone diacetate as well as for tetrahydrofurane. In this case only one very broad endothermic peak is observed on heating, which is shown for the isopropyl alcohol solvate as a representative (Fig. 5, left). If the residue obtained after this peak is investigated by X-ray powder diffraction it can be shown that it is amorphous against X-rays. Therefore, desolvation and melting must occur simultaneously. The second type of DSC curves is found for acetone, methyl acetate, 2-butanone and 1-butanol. In this case two endothermic peaks are observed which can be explained as a separation of both processes, desolvation and melting. This behavior is shown for the methyl acetate solvate as a representative (Fig. 5, right). It must be pointed out that the vaporization point of the embedded solvent does not affect the appearance of one or two peaks in the DSC measurements but there is a rough correlation between the solvents. For most of the solvents which form additional O–H· · ·O hydrogen bonds to the host structure desolvation and melting overlaps, whereas for the others both thermal events occur simultaneously. This indicates that the solvates containing hydroxyl group are extremely stable and therefore, the desolvation temperature is in the range of the melting point of the desolvated phase.

To investigate which modification has formed after the first thermal event of the acetone and the methyl acetate solvate, both measurements were stopped after the first signal and the residues obtained were investigated by X-ray powder diffraction. For the

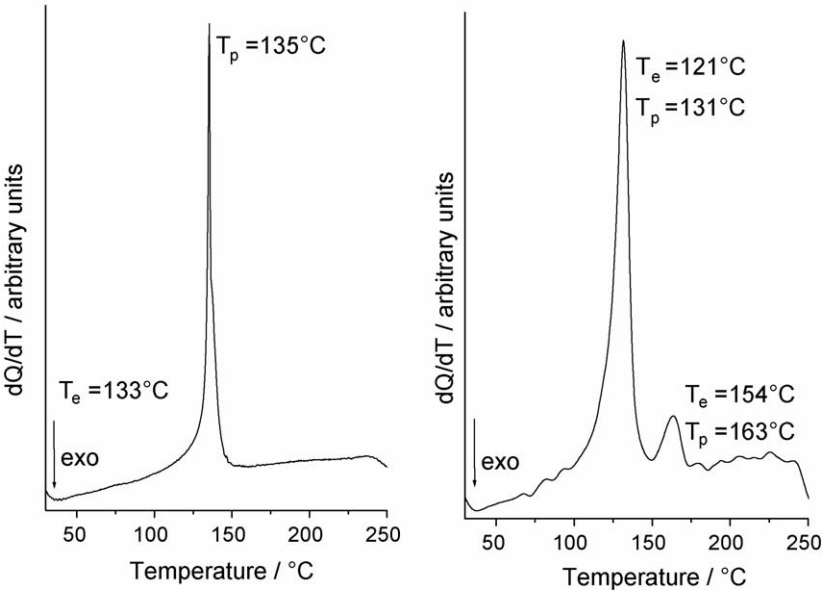

Fig. 5. DSC curves for the isopropyl alcohol solvate (left) and the methyl acetate solvate (right) (Al pan; nitrogen atmosphere; heating rate: 3 °C/min; T_p = peak temperature; T_e = extrapolated onset temperature).

acetone solvate an amorphous residue is obtained (not shown) but for the methyl acetate solvate a powder pattern is observed, which is different from that of the pristine material and of that of form A (Fig. 6). Therefore, it can be assumed that a new polymorphic modification (form C) has formed.

3.6. Desolvation experiments

From the DTA–TG–MS and DSC measurements it was found that on desolvation in most cases amorphous residues are formed. Therefore, we investigated the desolvation process at room-temperature under normal pressure and in vacuum (Fig. 7). In these experiments samples of the solvates were stored for some time in air or under vacuum and afterwards investigated by X-ray powder diffraction. This process was repeated until no change of the powder pattern was observed. Dependent on the solvate which was investigated and if vacuum or normal pressure was used this needs some hours up to several days for the most stable solvates. These experiments clearly show that all solvates decompose into the commercial available form A (Fig. 7).

Because desolvation as room-temperature needs much of time for some solvents we investigated the desolvation process at 80 °C, far from the melting point of the solvent free phase. If the residues obtained in these experiments are investigated by X-ray powder diffraction a powder pattern is observed which is different from that of the pristine material and from that of form A (Fig. 8), which indicates the formation of a new polymorphic form (form D). However, the X-ray powder pattern is very complicated and most of the peaks are very broad. There-

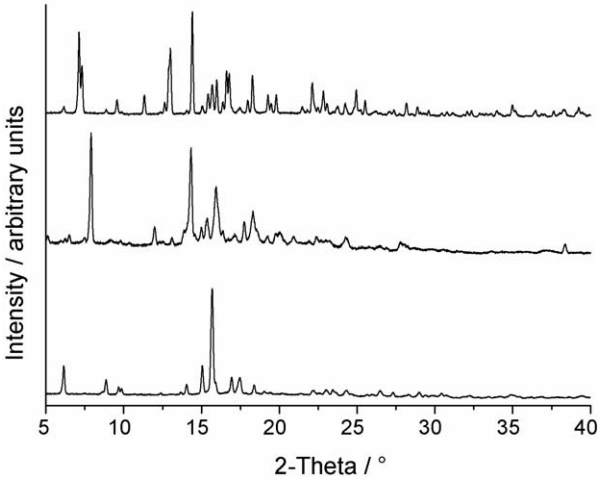

Fig. 6. Experimental X-ray powder pattern of the methyl acetate solvate of triamcinolone diacetate (top), the residue isolated after the first signal in the DSC curve at 147 °C (form C; mid) and of the commercial available solvent free modification form A (bottom).

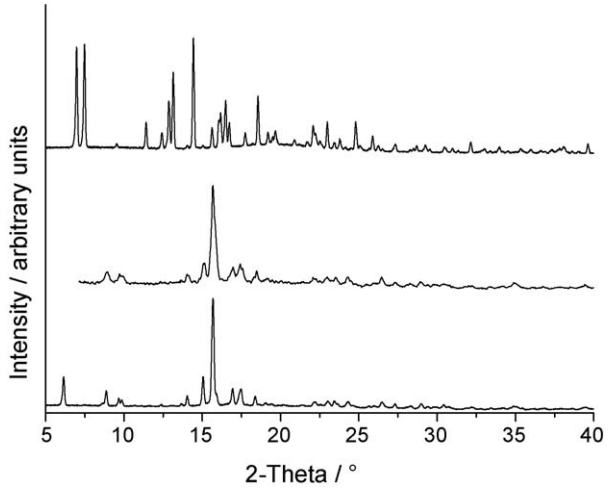

Fig. 7. Experimental X-ray powder pattern of the isopropyl alcohol solvate of triamcinolone diacetate (top) and the residue obtained after storing this sample at room-temperature under normal pressure (mid) and in vacuum (top).

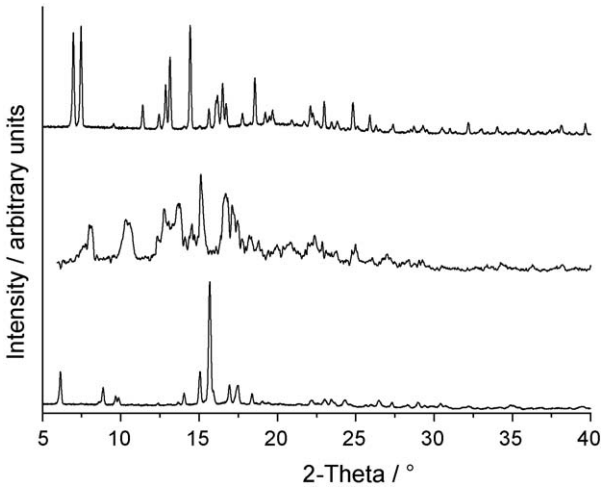

Fig. 8. Experimental X-ray powder pattern of the isopropyl alcohol solvate of triamcinolone diacetate (top), the residue isolated after the storing this sample at 80 °C for 7–9 days (form D; mid) and experimental X-ray powder pattern of the commercial available form A (bottom).

fore, it cannot be proved if a single phase has formed. Infrared and Raman measurements of this form show that the spectra are very similar to that of form A. Therefore, decomposition can be excluded.

4. Conclusion

In the present contribution we have shown that triamcinolone diacetate exists in different polymorphic and pseudopolymorphic forms. The form which is commercial available and used in therapy is the thermodynamically most stable solvent free form at room-temperature. From DSC investigations there are no hints for a polymorphic transition of this form and only melting is observed. X-ray powder measurements of the solidified melt prove that it is amorphous against X-rays. However, in most solvents several pseudopolymorphic forms are obtained which are isotypic and which crystallizes orthorhombic in space group $P2_12_12_1$. In all of these forms the solvent molecules are located in channels. If the solvents are removed at elevated temperatures using DTA–TG–MS measurements the remaining residues are amorphous against X-rays. If the desolvations process is investigated using DSC measurements desolvation and melting can be resolved and in some cases the formation of a new solvent free polymorphic form is observed. In contrast, desolvation of form B at room-temperature and in vacuum leads to the formation of modification A. If the desolvation of form B is performed by storing samples of form B at 80 °C, depending on the solvents an additional polymorphic form is observed. Infrared and Raman investigations of forms A, C and D as well as of the amorphous residues reveal practically no differences, which show that these methods are not suitable to differ between the different modifications. However, they prove that no decomposition take place by desolvation at higher temperatures. Unfortunately no structural information of the new forms C and D could be extracted. Therefore, this will be the subject of further investigations.

Acknowledgements

This work was supported by the State of Schleswig-Holstein. We are very thankful to Professor Dr. Wolfgang Bensch for the facility to use his experimental equipment.

References

Allen & Kennard, 1993. Crystal Structure Database (CSD), ConQuest, Version 1.6, 2005.

Beancone, L.M., Ferrari, H.J., 1966. Applications of differential thermal analysis in the examination of synthetic organic compounds. Microchem. J. 10, 370–392.

Bechtlov, B., Nordhoff, S., Ulrich, J., 2001. Pseudopolymorphism in industrial use. Cryst. Res. Technol. 36, 1315–1328.

Bernstein, J., 1984. In: Horn, A.S., De Ranter, C.J. (Eds.), X-ray Crystallography and Drug Action. Clarendon Press, Oxford, p. 23, and references cited therein.

Bernstein, J., 1987. Organic solid state chemistry. In: Desiraju, G.R. (Ed.), Conformational Polymorphism. Elsevier, Amsterdam, p. 470, and references cited therein.

Bernstein, J., Davey, R., Henck, O., 1999. Gleichzeitig auftretende polymorphe Modifikationen. Angew. Chem. 111, 3646–3669;
Bernstein, J., Davey, R., Henck, O., 1999. Concomitant polymorphs. Angew. Chem. Int. Ed. 38, 3440–3461.

Bernstein, S., Lehnard, R.H., Allen, W.S., Heller, M., Littell, R., Stolar, S.M., Feldman, L.I., Blank, R.H., 1956. The synthesis of the 16α-hydroxy derivateives of 9α-halo-steroids. J. Am. Chem. Soc. 78, 5693–5694.

Bernstein, S., Lehnard, R.H., Allen, W.S., Heller, M., Littell, R., Stolar, S.M., Feldman, L.I., Blank, R.H., 1959. The synthesis of the 16α-hydroxy derivatives of 9α-substituted steroids. J. Am. Chem. Soc. 81, 1689–1696.

Brittain, H.G. (Ed.), 1999. Polymorphism in Pharmaceutical Solids, vol. 95. Marcel Dekker Inc., New York.

Brittain, H.G., 2000. The Impact of polymorphism on drug development: a regolatory viewpoint. Am. Pharm. Rev. 3, 67–68.

Chemburkar, S.R., 2000. Dealing with the impact of ritonavir polymorphs on the late stages of bulk drug process development. Org. Process. Rev. Dev. 4, 413–417.

Desiraju, G.R. (Ed.), 1989. Crystal Engineering, Mat. Sci. Monogr. Elsevier, Amsterdam, and references cited therein.

Dunitz, J.D., 1995. Phase changes and chemical reactions in molecular crystals. Acta Cryst. B51, 619–631.

Dunitz, J.D., Bernstein, J., 1995. Disappearing polymorphs. Acc. Chem. Res. 28, 193–200.

Florey, K., 1972. Analytical Profiles of Drug Substances, vol. 1. Academic Press, New York, pp. 422–442.

Jacobson, H., 1972. Triamcinolone diacetate. In: Florey, K. (Ed.), Analytical Profiles of Drug Substances, vol. 1. Academic Press, New York, p. 441.

Morris, K.R., Griesser, U.J., Eckhardt, C.J., Stowell, J.G., 2001. Theoretical approaches to physical transformations of active pharmaceutical ingredients during manufacturing processes. Adv. Drug. Deliver. Rev. 48, 91–114.

Näther, C., Jeß, I., Havlas, Z., Nagel, N., Bolte, M., Nick, S., 2002. Trimorphism of 4,4′-di(*tert*-butyl)-biphenyl: structural, thermodynamic and kinetic aspects. Solid State Sci. 4, 859–871.

Näther, C., Nagel, N., Bock, H., Seitz, W., Havlas, Z., 1996. Structural, kinetic and thermodynamic aspects of the conformational dimorphism of diethyl 3,6-dibromo-2,5-dihydroxyterephthalate. Acta Cryst. B52, 697–706.

Näther, C., Jeß, I., 2006. News from an old drug: Investigations on the polymorphism of triamcinolone acetonide. Angew. Chem., in press.

Sheldrick, G.M., 1997. SHELXS-97 and SHELXL-97: Programs for the Solution (XS) and the Refinement (XL) of Crystal Structures. University of Göttingen, Germany.

Sieh, D.H., 1982. Triamcinolone diacetate. In: Florey, K. (Ed.), Analytical Profiles of Drug Substances, vol. 11. Academic Press, New York, pp. 651–661.

STOE & CIE, 1999. WinXPOW, Version 1.06. STOE & CIE, GmbH, Darmstadt, Germany.

Suitchmezian, V., Jeß, I., Näther, C., 2006. Triamcinolonediacetate chloroform solvate. Acta Cryst. E62, o788–o790.

Thoma, R.W., Fried, J., Bonanno, S., Grabowich, P., 1957. 16α-Hydroxylation of 9α-fluorohydrocortisone and 9α-fluoroprednisolone by streptomyces roseochromogenus. J. Am. Chem. Soc. 79, 4818–4818.

Vippagunta, S.R., Brittain, H.G., Grant, D.J.W., 2001. Crystalline solids. Adv. Drug. Deliver. Rev. 48, 3–26.