Polymorphism of Alprazolam (Xanax®): A Review of its Crystalline Phases and Identification, Crystallographic Characterization, and Crystal Structure of a New Polymorph (Form III)

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ABSTRACT: A new polymorphic form of Alprazolam (Xanax®), 8-chloro-1-methyl-6-phenyl-4H-[1,2,4]triazolo-[4,3-α][1,4]benzodiazepine, $C_{17}H_{13}ClN_4$, has been investigated by means of X-ray powder diffraction (XRPD), single crystal X-ray diffraction, and differential scanning calorimetry (DSC). This polymorphic form (form III) was obtained during DSC experiments after the exothermic recrystallization of the melt of form I. The crystal unit cell dimensions for form III were determined from diffractometer methods. The monoclinic unit cell found for this polymorph using XRPD after indexing the powder diffractogram was confirmed by the cell parameters obtained from single crystal X-ray diffractometry on a crystal isolated from the DSC pans. The single crystal unit cell parameters are: $a = 28.929(9)$, $b = 13.844(8)$, $c = 7.361(3)$ Å, $\beta = 92.82(3)^\circ$, $V = 2944(2)$ Å^3, $Z = 8$, space group $P2_1$ (No.4), $Dx = 1.393$ Mg/m^3. The structure obtained from single crystal X-ray diffraction was used as initial model for Rietveld refinement on the powder diffraction data of form III. The temperature phase transformations of alprazolam were also studied using high temperature XRPD. A review of the different phases available in the Powder Diffraction File (PDF) database for this drug is described bringing some clarification and corrections. © 2007 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 96:1114–1130, 2007

Keywords: X-ray powder diffractometry; differential scanning calorimetry (DSC); solid state; crystallography; polymorphism; phase transformations; Rietveld refinement; alprazolam

INTRODUCTION

Polymorphism, the ability of a molecule to crystallize into more than one crystal arrangement, can have a profound effect on the shelf life, solubility, and processing properties of a drug. Different polymorphs and solvates (also called pseudopolymorphs) of a drug can have different rates of uptake in the body, leading to lower or higher biological activity than desired.[1,2] It is vital that researchers involved in the formulation of crystalline products be able to select the polymorph with the desired properties and anticipate problems such as the unwanted crystallization into other polymorphs. The knowledge of the polymorphic

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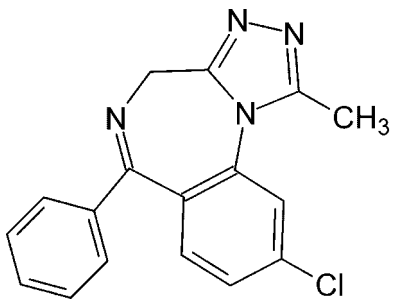
forms is also important for patenting and registration purposes.

Polymorphism can be evidenced using a variety of experimental techniques ranging from optical microscopy to more sophisticated methods of analysis such as: differential scanning calorimetry (DSC), hot stage polarizing microscopy, X-ray powder diffraction (XRPD), single crystal diffraction methods, IR- and Raman spectroscopy, and NMR-spectroscopy. In spite of the fact that any of the above mentioned techniques could in principle be used to detect polymorphism, a proper structural description of the different modifications of one polymorph needs the use of X-ray diffraction techniques to identify the correct crystalline phase and determine, when possible, the three-dimensional crystal structure of the chemical entity.

Alprazolam (IUPAC name: 8-chloro-1-methyl-6-phenyl-4H-[1,2,4]triazolo-[4,3-α][1,4]benzodiazepine, CAS 28981-97-7, $C_{17}H_{13}ClN_4$, M.W. 308.76, Scheme 1), is commercialized, among other brand names, as Xanax® and Xanor®. This triazolobenzodiazepine is used to treat anxiety disorders, insomnia, muscle spasms, and panic attacks.[3] Alprazolam (Xanax®) and Xanax XR®, its long-acting formulation, are among the most marketed drugs in the United States and Europe, being the most prescribed medication of its kind in the USA.[4] In the United States, alprazolam is a prescription drug and is assigned to Schedule IV of the Controlled Substances Act by the Drug Enforcement Administration and included under the United Nations Convention on Psychotropic Substances.

It has been reported in the literature that this drug crystallizes in different polymorphic forms, hydrates, and solvates depending on the crystallization solvents used. Plate-shaped crystals of anhydrous alprazolam (known as form I or β-alprazolam, melting point: 224–228°C) are obtained by recrystallization from dry methanol while a dihydrate is formed when this recrystallization occurs in presence of not well-dried methanol.[5] Furthermore, recrystallization of alprazolam from highly supersaturated solutions of dry ethanol and dry acetonitrile, leads to the formation of the respective solvates.[5] Desolvation of the dihydrate and the ethanol solvate of alprazolam results in polymorphic form I, as confirmed by the same authors using XRPD. On the other hand, desolvation of the acetonitrile solvate leads to the formation of an unidentified polymorph.[5] In a related study, Reck et al.[6] described also the single crystal structures and powder diffraction data of form I, the dihydrate, and another polymorph (form II or α-alprazolam, as they called) of this drug. These authors reported that form II can be obtained from recrystallization in ethylacetate and form I from flash cooling of an isopropanol solution. They briefly also stated that form II crystals could be formed after melting form I crystals, depending on the initial crystal size and heating rate used. This possible thermal transformation of polymorphs mentioned by Reck et al.[6] has been further studied in the present work using DSC and high temperature X-ray powder diffraction (HT-XRPD). Alprazolam polymorphism and stability has also been studied by Laihanen and coworkers,[7,8,9] unfortunately these studies present some deficiency, particularly in the use of XRPD for identification and crystallinity determination. They classified some crystalline forms of alprazolam introducing some confusion in the classification of its polymorphs and solvates. This will be further discussed at the end of the present work.



Scheme 1. Structural formula of alprazolam.

Form II needle-shaped crystals is the modification reported in the USP XXII and other literature[10] with a melting point of 228–231°C. The dihydrate form could be used for pharmaceutical production due to its biodisponibility and stability behaviors.[6] Since hydrates are generally less soluble, polymorphism of alprazolam seems not to be of concern for bioavailability and activity. The bioavailability of alprazolam is high (80–90%) in contrast to those of midazolam and triazolam, suggesting that alprazolam is unlikely to undergo extensive intestinal first-pass metabolism.[11]

The *Powder Diffraction File* (PDF) database PDF-4/Organic 2005[12] is the world's largest XRPD database for organic and organometallic compounds and an indispensable tool to identify the most complex formulations, identification of polymorphs, and other physical and chemical data. There are six entries in the PDF referring to crystalline phases of alprazolam. Among these entries, PDF 48-2348 and PDF 48-2349 refer to

form I and form II of alprazolam, respectively. From the six entries, some of them are duplicated, ambiguous or the crystal data are incomplete or unpresent. In the present work we intend to shed light to these problems for alprazolam polymorphic forms, analyzing the available entries and suggesting the replacement of some of them with more precise and correct values. In addition, precise crystal data and XRPD data of a new polymorph of alprazolam (form III) are reported, as well as its crystal structure solved from single crystal X-ray diffraction. This new polymorph of alprazolam was obtained during DSC characterization of alprazolam form I, which melted followed by an exothermic recrystallization into the new crystalline form III. In some DSC experiments this form III was found concomitant with known form II. In order to identify and characterize this new polymorph, the DSC pans content was analyzed by X-ray diffraction methods. The structure obtained from single crystal X-ray diffraction for this new form was used as a model for Rietveld refinement on powder diffraction data of the pure crystalline phase of form III, confirm that it is not a mixture of polymorphic forms.

EXPERIMENTAL

A white crystalline powder sample of alprazolam supplied by Pfizer (Brussels, Belgium) was used for these studies. The drug sample complied with all the necessary standards of quality control required by Pfizer. XRPD analysis indicated that this material was alprazolam form I.

Differential Scanning Calorimetry (DSC)

The DSC measurements were performed using an 822^e Mettler-Toledo (Mettler Toledo, Greifensee, Switzerland). Cooling was provided with an intercooler. Data were treated using the resident STAR^e Software v.6.10.[13] Calibration was carried out using indium and zinc as reference materials. The samples were analyzed in 40 μL closed aluminium pans under a nitrogen purge. During the study, the samples were heated from 25°C to 210°C at a heating rate of 10°C/min and in a final heating ramp from 211°C to 245°C at a heating rate of 1°C/min. After the DSC temperature scan, the samples were cooled to room temperature (RT) and the DSC pans were opened and visually inspected using optical microscopy.

X-Ray Powder Diffraction (XRPD)

Room Temperature XRPD

The colorless plate-shaped crystals obtained in some DSC pans were gently grounded in an agate mortar until a fine powder was obtained. The powder was introduced in a capillary of 0.7 mm diameter in order to minimize preferred orientation. The specimen was analyzed by XRPD using CuKα_1 radiation (1.540598 Å). A STOE STADI P powder diffractometer system in transmission mode, powered at 50 kV and 30 mA, and equipped with a focusing symmetric curved Ge (111) primary monochromator, was operated in a step-scanning mode (Debye-Scherrer/2θ) over a 2θ range of 1–64.98°. A linear PSD detector was used in moving/fixed ω mode with scan time/step of 240 s and a scan resolution of 0.02° in 2θ. The precise determination of the peak positions was carried out using the measurement and data processing program WinXPOW version 2.01.[14] Throughout the experiment the ambient temperature was maintained at 298(1) K. The intensities of the diffraction lines were measured as peak heights above background and expressed as a percentage of the strongest line.

High Temperature XRPD

For the HT-XRPD study the same STOE STADI P powder diffractometer system equipped with focusing symmetric curved Ge (111) primary monochromator in transmission mode was used, but with a STOE capillary furnace with graphite heating element (inner diameter of the quartz-capillary: 1.0 mm). The furnace was calibrated with Ammonium nitrate. The instrument X-ray generator was powered at 40 kV and 40 mA (CuKα_1 radiation (1.540598 Å)). The data were collected in Debye-Scherrer/2θ mode over a 2θ range of −13.000–77.000. A curved image plate position sensitive detector was used in stationary/fixed ω mode with scan time/step of 600 s and a scan resolution of 0.015° in 2θ. Two HT-XRPD experiments were performed. In the first experiment the temperature program used was as follows: started at 30°C, heating up in six steps of 25–180°C, one 20°C-step to 200°C and then in 1°C-steps to 250°C. The second experiment started also at 30°C, heating up in steps of 10–200°C and then in 1°C-steps to 225°C, then the system was cooled in steps of 1°C from 225°C to 200°C and in steps of 10–30°C. The software used for data collection and control was WinXPOW

version 2.01.[14] The diffractograms were analyzed using the POWDER3D program.[15]

Single Crystal X-Ray Diffraction

Single crystal data for an alprazolam plate-shaped crystal (found to be form III), was measured on a Siemens P4 four-circle diffractometer with graphite monochromated Cu-Kα radiation (1.54178 Å). The unit cell dimensions were obtained by least-squares fit of 55 centered reflections ($6.1 < 2\theta < 50^\circ$). The intensity data were collected using $\omega - 2\theta$ scans, with ω scan width equal to the low range plus the high range plus the separation between the Kα_1 and Kα_2 positions; 5949 reflections were measured. Empirical absorption corrections, via ψ scan were applied.[16] Three standard reflections were monitored every 100 reflections and no intensity decay was observed. The structure was solved by direct methods and subsequent Fourier synthesis. Non-H atoms were refined anisotropically by full-matrix least-squares techniques. H atoms were calculated geometrically and included in the refinement, but were restrained to ride on their parent atoms. The isotropic displacement parameters of the H atoms were fixed to 1.3 times U*eq* of their parent atoms. The program used for data collection, cell refinement, and data reduction was XSCANS.[17] The program used to solve the structure was SIR92[18] and SHELXL97[19] was used for the structure refinement. Molecular graphics were generated with DIAMOND.[20] PLATON[21] was used to prepare material for publication and crystallographic report (Crystallographic Information File, CIF).

RESULTS AND DISCUSSION

Alprazolam Form III, a New Polymorph

Thermal Behavior

During the final heating ramp of alprazolam form I, a recrystallization from the melt of form I was observed (Fig. 1). Form I melts (m.p. = 222.0°C, first endothermic signal in Fig. 1), and recrystallizes during further heating into another crystalline form (exothermic signal at 223.2°C) and then this second crystalline form melts at 227.02°C (second endothermic signal), with a enthalpy of fusion 99.37 J/g. Subsequently, the DSC samples were cooled to RT.

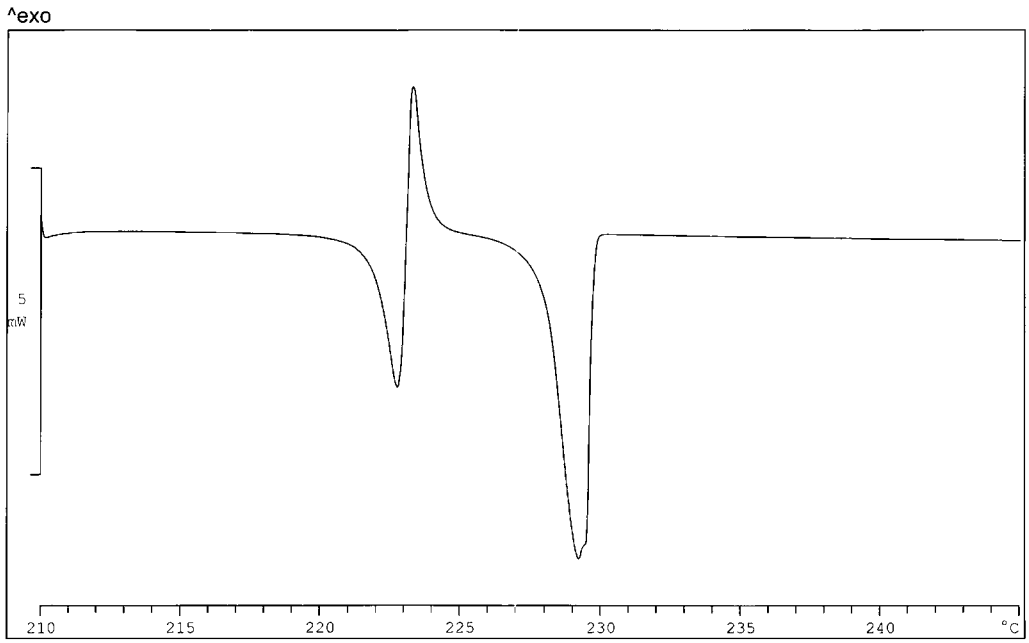


Figure 1. DSC trace of alprazolam: initial alprazolam form I melts followed by an exothermic recrystallization into a new crystalline form. The new form obtained (form III), was identified and characterized by XRPD and single crystal diffraction. In some DSC experiments crystals of form II were also observed, as a concomitant polymorph.

Visual inspection of the DSC pan content under an optical microscope showed in some cases plate-shaped crystals and in some others two different coexisting crystal types (needles and plates). Afterwards it was confirmed, using *ex situ* XRPD and single crystal diffraction that the sample heated above 223°C and cooled to RT contained plate-shaped crystals that correspond to a new polymorphic form of alprazolam (form III). The needle-shaped crystals correspond to crystals of form II (further discussed in the next sections).

X-Ray Powder Diffraction Analysis

Figure 2c shows the XRPD pattern for form III of alprazolam. From the analysis of the diffraction

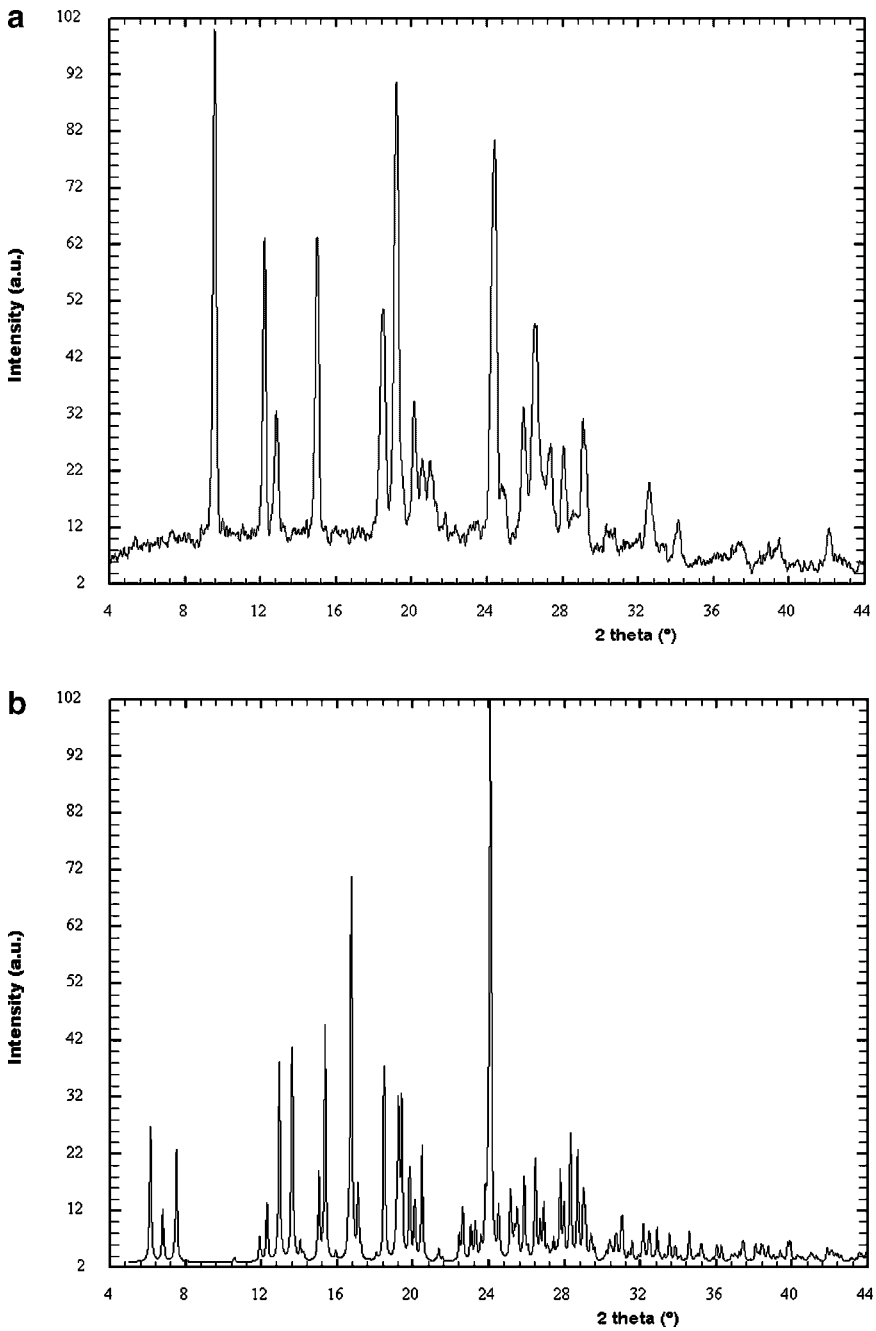


Figure 2. Diffractograms of different polymorphs of alprazolam: (a) experimental XRPD of form I at room temperature, (b) calculated XRPD of form II from its crystal structure, (c) experimental XRPD of form III at room temperature.

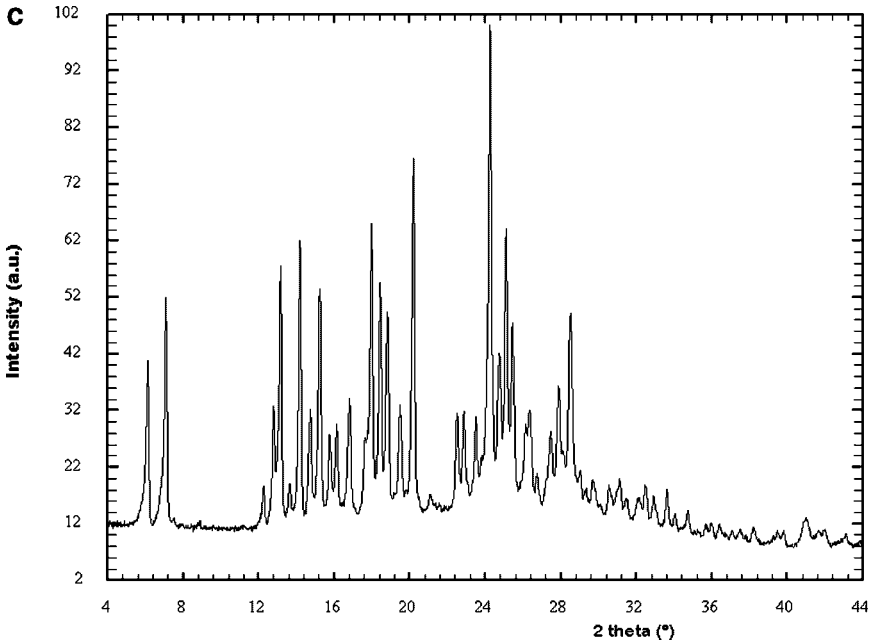


Figure 2. (*Continued*)

pattern, the precise determination of the peak positions was carried out using the pattern decomposition and peak search routine available in the WinXPOW[14] program of the STOE-STADI P powder diffractometer, resulting in 49 lines. The first 20 peaks were initially used for indexing by means of the dichotomy method implemented in the program DICVOL04.[22] A solution with monoclinic symmetry was proposed by the program with the following unit cell dimensions: $a = 28.895(12)$, $b = 13.840(6)$, $c = 7.340(2)$ Å and $\beta = 92.90(4)^\circ$ with figure-of-merit (FOM) of $F20 = 29$ (0.010, 101).[23] The indexing of the diffraction lines is presented in Table 1. The data in Table 1 for form III were reviewed using the NBS*AIDS83[24] program and refined cell parameters were obtained by least-squares refinement of all lines: $a = 28.895(12)$, $b = 13.834(4)$, $c = 7.345(2)$ Å, $\beta = 92.89(3)^\circ$ with FOM[23,25] $M20 = 16$ and $F20 = 41$ (0.0084, 88). The crystallographic density from the indexed powder specimen of form III suggests the presence of eight molecules in the unit cell, $Z = 8$, ($Dx = 1.399$ Mg/m^3; space group $P2_1$ (No. 4) or $P2_1$/m (No. 11)).

Structure Determination by Single Crystal X-Ray Diffraction and Rietveld Refinement of the Powder Diffraction Data of Form III

The unit cell dimensions determined by single crystal diffraction data on a plate-shaped crystal of form III of alprazolam [$a = 28.929(9)$, $b = 13.844(8)$, $c = 7.361(3)$ Å, $\beta = 92.82(3)^\circ$, $V = 2944.46$ Å^3], confirms those obtained from the powder diffraction analysis and hence the indexing of the powder pattern of form III.

The first entry reported for alprazolam in the PDF[12] corresponds to PDF 42–1854, which includes just some powder diffraction lines and happens to be incomplete. Later, the entry PDF 51–1919 was included in this database reporting also the crystal data of the alprazolam crystalline phase. These data are in a very good agreement with the reported diffraction lines of the existing PDF 42–1854 but including weak reflections not reported in the early entry. Nothing is mentioned on these entries about polymorphism neither how they were obtained. Table 1 shows a comparison of the powder diffraction lines reported in the PDF 42–1854 and PDF 51–1919 entries. The cell parameters reported in PDF 51–1919 correspond to a monoclinic unit cell [$a = 28.0324$, $b = 7.8576(7)$, $c = 14.6171(8)$Å, $\beta = 95.26(7)^\circ$, $V = 3206.11$ Å^3]. Despite the reasonable good values of the FOM's for the reported indexing, the indexing and crystal data in PDF 51–1919 do not match with those of form III.

We could also conclude, after comparison with the XRPD pattern (data not shown) of the undescribed polymorph obtained after desolvation of the acetonitrile solvate,[5] that form III does not match this pattern, which suggests that the

Table 1. X-ray Diffraction Data Reported in the *Powder Diffraction File* (ICDD, 2006) Database PDF 42–1854, PDF 51–1919 as 'alprazolam' and the New Data of the Form III of This Compound

PDF 42–1854		PDF 51–1919		Alprazolam form III					
d_{obs} (Å)	I/Io_{obs} (%)	d_{obs} (Å)	I/I_{obs} (%)	$2\theta_{obs}$	d_{obs} (Å)	I/Io_{obs} (%)	d_{calc} (Å)	I/Io_{cal} (%)	*hkl*
		14.57	40						
14.42	41			6.118	14.44	40	14.45	46	200
12.45	60	12.45	61	7.081	12.47	53	12.48	58	$\bar{1}10$
				8.841	10.00	3	10.00	2	210
							9.63	<1	003
		9.30	3						
7.89	11	7.87	12	11.201	7.89	3	7.91	1	$\bar{3}10$
		7.28	2						
7.20	19	7.20	20	12.251	7.22	17	7.22	9	400 $\bar{1}01$
		6.97	5						
				12.795	6.9129	33	6.9219	26	020
6.8587	11	6.8560	11						
6.7126	90	6.7145	91	13.148	6.7281	57	6.7315	54	120
6.4879	3	6.5123	3	13.639	6.4873	19	6.4932	6	011
							6.3992	3	$\bar{1}11$
6.2256	19	6.2295	19	14.187	6.2379	62	6.2425	64	$\bar{2}20$
6.0876	5	6.0890	5	14.725	6.0109	32	6.0204	30	$\bar{2}11$
				15.225	5.8146	54	5.8286	56	211
							5.7101	3	103
5.5754	100	5.5787	100	15.766	5.6163	27	5.6211	17	320
5.4471	10	5.4445	10	16.128	5.4913	30	5.4958	24	$\bar{3}11$
5.2124	18	5.2157	18	16.802	5.2725	34	5.2787	26	$\bar{4}01$ 311
5.0059	36	5.0144	36	17.645	5.0224	27	5.0380	20	021 401
				17.761	4.9899	7	4.9950	15	420 $\bar{1}21$
				17.965	4.9336	66	4.9368	77	$\bar{4}11$ 121
4.8025	55	4.8055	56	18.427	4.8110	53	4.8157	48	600 $\bar{2}21$
				18.813	4.7130	49	4.7240	45	411 221
4.6595	2	4.6562	2						
4.5658	36	4.5599	36	19.481	4.5530	30	4.5521	22	130
4.4732	8	4.4756	8						
4.3841	37	4.3867	38	20.189	4.3949	78	4.3959	72	321 $\bar{2}30$
4.2414	1	4.2440	1	21.085	4.2100	17	4.2262	3	511
							4.2002	3	$\bar{1}24$ $\bar{1}$ $\bar{2}4$
4.1651	1	4.1677	1				4.1616	1	033 0 $\bar{3}3$
							4.1225	2	$\bar{1}06$
4.0004	2	4.0029	2				4.0693	1	124 $1\bar{2}4$
				22.498	3.9488	32	3.9511	27	710 $\bar{6}20$ +
3.8863	16	3.8888	16	22.867	3.8859	30	3.8868	20	430 $\bar{1}31$
3.8105	9	3.8183	9	23.506	3.7816	30	3.7896	22	611
				23.832	3.7307	23	3.7363	8	521
3.6858	42	3.6860	43	24.247	3.6677	100	3.6762	100	002 $\bar{7}01$ +
3.6413	8	3.6435	8						
3.5952	20	3.6003	20	24.733	3.5967	42	3.6041	36	$\bar{5}30$ $\bar{2}02$
3.5336	28	3.5407	28	25.099	3.5452	63	3.5469	57	012 $\bar{1}12$+
3.5023	18	3.5045	18	25.441	3.4982	46	3.5062	40	112
3.3936	1	3.3957	1	26.123	3.4085	30	3.4160	21	212 711
3.3680	6	3.3690	6	26.337	3.3812	32	3.3860	25	$\bar{3}12$
				26.725	3.3330	20	3.3328	8	$\bar{4}02$ $\bar{6}30$
3.2515	13	3.2647	13	27.458	3.2457	27	3.2466	17	$\bar{4}12$ 022+
3.2224	3	3.2280	3	27.883	3.1972	35	3.1975	29	$\bar{8}20$ 531
3.1815	6	3.1836	6	28.124	3.1703	23	3.1732	14	801 $\bar{5}02$+
3.1461	21	3.1492	21	28.507	3.1286	49	3.1355	43	041 222

DOI 10.1002/jps

Table 1. (*Continued*)

PDF 42–1854		PDF 51–1919		Alprazolam form III					
d_{obs} (Å)	I/Io_{obs} (%)	d_{obs} (Å)	I/I_{obs} (%)	$2\theta_{obs}$	d_{obs} (Å)	I/Io_{obs} (%)	d_{calc} (Å)	I/Io_{cal} (%)	*hkl*
3.0973	15	3.0982	15	29.004	3.0761	21	3.0750	10	730 $\bar{2}41+$
				29.308	3.0449	17	3.0471	6	241
				29.712	3.0044	19	3.0094	10	$\bar{4}22$
2.9657	2	2.9659	2						

mentioned desolvated phase corresponds to another possible polymorph of alprazolam.

Crystal Structure of Form III[1]. From a single-crystal of the identified form III, the crystal structure was solved and refined, as described in the experimental section. The space group was confirmed to be $P2_1$ (No. 4). The relative high crystallographic *R*-value of the refinement ($R = 14\%$) is due to the poor diffraction quality of the crystal.

The crystal structure obtained corresponds to a new crystal structure of alprazolam not reported previously in the Cambridge Structural Database version 5.27.[26] In form III there are four independent molecules of alprazolam in the asymmetric unit, hereafter labeled as molecules A–D (Fig. 3). The molecules are related among them by pseudo-symmetry. Selected torsion angles (Crystallographic Information File available on request[1]) of pseudosymmetrically related molecules are similar in magnitude but of opposite sign. Bond lengths and bond angles of the four independent molecules are in the expected ranges and in good agreement with those found in the molecules of both form I and form II polymorphs. Since there are no donor groups in the molecule, no classic hydrogen bonds were found. Instead, the packing of the molecules (Fig. 4c) in the crystal is dictated by van der Waals interactions and π–π electronic interactions. The triazol rings in molecules A–B and C–D stack face to face with a distance between the centroids of 4.4 Å and 4.3 Å, respectively. The phenyl rings in molecules B–C stack face to edge with a distance between ring centroids of 5.0 Å. Following the packing of the molecules in the unit cell, the phenyl rings in C and D of the neighboring cell stack at a distance of 5.3 Å between ring centroids. Figure 4a–c shows the packing of alprazolam as in form I, form II, and form II, respectively.

Rietveld Refinement Using the Form III Powder Data and the Obtained Structural Model. The spatial coordinates obtained from the single-crystal structure determination were introduced as structural model for refinement using the Rietveld method, using the XRPD data of pure form III crystalline phase. The raw data were transferred to the FullProf2000 Rietveld program package[27] and the powder pattern was initially fitted by refining the following parameters: zero point, background (polynomial function), profile peak shape (pseudo-Voigt function), and unit cell parameters from powder data. The final cycle of refinement resulted in the following *R* values: $R_p = 5.01$, $R_{wp} = 6.51$, and Bragg *R* factor = 8.48. The difference plot comparing the experimental powder pattern and the calculated powder pattern is shown in Figure 5. The Rietveld refined unit cell parameters were: $a = 29.9339(9)$ Å, $b = 13.8548(3)$ Å, $c = 7.3540(1)$ Å, $\beta = 92.911(2)^\circ$, and $V = 2944.22(13)$ Å^3.

This confirms that the crystal structure of form III of alprazolam in the single crystal is the same as in the polycrystalline powder phase of form III and provides that it can be formed as a pure (polymorphic) phase. Table 2 shows a comparison of the observed diffraction lines of form III and the calculated lines from the single crystal structure of this form. Furthermore, the absence of spurious peaks and the full correspondence in the peak positions confirms that the powder data are not taken from a mixture of polymorphs. The crystal structure of this new form has been elucidated and refined combining the findings of these techniques, demonstrating the packing arrangements of the molecules in this crystal form (Fig. 4) are different from that of form I and form II.

[1]CCDC 609681 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

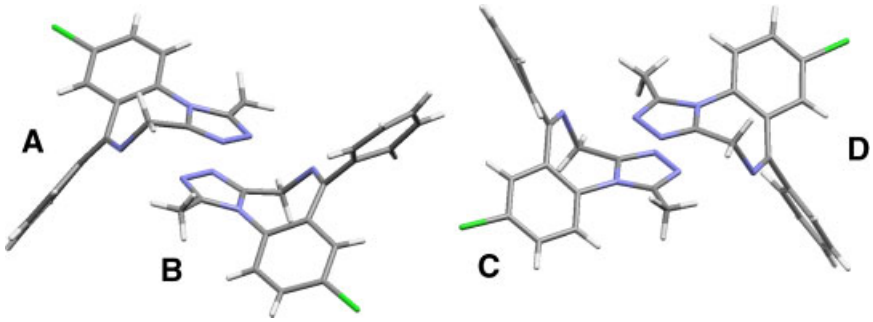


Figure 3. Perspective view of the four independent molecules of alprazolam as found in form III.

Alprazolam Form II

The entry PDF 48–2349 in the PDF[12] corresponds to the form II of this drug. There is some uncertainty in the melting point value for form II: a characteristic melting point of 228–231°C has been reported,[6] while in the PDF 48–2349 entry the reported value is somewhat higher: 231–234°C. Following the recommendations of Bar and Bernstein,[28] the XRPD pattern computed from the single crystal data is the best representation of the pure material. In this matter, the calculated pattern from the single crystal structure of this polymorphic form II, along with the experimental XRPD data, was reported by Reck et al.[6] The powder data correspond to that reported in PDF 48–2349; nevertheless, some differences can be observed (see Tab. 2). Reck et al.[6] noticed variations in the intensities of 18 different measured powder diffraction patterns of this polymorphic form when compared to the calculated one from the single crystal analysis. They

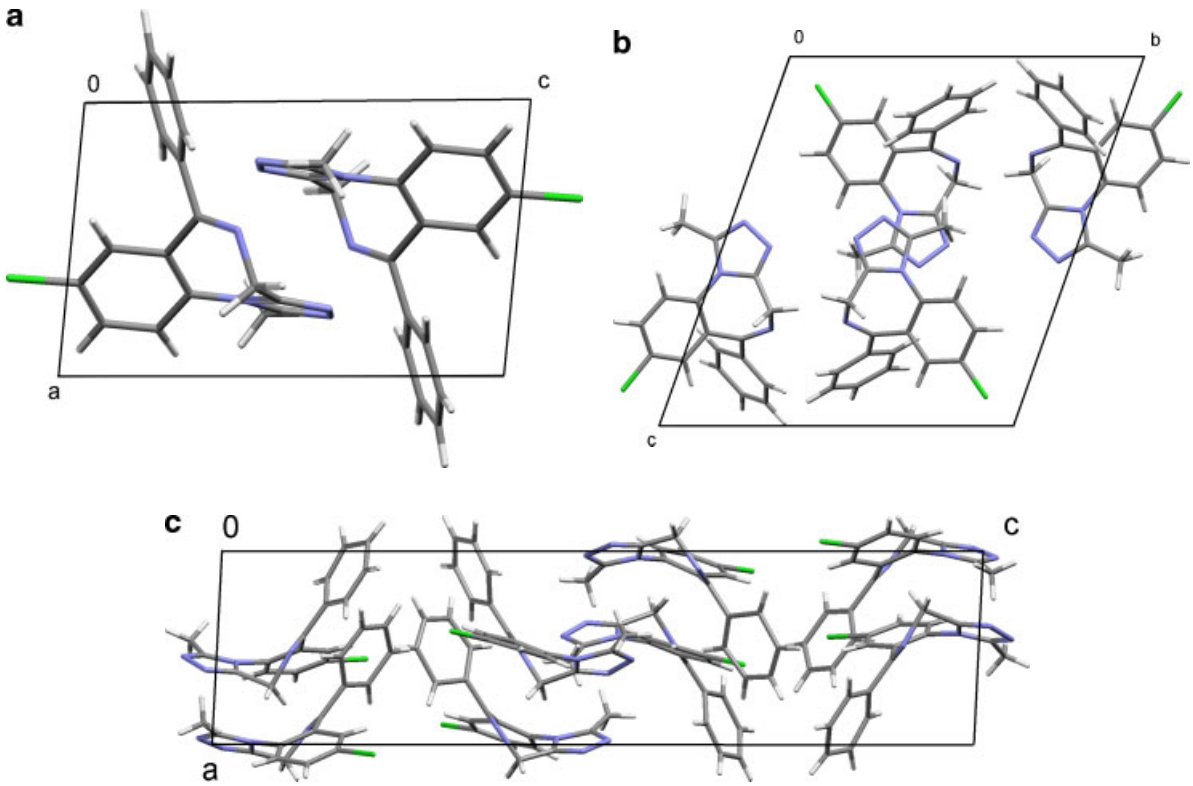


Figure 4. Packing of the alprazolam molecules in the unit cell of the different crystal structures (a) form I molecules projected onto the plane *ac*, (b) form II molecules projected on the plane *bc*, (c) form III molecules projected onto the plane *bc*.

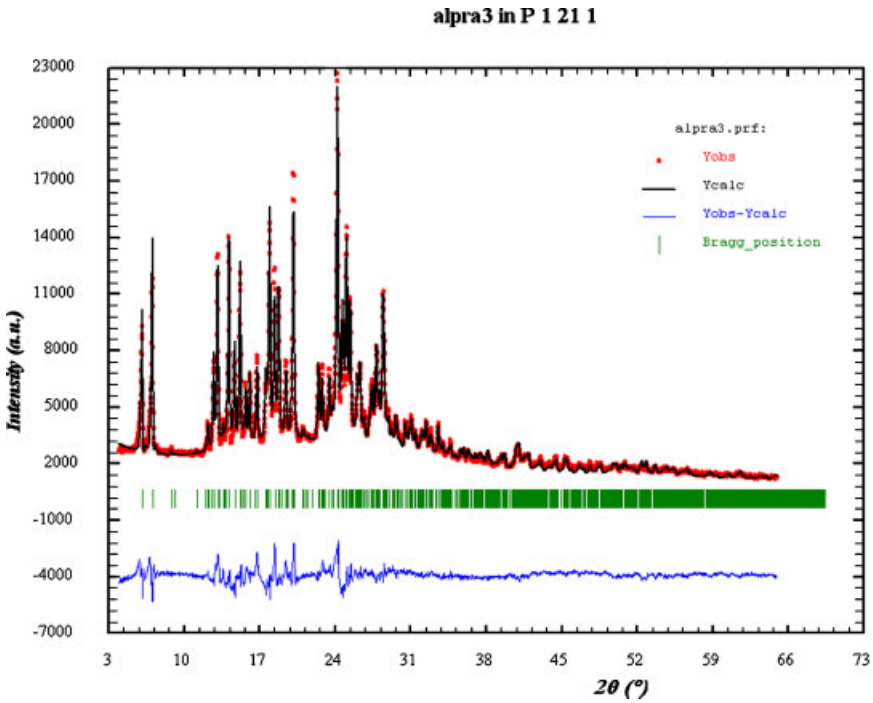


Figure 5. Observed (circles) and calculated (solid line) profiles for the Rietveld refinement of alprazolam form III. The difference plot is on the same intensity scale.

suggested the use of four lines for the identification of this form II: reflections (001), (002), (003), and (200), which showed always closely the same intensities in the 18 measured patterns. They excluded that these differences were due to texture problems (preferred orientation effects due to sample preparation). Instead they mentioned that other possible modifications of this form II could exist, and that they have selected for their single-crystal analysis only one of these possible modifications. Their Weissenberg photographs also displayed some intensity variations in symmetry related reflections that must have been equal, and in most of the crystals they studied twining along (100) was observed. All this is reflected in the relatively high crystallographic R-value ($R = 10.6$ %) during the crystal structure refinement of form II. This R crystallographic value denotes the agreement between the observed intensities from the single crystal experiment and those calculated from the refined model.

The intensities of an experimental powder diffraction pattern could be affected by preferred orientation, causing the calculated intensities to differ from those observed in the (ideal) case of single crystal diffractometry.[29] To evaluate the reliability of the experimentally obtained intensities, Lowe-Ma[30] proposed the intensity FOM, $I_x(N)$. This FOM is based on an average percent difference between observed and calculated intensities for a limited number of strong and moderately strong lines (usually about 10 lines). The calculation of $I_{20}(10)$ for the reported experimental powder pattern of form II gave a value of 32%, indicating that the intensities of the 10 strongest lines differ in average 32% from the calculated (ideal) values. When $I_x(N) > 20\%$ (the so called 20% "rule-of-thumb" range of intensity variations, which is the expected range of variations used in search/match procedures for identification in powder diffraction), this value suggests potential problems with preferred orientation. The comparison of the measured intensities and the calculated intensities from the single crystal structure data (Tab. 2) of this form confirms that preferred orientation could affect the (0–11), (003), and (1–22) reflections with 48%, 91%, and 39% differences, respectively. However, Reck et al.[6] excluded preferred orientation effects to be the cause of the discrepancy of the measured intensities, suggesting being more a problem of a mixture of modifications (other crystalline forms) in the powder samples used for XRPD data

Table 2. Comparison of the X-ray Diffraction Data Reported in PDF 48-2349 and that by Reck et al. (1996)[6] for the Polymorphic Form 2 of Alprazolam

PDF 48-2349		Data form II (Reck et al., 1996)[6]				
d_{obs} (Å)	*I*/*Io* (%)	d_{obs} (Å)	*I*/*Io* (%)	d_{calc} (Å)	I/Io_{calc} (%)	*hkl*
14.38	42	14.40	26	14.40	19	001
13.00	27	13.10	9	13.01	14	010
12.45[a]	27					
11.77	35	11.80	14	11.79	27	$0\bar{1}1$
8.37	15					
7.88[a]	15					
7.41	18	7.47	7	7.43	5	$0\bar{1}2$
7.19	26	7.21	20	7.20	11	002
6.83	58	6.85	37	6.838	38	$0\bar{2}1$
6.71	37	6.71	51	6.736	1	$\bar{1}01$
6.50	61	6.52	33	6.505	43	020
6.31	18	6.28	6	6.304	3	1 0 1
6.23	20	6.22	10	6.220	1	$1\bar{1}1$
6.09[a]	16					
5.89	31	5.91	17	5.893	19	$0\bar{2}2$
5.78	68	5.79	31	5.769	47	$\bar{1}11$
5.61[a]	28					
5.57	47	5.56	41	5.566	1	012
5.29	100	5.31	45	5.293	71	021
5.19	34	5.22	19	5.185	12	111
5.01[a]	27					
4.80	55	4.81	67	4.799	35	003
				4.642	8	$\bar{1}12$
4.62	55	4.61	39	4.615	28	$1\bar{2}2$ $0\bar{3}1$
4.58	68	4.58	40	4.575	31	$\bar{1}\bar{2}2$
4.48	40	4.50	20	4.478	20	$\bar{1}21$
4.40	33	4.41	29	4.417	11	$0\bar{3}2$
4.33	43	4.35	23	4.336	23	030
		4.16	3	4.159	4	$\bar{1}03$
		3.94	14	3.961	4	$0\bar{3}3$
				3.929	12	$1\bar{2}3$
		3.88	18	3.858	5	$\bar{1}30$
		3.85	20	3.850	2	$1\bar{3}2$
		3.82	13	3.818	9	0 31 $0\bar{1}4$
				3.771	3	$\bar{1}\bar{3}1$
				3.735	9	$0\bar{2}4$
				3.713	16	$\bar{1}32$ $\bar{1}13$
		3.70	81	3.696	100	$\bar{1}\bar{3}2$ $\bar{1}13$
			22	3.688	20	
		3.64	24	3.631	10	200
		3.60	1	3.621	1	004

[a]These lines (a) in the PDF 48−2349 actually correspond to traces of the polymorphic form III (Tab. 1).

collection. The strong reflection (003), suggested for identification by these authors for this material, is severely affected by intensity discrepancy. This is also the case of the moderately strong reflections (002) and (200), affected with an 81% and 140% difference with respect to the calculated values. The low angle reflection (100) in form II is less affected but still shows a difference of 36% with respect to its calculated counterpart. These lines should not be considered for identification

purpose. The differences in intensities are most probable due to the presence of other modifications of form II (other polymorphic form), as the same authors suggested. Indeed, these lines overlap with some lines of form III: reflection (002), (003), and (200) overlap with reflections (400), (600), and the strongest line (002) of form III, respectively (see Tabs. 1 and 2).

From the comparison of the d values of the form II (Tab. 2), it can be seen that some lines (d values (Å): 12.45, 8.37, 7.88, 6.09, 5.61, 5.01) present in PDF 48–2349 are not in the calculated powder pattern from the single crystal structure of form II, neither in the reported observed lines obtained by Reck et al.[6] Nevertheless, these lines can be clearly seen in Table 1, as strong and moderately strong lines for form III of this drug (except for the weakest line $d = 8.37$ Å). These findings indicate that the pattern in PDF 48–2349 (reported as form II), is in fact a mixture of two polymorphic forms of alprazolam with the dominant phase being that of form II and a second phase corresponding to impurities of the form III. On the other hand, the reported unit cell dimensions in PDF 48–2349 for form II ($a = 15.27$ Å, $b = 14.03$ Å, $c = 12.65$ Å, $\alpha = 79.51^\circ$, $\beta = 95.74^\circ$, $\gamma = 109.99^\circ$) are incorrect. Furthermore, the entry PDF 48–2350 corresponds also to form II of alprazolam but it is incomplete and without reported crystal data.

In our studies of polymorphic form III, we found in some cases two types of microcrystals inside the DSC pans (concomitant polymorphs) after recrystallization from the melt of form I and cooling to RT: plate shaped crystals, which turned out to correspond to form III and needle-shaped ones. One of these needle-shaped crystals was mounted on a Siemens P4 single crystal diffractometer, in order to determine the cell dimensions. A triclinic unit cell ($a = 7.427(3)$ Å, $b = 13.877(9)$ Å, $c = 15.303(7)$ Å, $\alpha = 109.37(4)^\circ$, $\beta = 92.84(5)^\circ$, $\gamma = 93.16(3)^\circ$) that corresponds to that of a crystal of form II reported by Reck et al. (1996)[6] was found. Since the conformation of the individual molecules is the same in form II and form III crystal structures, the differences are due to the different stacking (packing) of molecules in the crystal to form one polymorph or the other. The presence of peaks of the form III in PDF 48–2349 (supposed to be the pure form II) and the presence of two different types of crystals in some DSC pans is an indication that these two phases could coexist at a certain range of temperature. For this reason, HT-XRPD was used for studying and monitoring the possible polymorphic transformations as a function of the temperature.

Study of Phase Transformations Using HT-XRPD

Caira et al.[5] mentioned a possible structural phase change of alprazolam with a melting onset of 218°C and 221°C for two endothermic peaks present in the DSC. Reck et al.[6] briefly stated that form II crystals could be formed after melting form I crystals, depending on the initial crystal size and heating rate used. However, they did not provide any experimental evidence (DSC nor XRPD experiments) of this phase transformation. Our HT-XRPD experiments demonstrated that in fact form III is the polymorphic form obtained after the recrystallization of the melt of the form I.

Two kinds of HT-XRPD experiments were performed and the difractograms were taken as described in the experimental section. In the first HT-XRPD experiment the alprazolam form I was subjected to increase in temperature starting from RT until the material fully decomposed. In the second experiment the alprazolam form I was subjected to the same conditions as in the first experiment but the heating flux was stopped after the observed phase transformation took part and the new form was fully formed, then the sample was cooled back to RT.

During the first HT-XRPD experiment (Fig. 6a) the alprazolam undergoes a phase transformation with a new phase fully present at about 225°C, as observed in the DSC experiments. This phase melts and finally decomposes at temperatures higher than 245°C. The polymorphic form obtained after the recrystallization of the melt of form I corresponds to form III. This was confirmed indexing a selected XRPD pattern of those obtained after the phase transformation occurred. The indexing was done using the program X-Cell of the Accelrys Material Studio suit of programs (MS Modeling, version 3.2)[31] on a diffractogram at 225°C. Then the cell obtained was subjected to a Pawley refinement procedure, a helpful tool for confirming the indexing results that refines the cell parameters, peak shape, and background parameters. These parameters are adjusted to minimize the weighted R_{wp} a factor that describes the agreement between the experimental XRPD pattern and the simulated one. Figure 7 shows the results of the Pawley refinement that gave a unit cell corresponding to that of form III with slightly different values due to the effects of the cell expansion at high temperature (reflected as a

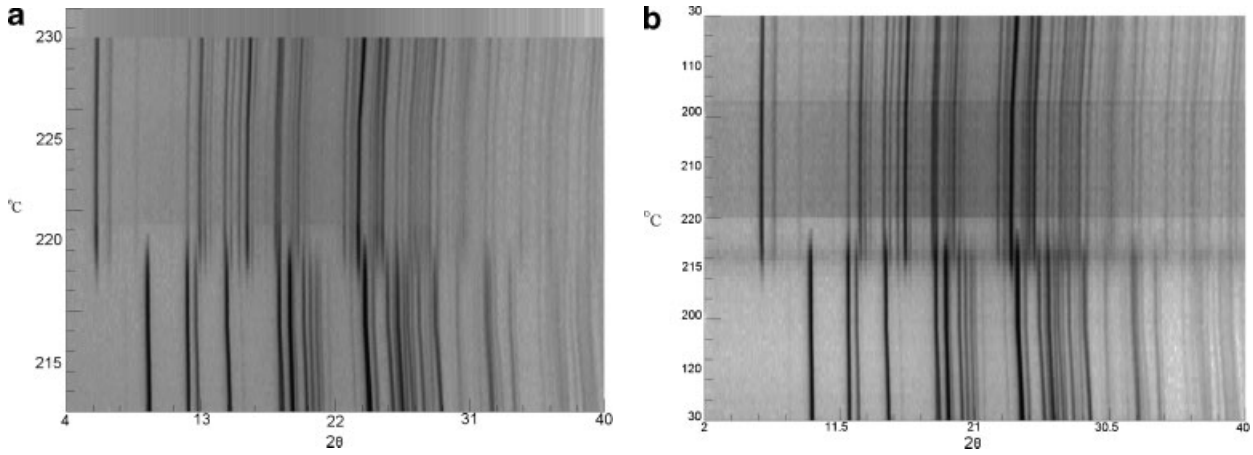


Figure 6. High temperature X-ray powder diffraction experiments: (a) simulated Guinier film plots of the diffractograms showing a phase transformations of the initial alprazolam form I at 218°C that melts and recrystallizes into the new form III which melts then at 230°C (diffractograms from RT to 213°C, where the form I is the only present, were omitted in the plot); (b) simulated Guinier film plots of the diffractograms showing phase transformations from room temperature until a temperature where the new phase (form III) is fully formed but not yet melted, and then cooling this new phase to room temperature.

displacement of the diffraction peaks as a function of the 2θ with the temperature in the XRPD pattern): $a = 29.34(4)$ Å, $b = 13.92(2)$ Å, $c = 7.826(11)$ Å, $\beta = 93.342(3)^\circ$, and $V = 3190.8$ Å^3. For the selected diffractogram the agreement factors obtained were $R = 6.23\%$ and $R_{wp} = 9.07\%$. . The unit cell expands more in the c direction and an average difference of 6% is observed in the unit cell parameters compared to those of form III at RT. The unit cell volume expands 8% at high temperature.

To check whether form II could be obtained during the cooling off of the formed form III to RT, the second HT-XRPD experiment was carried out. No phase transformations were observed during cooling the sample to RT (Fig. 6b). In this case, the last diffractogram before reversing the heating ramp to lower temperatures (form III pattern at

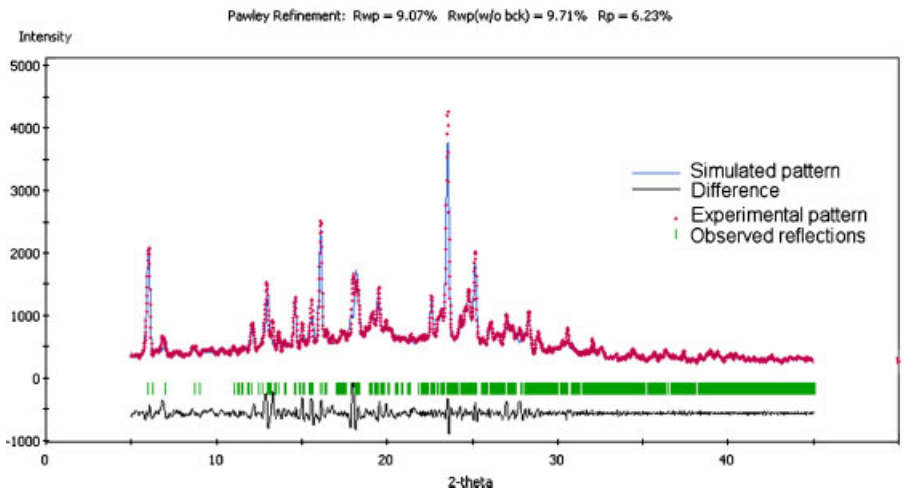


Figure 7. Pawley Refinement profile of a selected diffractogram measured at 225°C. The obtained and refined unit cell corresponds to that of alprazolam form III (see HT-XRPD cell in Tab. 4).

high temperature), corresponds well with the last diffractogram taken after cooling the sample to RT. In other words, the new-formed phase after 223°C remains until RT is reached. The only difference is the displacement of the diffraction peaks as a function of the 2θ due to the temperature difference (cell contraction at RT/ cell expansion at high temperature).

In both HT-XRPD experiments no evidence of the formation of form II was found. The form III obtained from the exothermic recrystallization of the melt of form I, stayed as such until RT was reached (Fig. 6a,b).

Alprazolam Form I and the Dehydrated Form

This polymorphic form of alprazolam is reported in PDF 48–2348 and can be obtained after dehydration of the dihydrate form (reported by some authors as pseudopolymorphism), PDF 48–2351. It has the lowest melting point, with characteristic values in the interval 224–228°C (first endotherm in Fig. 1). The XRPD data and crystal data for form I, reported in the PDF 48–2348 entry, are in good agreement with those obtained from the single crystal structure determination (Tab. 3). This is also the case of the dihydrated form of alprazolam reported in PDF 48–2351 with respect to the XRPD diffractogram calculated from the crystal structure solved by Reck et al. (data not shown).[6]

The polymorphic form II of alprazolam is a metastable phase,[6] and as mentioned previously, these authors suggested that other modifications could exist or coexist for form II crystals showing a different packing, in other words some other polymorph could be obtained (concomitant polymorph). We have shown in the present study that this modification is the new form III. They also demonstrated that form II transforms into form I after stirring a saturated solution of form II in isopropanol at RT. These authors stated that form I is the most stable at RT and cannot exist at a temperature above the transition point to form the polymorphic form II, but the latter form can exist below the transition point, as a metastable form.[6] On the other hand, they have reported that no transformation is observed from the metastable polymorphic form II into the RT stable form I, after years of storage. Since kinetics can prevent transformation in the solid state, the transformation of form II into from I observed in slurries in isopropanol demonstrates that at RT form I is the stable form. The present work allows a comparison of the density of alprazolam forms I, II, III, and the dihydrate one from crystallographic data (Tab. 4). In the case of alprazolam form II and III the nature of the packing interactions and the density values are similar. These facts corroborate the issue that these two modifications can exist as concomitant polymorphs. Bernstein et al.[32] have published an exhaustive review to this particular phenomenon not widely recognized but associated with crystallization in polymorphic systems. Table 4 shows a comparison of the unit cell parameters, density, and number of molecules per unit cell for the different crystalline forms of alprazolam.

Table 3. Comparison of the X-ray Diffraction Powder Diffraction Data Reported in PDF 48-2348 and the Calculated one from the Single Crystal Structure of Form I (Reck et al., 1996)[6]

PDF 48–2348		Form I		
d_{obs} (Å)	I/Io (%)	d_{calc} (Å)	I/Io_{calc} (%)	hkl
11.04	1	11.014	1	0 0 1
9.25	100	9.205	100	0 1 0
7.27	67	7.236	64	0 1 $\bar{1}$
6.93	14	6.900	14	0 1 1
6.86	10	6.826	11	1 0 0
6.70	<1	6.659	1	0 $\bar{1}$ 0
6.12	<1			1 0 $\bar{1}$
5.90	73	5.871	70	0 $\bar{1}$ $\bar{1}$
5.57	2			1 0 1
5.56	<1	5.546	2	1 $\bar{1}$ 1
5.52	<1	5.501	1	0 0 2
4.85	29	4.828	28	0 1 $\bar{2}$
4.79	35	4.769	34	1 1 0
4.64	20	4.631	26	0 1 2
4.63	81	4.599	80	1 $\bar{2}$ 0
4.62	4			0 2 0
4.56	8	4.541	10	1 1 $\bar{1}$
4.54	2			1 0 $\bar{2}$
4.41	43	4.388	41	1 $\bar{1}$ $\bar{2}$
4.34	19	4.321	18	0 2 $\bar{1}$
4.30	7	4.278	7	1 $\bar{2}$ $\bar{1}$
4.24	17	4.225	11	1 $\bar{2}$ 1
4.19	10	4.177	10	0 2 1
4.13	<1			1 $\bar{1}$ 2
4.10	3	4.083	3	1 0 2
3.81	3	3.792	3	1 1 2
3.68	30	3.671	27	0 0 3
3.64	76	3.619	68	2 $\bar{1}$ 0
3.63	<1			0 2 $\bar{2}$
3.58	23	3.569	20	1 $\bar{2}$ $\bar{2}$
3.56	3	3.537	4	2 $\bar{1}$ $\bar{1}$

The data are presented for d values until an equivalent of $2\theta = 25°$.

Table 4. Comparison of Crystallographic Data for the Most Common Crystalline Forms of Alprazolam

	Form I[6]	Form II[6]	Form III Rietveld[a]	Form III single crystal[a]	Form III HT-XRPD[b]	Dihydrate[6]
a(Å)	7.275(8)	7.414(10)	28.9339(9)	28.929(9)	29.34(4)	8.570(7)
b (Å)	9.774(5)	13.806(4)	13.8548(3)	13.844(8)	13.92(2)	13.630(5)
c (Å)	11.074(5)	15.269(4)	7.3540(1)	7.361(3)	7.826(11)	14.868(2)
α (°)	90.80(3)	109.17(2)	90.00	90.00	90.00	84.26(2)
β (°)	95.34(5)	92.15(6)	92.911(2)	92.82(3)	93.342(3)	81.92(3)
γ (°)	109.46(5)	93.03(6)	90.00	90.00	90.00	87.07(5)
Z	2	4	8	8	8	4
V (Å^3)	738.37	1471.67	2944.22	2944.46	3190.80	1709.64
Dx (g/cm^3)	1.389	1.394	1.394	1.394	1.286	1.340

[a] At room temperature data.
[b] From X-ray powder diffractogram measured at 225°C.

Finally, it is worth to mention that unfortunately there is an inconsistency in the labeling of polymorphs,[1] and that is the case of alprazolam polymorphs. Alprazolam polymorphism and stability has also been studied by Laihanen and coworkers.[7,8,9] The four polymorphic forms mentioned in these works introduce confusion to the classification of polymorphs of alprazolam. From the analysis of the scarce reported XRPD data, it suggests that what they called to be form II (recrystallized from 1-butanol) resembles in fact the diffractogram of the form III described in the present work (their reported lines (2θ) are 6.13, 7.09, 14.19, 15.82, which are in correspondence with the lines (2θ) 6.118, 7.081, 14.187, 15.766 reported by us for form III in Tab. 1). They also termed the monohydrate (recrystallized from distilled water) as form III, and the known alprazolam dihydrate as form V. However, this is not the most common way of naming solvates (or pseudopolymorph), since this nomenclature is used commonly for naming *true* polymorphs.[1] The described XRPD data by Laihanen and coworkers for form IV does not correspond to any of the described known forms of alprazolam,[5,6] thus this is still another possible polymorph for this drug that needs further characterization. The reported form I by these authors corresponds to the form I reported in the literature.[5,6] We recommend the labeling of polymorphs of alprazolam as reported in Caira et al.,[5] Reck et al.,[6] and in the PDF[12] database, as used in the present work. It is important for those studying polymorphism to be aware of previous works to try to identify the correspondence between the newly discovered forms and those previously reported in the scientific literature.

CONCLUSIONS

A new polymorph of alprazolam drug (form III) was identified and characterized by means of DSC and XRPD. A review of the different phases available in the PDF for this drug was done, bringing some corrections to the form II, in which the available entry displays in fact a mixture of two polymorphic forms: form II and the identified form III. Its crystal structure was solved from single crystal X-ray diffraction and the obtained coordinates were used as structural model for refinement using the Rietveld method, on the XRPD data of pure form III crystalline phase. The crystallographic agreement factors from the Rietveld refinement confirm that the crystal structure of form III of alprazolam in the single crystal is in correspondence to that of the polycrystalline powder phase of form III and that it can be formed as a pure (polymorphic) phase. The polymorphic phase transformations were studied by HT-XRPD showing that form I transforms into form III at high temperature. No evidence of form II was observed during HT-XRPD experiments. However, there are indications that form II can be obtained in this range of temperatures under certain conditions (as concomitant polymorph), as we observed DSC pans containing both polymorphic forms coexisting. Previous reports suggested that form II could exist as other "modification." We have demonstrated that this "modification" is a distinctive polymorphic form of alprazolam (form III). During the HT-XRPD studies no evidence of the formation of form II was found, despite the presence after the DSC experiment, at RT and in some cases, of needle-shaped crystals of this polymorph coexisting with

plate-shaped ones of form III. Parallel measurement of different specimens using HT-XRPD and DSC, and combination of both data as done in the present work for alprazolam, are the common way of studying thermal reactions in solids, particularly phase transitions. However, the disadvantage is that many chemical reactions of solids are kinematical and depend on the experimental conditions (e.g., the nature of the atmosphere, shape or geometry of the sample containers, heating rate, thermal history). Further studies using simultaneous XRPD and DSC measurements on the same sample under the same environmental conditions would be necessary to explore the sometimes observed formation of crystals of form II during the transformation of form I in III (concomitant polymorphism of alprazolam).

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