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Phase transition studies of dutasteride crystalline forms

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Three crystalline forms of dutasteride known in literature as forms: I, II and III were studied. It has been proved that only form I is an unsolvated form. Both forms II and III are hydrates (pseudopolymorphs). Phase transition studies performed by thermoanalytical techniques and variable temperature PXRD measurements, in the temperature region from 30 to 180 °C, revealed that dehydration leads to an unstable phase which finally transforms into form I. Details of crystal and molecular structure of form I are presented. Dutasteride form I crystallizes in the orthorhombic $P2_12_12_1$ space group with one molecule in the asymmetric part of the unit cell. Dutasteride molecules form a herringbone bond-like pattern with pairs of neighboring 'heads' of lactam groups.

Introduction

Recommendations of the U.S. Food and Drug Administration [1] and the European Medicine Agency [2] suggest investigating whether a drug substance exists in different polymorphic (different arrangements and/or conformations of molecules in a crystal lattice), pseudopolymorphic (solvates) or amorphous (disordered arrangements of molecules) forms [3, 4]. All these forms of the drug substance can have different chemical and physical properties, influencing the stability of the drug substance as well as the dissolution and bioavailability of the drug product. There are a number of methods that are used to characterize crystalline and amorphous forms of the drug substance. A definitive evidence of polymorphism or pseudopolymorphism is a demonstration of a nonequivalent structure by single crystal X-ray diffraction [5, 6, 7]. X-ray powder diffraction can also be used to provide an unequivocal proof of polymorphism [8, 9, 10]. Other methods, including *e.g.*, differential scanning calorimetry (DSC), thermal gravimetric analysis (TGA), and infrared spectroscopy (IR) help to further characterize the crystalline forms [11, 12].

In this article the Authors verify the term of polymorphism in the case of dutasteride (which is chemically designated as *N*-[2,5-bis(trifluoromethyl)phenyl]-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide) (Fig. A1). It is an active pharmaceutical ingredient, a selective inhibitor of both type 1 and type 2 isoforms of steroid 5 alpha-reductase which is an intracellular enzyme that converts testosterone to dihydrotestosterone (DHT). DHT is involved in the development of benign prostatic hyperplasia (BPH) [13, 14, 15, 16].

According to patent publications US 7022854 B2 [17] and WO 2009/083258 A2 [18] dutasteride exhibits polymorphism (form I and form II) and exists as a hemihydrate (form III) as well as an amorphous form [17]. The synthesis of dutasteride forms 1 and 2 was described by Satyanarayana *et al.* [19]. Diffractogram comparisons of forms I with 1 and II with 2 proved that they are the same crystalline forms (Fig. A2). X-ray studies of dutasteride hemihydrate were described by Nanubolu *et al.* [20]. Dutasteride hemihydrate crystallizes in the orthorhombic space group $P2_12_12_1$ with the following unit cell parameters: a=8.2124(7), b=18.5162(17), c=34.876(3) Å. A diffractogram comparison of form III revealed in the International Patent Application [18] with a simulated powder diffractogram obtained from a single crystal data deposited by Nanubolu *et al.* [20] in The Cambridge Crystallographic Data Centre (refcode LATSIK) proved the existence of the same crystalline structures (Fig. A3).

In the official dutasteride monograph published in the European Pharmacopoeia 8.0 the identification is based on IR spectroscopy [21]. The IR spectra of dutasteride crystalline forms: I, II and III differ very well in the range of N-H (γ) vibrations (3500–3300 cm^{-1}) and C-H out of plane deformation vibrations of benzene derivatives (850–800 cm^{-1}). Form I differs from forms II and III in the range of C-F stretching vibrations (1350–1120 cm^{-1}) (Fig. A4, Table A1). However, phase analyses of dutasteride forms in mixtures proved that X-ray powder diffraction (Fig. A5, table A2) is characterized by a much better sensitivity for the detection of each form in the mixture than IR. For this reason X-ray powder diffraction accompanied by thermoanalytical techniques such as DSC, and TGA was chosen for the phase transition studies of dutasteride

forms. Additionally, a single crystal X-ray structure of form I was solved. The crystal structure of form I dutasteride unambiguously showed that this form is unsolvated.

Experimental

Materials

Dutasteride crystalline forms: I, II and III were produced by Pharmaceutical Research Institute in Warsaw from a purified commercial sample (batch no. 20120501 Afine Chemicals Limited).

The crystal of form I was obtained by a vapor diffusion technique. 15 mg of dutasteride sample were dissolved in 1 mL of ethyl acetate in a small vial and then placed in a larger tube containing 3 mL of n-heptane. Then the tube was sealed.

The preparation of dutasteride form II. Dutasteride (3.02 g) was dissolved in ethyl acetate (75 mL) at reflux. The resulting solution was stirred at room temperature (r.t.) overnight. The crystals were filtered off, washed with the minimal amount of ethyl acetate, dried at r.t. for 2 days and finally at r.t. for 6 hours under reduced pressure to give the crystals of form II.

The preparation of dutasteride form III. Dutasteride (3.07 g) was dissolved in ethanol (25 mL) at reflux. A hot solution was added dropwise to the stirred water (40 mL) at r.t. The resulting suspension was stirred and cooled slowly to r.t. The crystals were filtered off and dried at r.t. for 2 days to give the crystals of form III.

Infrared spectroscopy

IR spectra were recorded on the Nicolet iS10 instrument (Thermo Scientific) in the range from 4000 to 400 cm^{-1} with the spectral resolution of 4 cm^{-1}. For one spectrum 16 scans were recorded. Solid samples were measured in KBr pellets. The sample concentration in the pellet was 0.74 %.

Differential scanning calorimetry

DSC measurements were performed by means of the DSC822e cell with IntraCooler (Mettler Toledo). About 7 mg (weighing accuracy 0.01 mg) of studied samples were weighed into standard aluminium pans (40 µL). The pans were hermetically sealed and perforated before measurements. The samples were heated from 25 to 170 ^{o}C at 5 ^{o}C/min. The measurements were performed in the nitrogen atmosphere.

Thermogravimetry

TGA measurements were performed by means of the TGA/SDTA851 cell (Mettler Toledo). About 7 mg (weighing accuracy 0.01 mg) of studied samples were weighed into standard aluminium pans (40 µL). The pans were hermetically sealed and perforated before measurements. The samples were heated from 30 to 300 ^{o}C at 10 ^{o}C/min in the nitrogen atmosphere. The measurements were blank curve corrected. A TGA analysis provides information on the content of volatile components. DTG is a first derivative of the TGA curve. SDTA is a single differential thermal analysis and provides similar results as the DSC analysis.

Variable temperature PXRD

VT–PXRD measurements were performed using the Bruker D8 Discover system working with the PSD detector VÅNTEC in the reflection mode. A parallel beam of CuKα radiation (line focus) was formed by Göbel mirror. Data were collected in the 2θ range from 3 to 40 °. The measurements were made with the step of 0.012 ° and the measuring time was 0.5 s/step. The samples were measured at 30 ^{o}C, then heated from 100 up to 140 °C at 10 ^{o}C intervals, then the measurements and heating continued in the range from 145 to 180 °C at 5 °C intervals. The sample temperature was stabilized by the Anton Parr DCS350 heating stage (with the accuracy of 0.1 °C). Mercury software [22] was used to generate a theoretical powder diffraction pattern of dutasteride forms I and III.

X-ray single crystal diffraction

X-ray diffraction data for dutasteride form I were collected using the BRUKER KAPPA APEXII ULTRA diffractometer controlled by the APEXII software [23], equipped with the MoKα rotating anode X-ray source (λ = 0.71 Å, 50.0 kV, 22.0 mA) with the radiation monochromatized by multi-layer optics, and the APEX-II CCD detector. The data collection for both compounds was carried out at 100 K using the Oxford Cryostream cooling device. The crystal was mounted on the Mounted CryoLoop with a droplet of Pantone-N oil and immediately cooled down. Indexing, integration and initial scaling were performed with the SAINT [24] and SADABS [25] software (Bruker AXS). The crystal was positioned at 50 mm from the CCD camera. 3700 frames were measured at 0.5° intervals with the counting time of 10-20 sec. The structures were solved by direct methods using the SHELXS-97 [26] program and refined with the SHELXL-97 [27]. The multi-scan absorption correction was applied in the scaling procedure. The refinement was based on F2 for all reflections except those with the negative intensities. Weighted R factors wR and all goodness-of-fit S values were based on F2, whereas the conventional R factors were based on the amplitudes, with F set to zero for negative F2. The $F2 > 2\sigma$ (F2) criterion was applied only for the R factors calculation and was not relevant to the choice of reflections for the refinement. The R factor based on F2 is about twice as large as that based on F. Scattering factors were taken from Tables 4.2.6.8 and 6.1.1.4 from the International Crystallographic Tables Vol.C [28].

Results and discussion

Single crystal X-ray diffraction of dutasteride form I

The crystal data and other important parameters related to the data collection of dutasteride form I are summarized in Table 1 and compared to the data of dutasteride hemihydrate (LATSIK) [20].

Table 1 Summary of Crystallographic Data and structure refinement for the dutasteride form I and LATSIK molecules.

	dutasteride form I	dutasteride hemihydrate (LATSIK)
Empirical formula	$C_{27}H_{30}F_6N_2O_2$	$2(C_{27}H_{30}F_6N_2O_2)\bullet H_2O$
Formula weight	528.53	1075.08

Temperature	100.01(10) K	294(2) K
Wavelength	0.71073 Å (MoKα)	0.71073 Å (MoKα)
Crystal system, space group	orthorhombic $P2_12_12_1$	orthorhombic $P2_12_12_1$
Unit cell dimensions		
a	7.48732(15) Å	8.2124(7) Å
b	9.95589(19) Å	18.5162(17) Å
c	33.0328(8) Å	34.876(3) Å
α, β, γ	90 °	90 °
Volume	2462.36(9) $Å^3$	5303.33 $Å^3$
Z, Calculated density	4, 1.426 mg/m^3	4, 1.346 mg/m^3
Absorption coefficient	1.038 mm^{-1}	0.115 mm^{-1}
F(000)	1104.0	2248
Theta range for data collection	2.68 to 76.80 °	2.27 to 20.57 °
Limiting indices	$-9 \le h \le 9$ $-12 \le k \le 10$ $-39 \le l \le 41$	$-9 \le h \le 9$ $-22 \le k \le 21$ $-41 \le l \le 41$
Reflections collected / unique	12099/5038 [R(int) = 0.0305]	51297/5243 [R(int) = 0.0427]
Completeness to Th_{max}	96.87 %	
Absorption correction	Semi-empirical from equivalents	none
Max. and min. transmission	0.951, 0.979	
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data / restraints / parameters	5038/59/376	5243/236/786
Goodness-of-fit on F2	1.040	1.121
Final R indices [I>2sigma(I)]	$R_1 = 0.0367$ $wR_2 = 0.0824$	$R_1 = 0.0660$ $wR_2 = 0.1770$
R indices (all data)	$R_1 = 0.0465$ $wR_2 = 0.0869$	$R_1 = 0.0761$ $wR_2 = 0.1893$
Largest diff. peak and hole	(0.30/-0.20) $eÅ^{-3}$	

Dutasteride form I (Fig. 1) crystallizes in the $P2_12_12_1$ orthorhombic space group (as dutasteride hemihydrate) with one molecule in the asymmetric part of the unit cell. All geometrical parameters for the structure of dutasteride are presented in Tables A3-A5.

Fig. 1 The molecular structure of dutasteride form I and labeling atoms. Thermal ellipsoids are drawn at the 50% probability level

Dutasteride is a modified steroid derivative with two functional groups: the α,β-unsaturated lactam group in the ring A and the 17β-carboxamide substituted on nitrogen atom by 2,5-bis(trifluoromethyl)phenyl substituent. One CF_3 group is found to be disordered and the fluorine atoms are refined over two positions with the refined site-occupation factors in the ratio 0.77:0.23. Two central six-membered rings B and C adopt a chair conformation, whilst the six-membered ring A and five-membered ring D a diplanar [(DP(N1α,C5α)] and a slightly distorted envelope [(EC12β)] conformations, respectively.

The distances between the carbon atoms in the α,β-unsaturated lactam moiety are from 1.33 to 1.54 Å. The carbonyl bond in the lactam group is equal to 1.241(2) Å [C(1)-O(1)]. The bonds between the N(1) nitrogen atom and the C(1) as well as C(5) vicinal carbons are longer, 1.334(2) and 1.459(2) Å respectively. This is affected by the nitrogen atom that participates in the amide resonance. Selected parameters describing the molecular geometry of the ring A are given in Tables 2 and 3.

The amide bond connects the ring D with the 2,5-bis(trifluoromethyl)phenyl substituent. C(19)–O(2) and C(19)-N(2) bond lengths are 1.215(3) and 1.385(2) Å, respectively. The amide bond and the substituted benzene ring lie on the same plane. The distances between the carbon atoms in the five-membered ring (D) are close to 1.55 Å which are standard values. Selected parameters describing the molecular geometry of the ring D are given in Tables 2 and 3.

Differences in amide bond lengths (HN-C=O ↔ HN^+=C─O^-) for the lactam and amide groups are caused by the amide resonance (HN-C=O ↔ HN^+=C─O^-) [20].

Table 2 Selected bond lengths (Å) for the dutasteride form I molecule

Ring A		Ring D	
C1 – C2	1.486(3)	C12 – C13	1.544(3)
C2 – C3	1.333(3)	C13 – C14	1.528(2)
C3 – C4	1.517(2)	C14 – C15	1.557(3)
C4 – C5	1.539(3)	C15 – C16	1.558(3)
C5 – N1	1.459(2)	C16 – C17	1.554(2)
N1 – C1	1.334(2)	C16 – C19	1.519(3)
C1 – O1	1.241(2)	C12 – C17	1.541(3)
		C19 – N2	1.385(2)

Table 3 Selected torsion angles (°) for the dutasteride form I molecule

Ring A		Ring D	
C4-C3-C2-C1	0.0(3)	C16-C12-C13-C14	46.31(18)
C3-C2-C1-N1	-15.0(3)	C12-C13-C14-C15	-35.06(19)
C2-C1-N1-C5	-9.5(3)	C13-C14-C15-C16	9.2(2)
C1-N1-C5-C4	45.4(2)	C14-C15-C16-C12	19.5(2)
N1-C5-C4-C3	-53.34(19)	C13-C12-C16-C15	-39.72(18)
C2-C3-C4-C5	33.7		

Dutasteride layers are formed by the molecules creating a herringbone bond-like pattern with pairs of neighboring 'heads' of lactam groups (Fig. 2). The molecule V-shape forms ribbons by fitting into two neighboring V-shapes, which involves the

"infinite" network. The distance between the nitrogen atom of the lactam group of one molecule and the oxygen atom of the partner lactam is 2.794(2) Å. For geometrical details see Table 4. The intermolecular hydrogen bonding between the N(1)-H(1)···O(1) hydrogen bond forms the chain C11(8) motif [29]. This H-bonding stabilizes the crystal packing. The contacts of tails (CF_3 group) form the V-shape arrangement of the molecules. The presence of the fluorine atom in the dutasteride molecule generates the interaction of the C–F…O type. The distance between the oxygen O(2) and the fluorine atom F(5) is 2.929 Å [30, 31, 32].

The dutasteride molecule forms two intramolecular hydrogen bonds: the first one N(2)-H(2)···F(1) with the bond distance between N(2) and F(1) atoms is 2.905(2) Å. The N(2)H(2)F(1) angle is equal to 128.0 °, the N(2)H(2)F(2) angle is equal to 115.4 ° (Table 4).

Fig. 2 The view of crystal packing along the Y-axis. The hydrogen bond is marked by the blue line

Table 4 Hydrogen-bond parameters for the dutasteride form I molecule (Å, °)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	(D—H···*A*)
N1—H1···O1^{i}	0.862(17)	1.940(17)	2.794(2)	171(2)
N2—H2···F1	0.88	2.28	2.905(2)	128.0
N2—H2···F2	0.88	2.44	2.931(2)	115.4

Symmetry code: (i) ½+x, 5/2 -y, 1-z

The PXRD experimental profile of dutasteride form I agrees very well with the PXRD pattern calculated from the single crystal data but differs substantially from the pattern of dutasteride hemihydrate (LATSIK) [20] (Fig. A6). (Fig. A6). Additionally, it has been proved by thermoanalytical techniques that form I is an unsolvated form (Fig. 3). According to the DSC results, form I melts at about 249 °C.

Fig. 3 TGA and SDTA curves of form I

Phase transitions during form II heating

In the temperature range from 30 to 140 °C, peak shifting towards lower angles is observed which is caused by the changes in the crystal lattice of form II during a dehydration effect (Fig. 4). Between 140-150 °C further dehydration proceeds and a new crystalline form I' arises up to 155–160 °C (in Fig. 4 the areas of form I' are indicated by rectangles). At 150 °C form I is formed (in Fig. 4 the peaks are indicated by arrows). The higher temperature, the larger crystallites of form I, which is illustrated by the higher intensity of its peaks.

Phase transitions during form II heating have been proved by thermoanalytical techniques. The DSC curve of form II characterizes three endotherms at: 166, 176 and 249 °C and two exotherms at 173 and 177 °C (Fig. 5). The thermogravimetric analysis has proved that the first broad endotherm at 166 °C comes from water evaporation (Fig. 6). The first exotherm, visible at 173 °C, comes from the crystallization of form I' that melts at 176 °C. Form I crystallizes at 177 °C and melts at 249 °C. A one-step mass loss calculated from the TGA curve (1.3 %) is similar to the water content determined by Karl Fischer titration (1.2 %). The results indicate that form II is actually a hydrate containing about 0.3 mol of water per 1 mol of dutasteride.

Fig. 4 VT-PXRD diffractograms of form II. Upper window - selected diffractograms, below – a 3D view

Fig. 5 DSC curve of form II

Fig. 6 TGA, DTG and SDTA curves of form II

Phase transitions during form III heating

In the temperature range from 30 to 100 °C, peak shifting towards lower angles is observed which is caused by changes in the crystal lattice of form III during a dehydration effect (Fig. 7). At 110 °C form II arises, which is demonstrated by a very small peak at 6.7 ° (in Fig. 7 the peak is indicated by rectangle). Form II manifests itself in the diffractograms recorded up to 145 °C. At 120 °C a new crystalline phase (form I'') (in Fig. 7 the peaks are indicated by arrows) appears with an accompanying partial amorphisation. The highest amorphous content is visible in the diffractogram recorded at 130 °C. At 140 °C form I is formed up to 180 °C on the amorphous background.

Fig. 7 VT-PXRD diffractograms of form III. Upper window - selected diffractograms, below – 3D view

The thermogravimetric analysis shows more complex effects in the temperature range from 120 to 190 °C caused by a three-step water evaporation (Fig. 8). The sum of individual mass losses is 2.3 % which is similar to the water content determined by Karl Fischer titration (2.0 %). The results indicate that form III is also a hydrate containing about 0.6 mol of water per 1 mol of dutasteride. Moreover, the experimental water content is higher than the theoretical water content in dutasteride hemihydrate (1.7%, [20]).

Fig. 8 TGA, DTG and SDTA curves of form III

Conclusions

It has been proved that among three dutasteride crystalline phases forms II and III are hydrates. According to the TGA results, form II dehydrates in one step and contains about 0.3 mol of water per 1 mol of dutasteride. By means of VT–PXRD measurements it was observed that form II loses water molecules and transforms through an unstable polymorph form I' into polymorph form I. A three-step dehydration effect is visible on the TGA curve of form III. In this case dehydration proceeds through the formation of form II and then an unstable

form I'' is formed which transforms into a stable form I. Also, the powder diffractogram of form III and the simulated powder diffractogram of dutasteride hemihydrate are the same but there is a 0.3 – 0.6 % difference between the water content (as well as mass losses) in form III and the theoretical water content in dutasteride hemihydrate. The dutasteride case shows that instead of IR spectroscopy X-ray powder diffraction should be included in the monograph of the European Pharmacopoeia for the form identification. Herein, we solved and refined the crystal structure of dutasteride form I. The comparison of simulated and experimental PXRD data revealed the presence of dutasteride obtained by our synthesis formed a polymorph I phase.

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† Single X-ray crystal data of the dutasteride form I were deposited at The Cambridge Crystallographic Data Centre. The deposition number CCDC 1032001 contains supplementary crystallographic data. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.htmL (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).

† Electronic Supplementary Information (ESI) available – Appendix A

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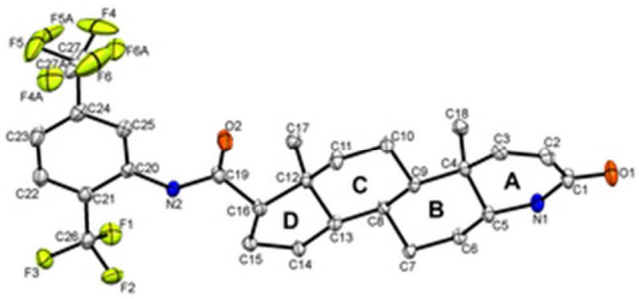

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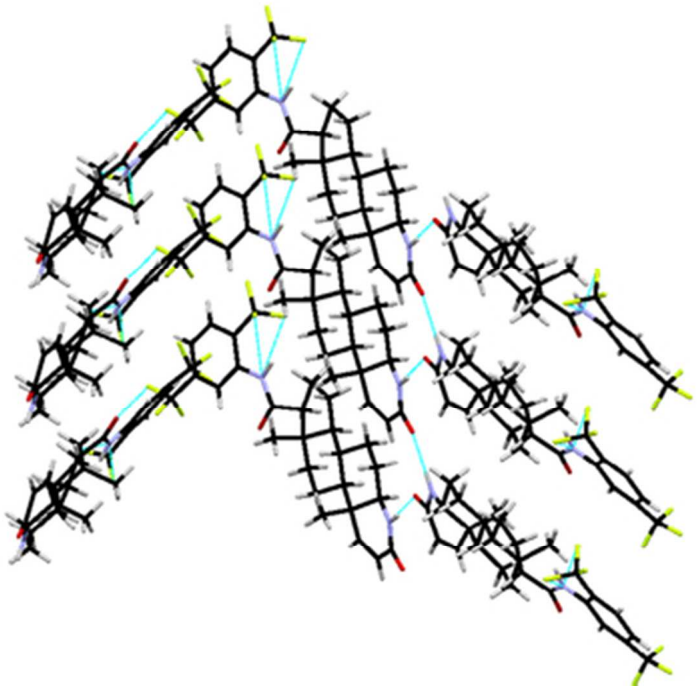

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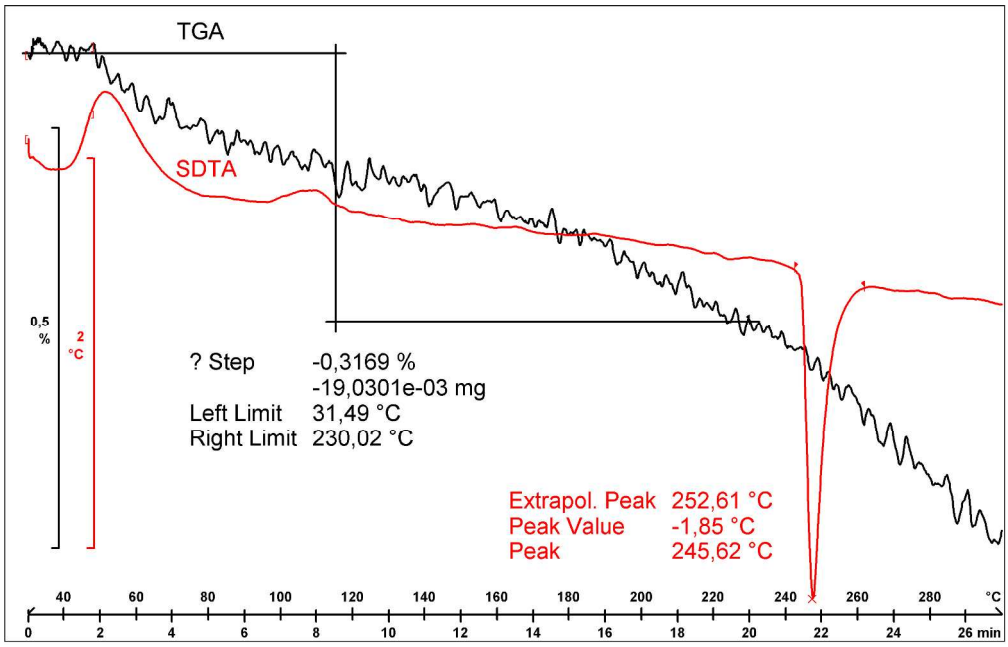

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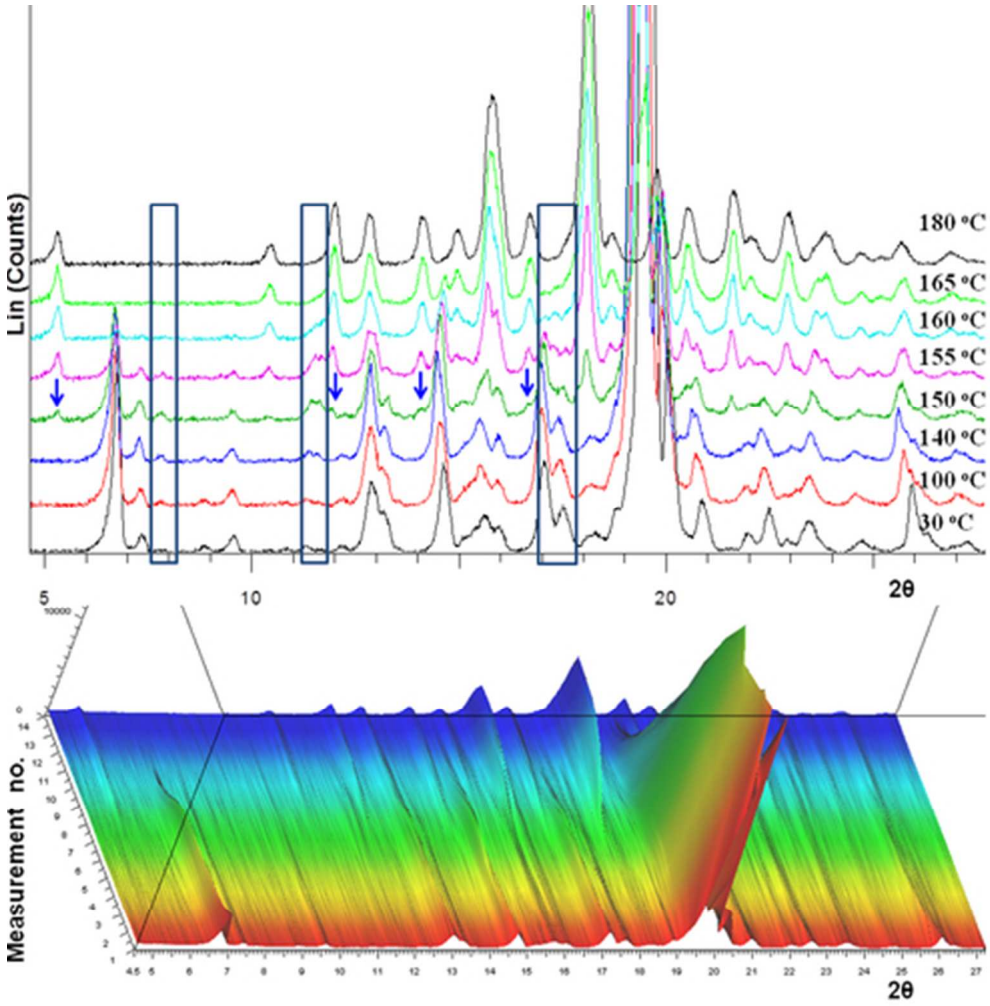
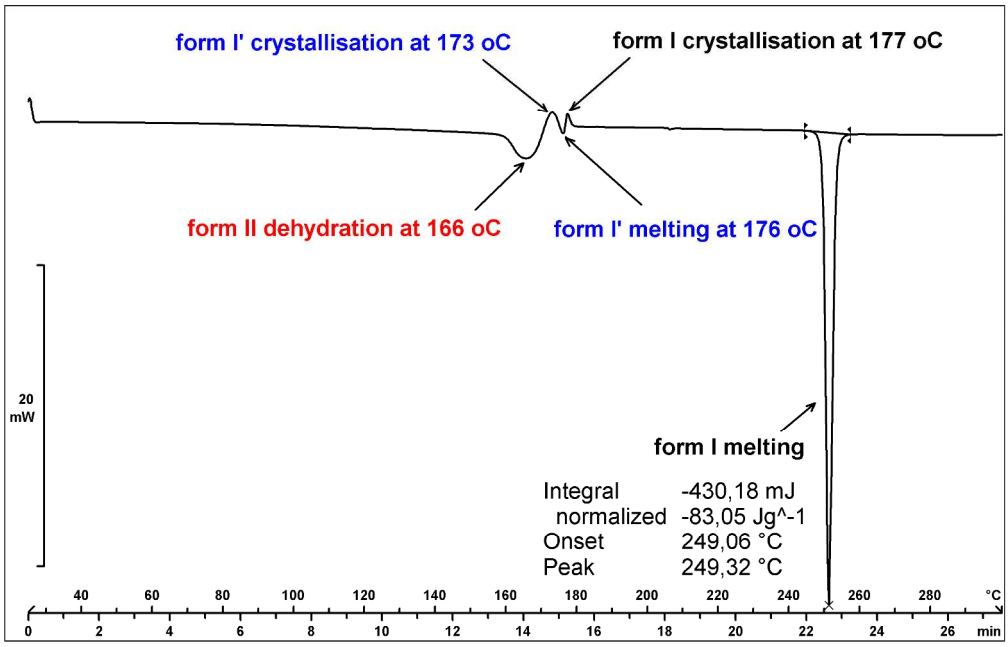


41x42mm (300 x 300 DPI)



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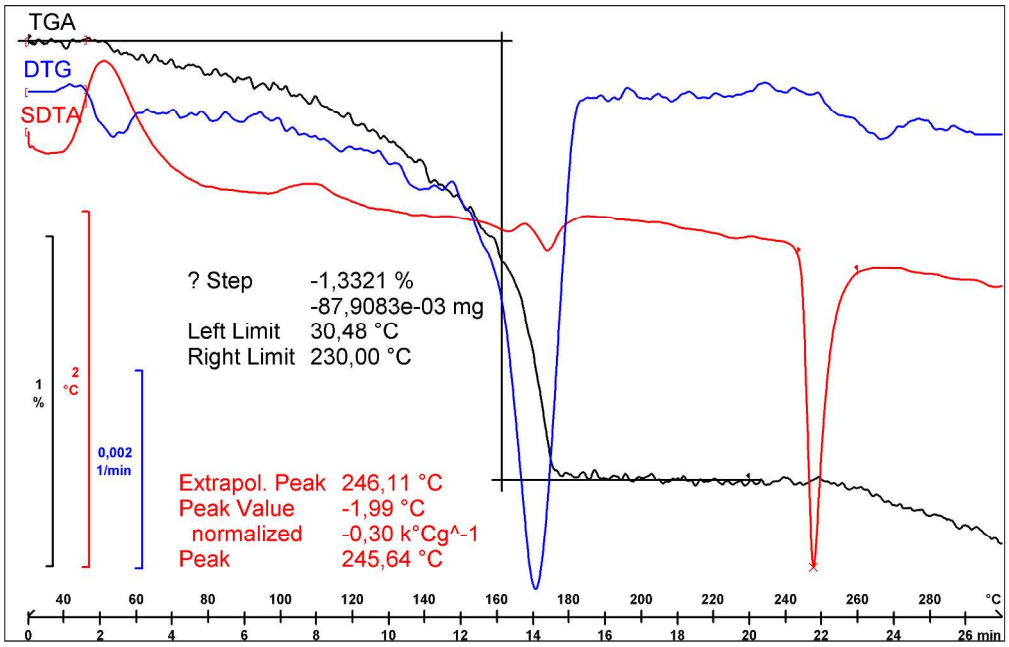

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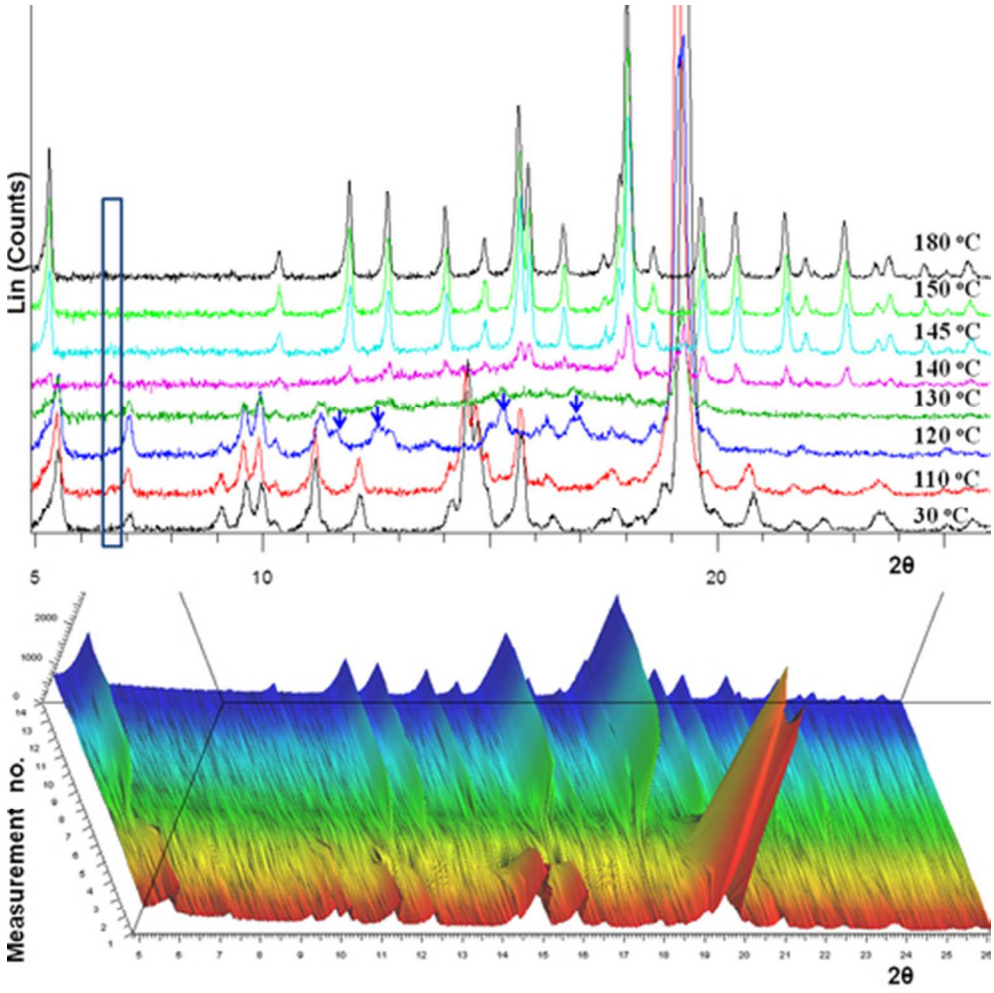
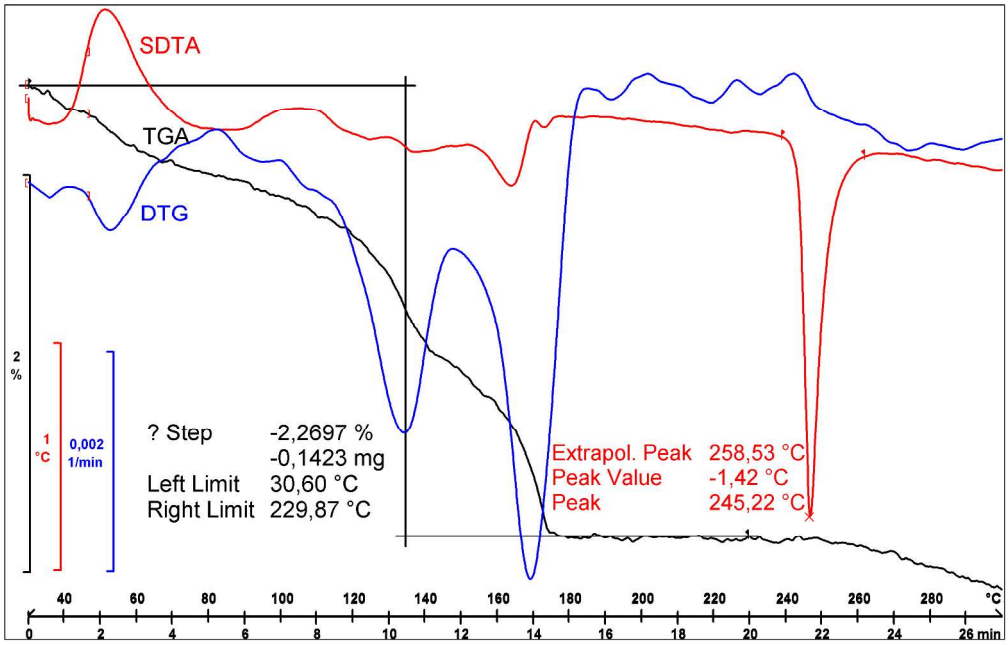


41x42mm (300 x 300 DPI)



793x507mm (96 x 96 DPI)

Polymorphism of dutasteride is studied. Details of crystal and molecular structure of unsolvated form I are presented.