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Polymorphic forms of antiandrogenic drug nilutamide: structural and thermodynamic aspects

Artem O. Surov,[a] Alexander P. Voronin,[a] Ksenia V. Drozd,[a] Matvey S. Gruzdev,[a] German L. Perlovich[a*]*

Jupally Prashanth[b], Sridhar Balasubramanian[b,c]*

[a]G.A. Krestov Institute of Solution Chemistry of the Russian Academy of Sciences, 1 Akademicheskaya St., 153045 Ivanovo, Russia

[b]Centre for X-ray Crystallography, Department of Analytical & Structural Chemistry, CSIR-Indian Institute of Chemical Technology, Tarnaka, Uppal Road, Hyderabad-500007, Telangana, India.

[c]Academy of Scientific and Innovative Research (AcSIR), Uttar Pradesh- 201 002, India

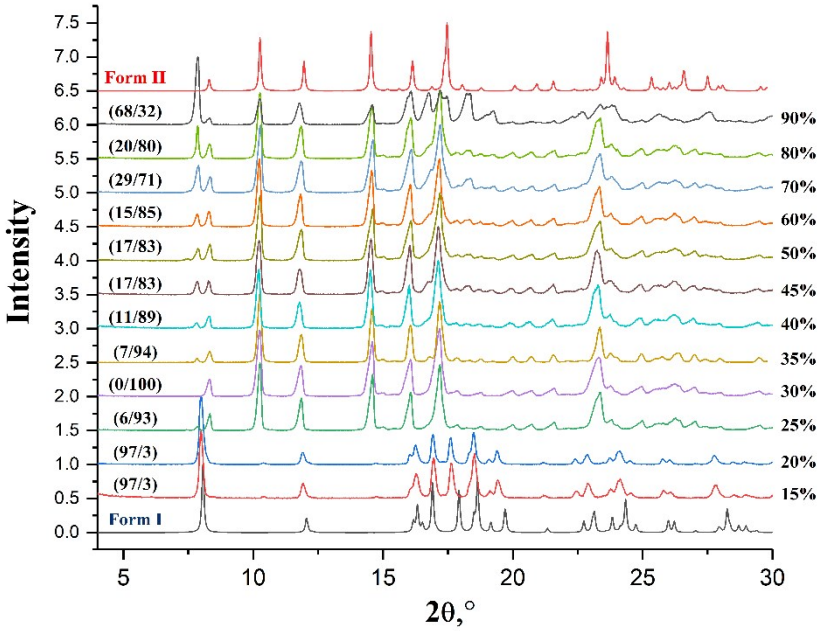

Figure S1. Results of PXRD analysis of the freeze-dried powders of nilutamide obtained from 1,4-dioxane/water solvents with different components ratio. The numbers show percentage of 1,4-dioxane in a 1,4-dioxane/water mixture. The numbers in parentheses correspond the relative amount of polymorphic forms (Form I/Form II) in the resulting products derived from quantitative analysis in the Bruker TOPAS6 software [1].

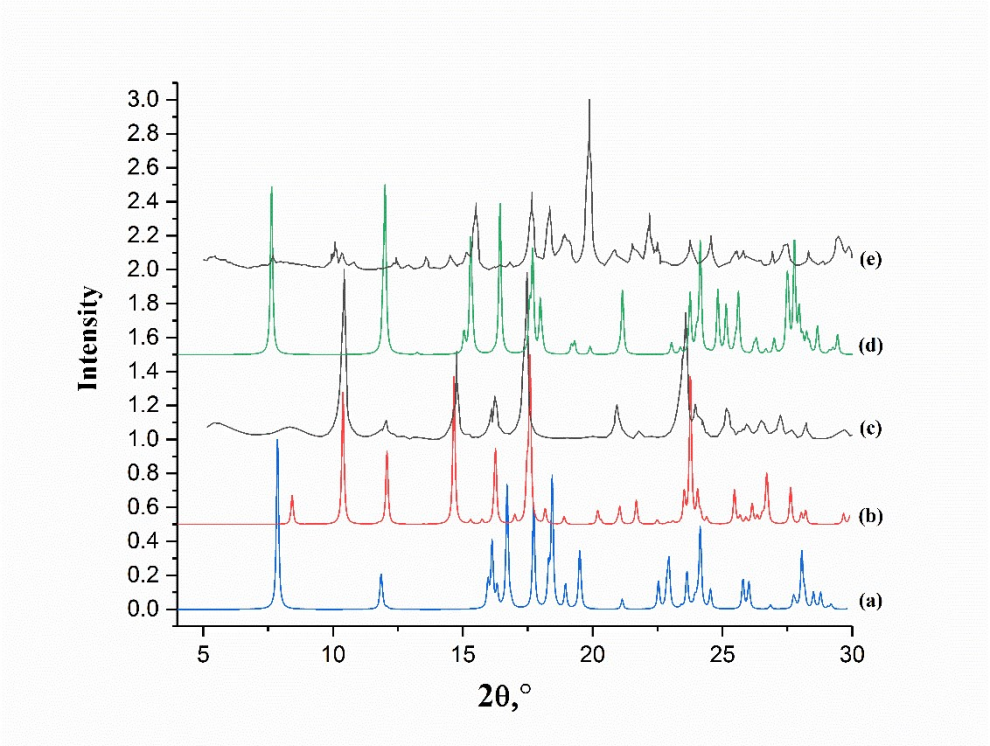

Figure S2. Calculated PXRD patterns of Form I (a) and Form II (b); experimental PXRD patterns of "metastable form I" (c) reproduced from Fig. 8 of the Trasi & Taylor paper [2]; calculated PXRD patterns of Form III (d); experimental PXRD patterns of "metastable form II" (e) reproduced from Fig. 8 of the Trasi & Taylor paper [2].

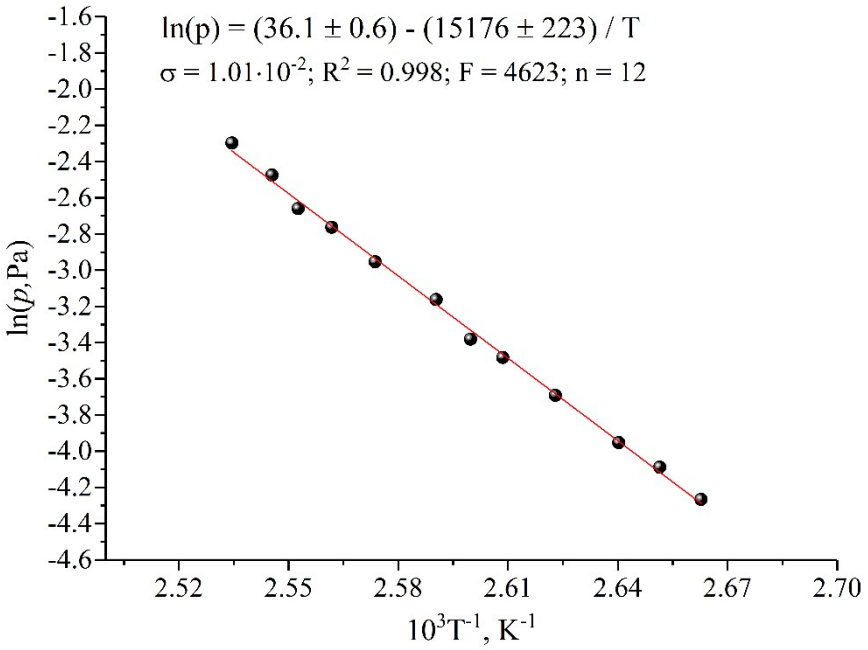

Figure S3. Plot of vapor pressure ln(p,Pa) against reciprocal temperature for nilutamide Form I

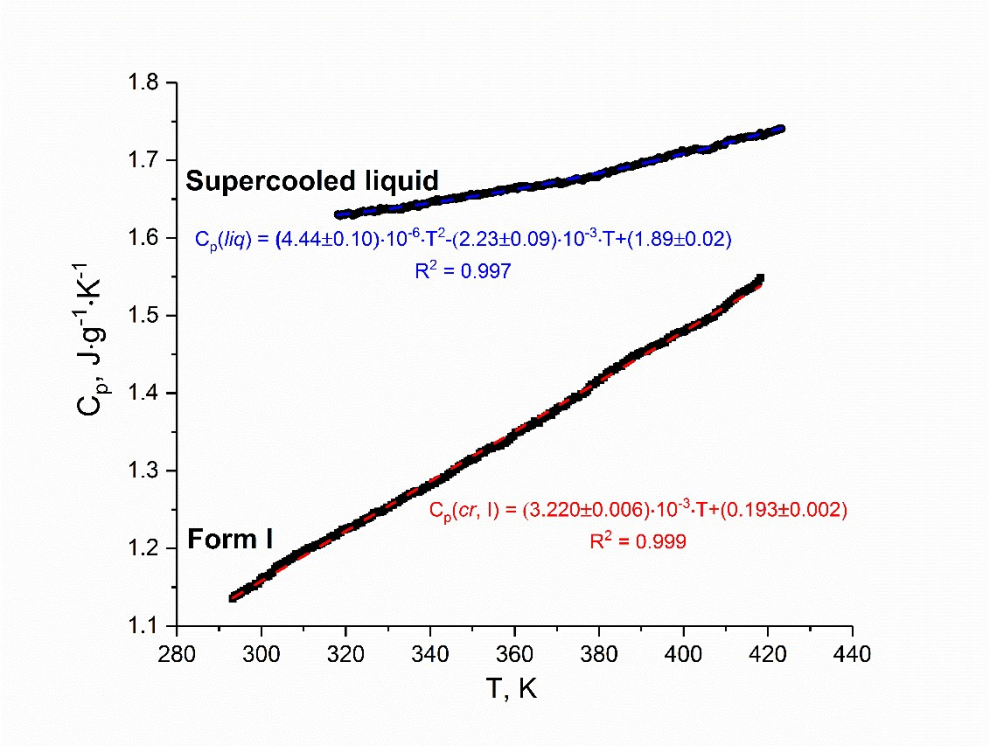

Figure S4. Experimental temperature dependences of C_p of Form I and the supercooled liquid of nilutamide

Table S1. Crystallographic data for Form II and Form III of nilutamide [3-5]

Compounds	Form II	Form III
CCDC numbers	2063187	2063188
	Crystal data	
Chemical formula	$C_{12}H_{10}F_3N_3O_4$	$C_{12}H_{10}F_3N_3O_4$
M_r	317.23	317.23
Crystal system, space group	Triclinic, *P*1	Monoclinic, *C*2/*c*
Temperature (K)	100	100
a, *b*, *c* (Å)	7.5763 (8), 8.5961 (9), 10.7211 (10)	11.1754 (5), 10.0868 (4), 23.6466 (10)
α, β, γ (°)	100.721 (3), 99.964 (3), 91.329 (4)	90, 101.8274 (19), 90
V (Å^3)	674.59 (12)	2608.95 (19)
Z	2	8
Radiation type	Mo *K*α	Mo *K*α
μ (mm^{-1})	0.14	0.15
Crystal size (mm)	0.24 × 0.20 × 0.08	0.36 × 0.30 × 0.15
	Data collection	
Diffractometer	Bruker D8 QUEST PHOTON-100	Bruker D8 QUEST PHOTON-100
Absorption correction	Multi-scan *SADABS*, Bruker, 2016	Multi-scan *SADABS*, Bruker, 2016
T_{min}, T_{max}	0.513, 0.746	0.659, 0.746
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	16594, 4137, 3505	17180, 3995, 3421
R_{int}	0.056	0.023
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0.716	0.716
	Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, *S*	0.043, 0.116, 1.07	0.037, 0.098, 1.06
No. of reflections	4137	3995
No. of parameters	205	205
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.41, −0.46	0.43, −0.31

Table S2. Hydrogen-bond geometry (Å, º) for Forms II and III.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
Form II				
N3—H3*N*···O3^{i}	0.894 (17)	2.008 (17)	2.8923 (12)	170.1 (16)
C12—H12*B*···O4^{ii}	0.98	2.55	3.4072 (15)	145
Form III				
N3—H3*N*···O3^{i}	0.880 (16)	2.083 (17)	2.9183 (11)	158.1 (15)
C11—H11*A*···O2^{ii}	0.98	2.60	3.5666 (14)	170
C11—H11*B*···O3^{iii}	0.98	2.52	3.4337 (14)	156

Form II - Symmetry codes: (i) −*x*, −*y*+1, −*z*+2; (ii) −*x*+1, −*y*+2, −*z*+2.

Form III - Symmetry codes: (i) −*x*+1, *y*, −*z*+1/2; (ii) *x*−1/2, −*y*+1/2, *z*−1/2; (iii) *x*−1/2, *y*−1/2, *z*.

Table S3. The weight, g (mg), solution concentrations, m (mol kg^{-1}), and solution enthalpies, $\Delta_{sol}H_m^0$ (kJ·mol^{-1}), of nilutamide polymorphs in ethanol at 25.0 ºC.

Form I			**Form II**		
g	$m\cdot10^{-3}$	$\Delta_{sol}H_m^0$	g	$m\cdot10^{-3}$	$\Delta_{sol}H_m^0$
29.72	4.08	30.6	41.67	5.74	29.2
30.06	4.10	30.5	22.23	3.10	29.5
21.52	3.01	30.4	15.20	2.10	29.4
25.63	3.55	30.8	10.76	1.48	29.4
22.59	3.13	30.3	15.08	1.98	29.4
	$\Delta_{sol}H_m^0$(I)	=30.5±0.2		$\Delta_{sol}H_m^0$(II)	=29.4±0.1

Table S4. Root-mean-square deviation of atomic positions ($RMSD_{15}$), excluding H atoms, between the experimental and the optimized structures calculated using the Crystal Packing Similarity module implemented in Mercury for the cluster consisting of 15 molecules

Method	Form I	Form II
GTO-DFT		
B3LYP-D3/6-31(F+)G(d,p)	0.044	0.117
B3LYP-D3/pob-TZVP-rev2	0.041	0.105
PBE-D3/6-31(F+)G(d,p)	0.075	0.114
M06-2X-D3/pob-TZVP-rev2	0.117	*0.319* (12 out of 15)
PBEh-3c/def2-mSVP	0.090	0.082
PBE0-D3/6-31(F+)G(d,p)	0.051	0.087
PW-DFT		
PBE-D3	0.027	0.043
B86BPBE-XDM	0.031	0.045

References

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2. Trasi, N.S. and L.S. Taylor, Nucleation and crystal growth of amorphous nilutamide – unusual low temperature behavior. CrystEngComm, 2014. 16(31): p. 7186-7195.

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4. Sheldrick, G.M, SHELXT - Integrated space-group and crystal-structure determination. Acta Crystallographica Section A, 2015. 71: p. 3-8.

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http://www.crystalimpact.com/diamond