Thermochemical Analysis of Venlafaxine Hydrochloride Polymorphs 1 – 5 †

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Thermochemical Analysis of Venlafaxine Hydrochloride Polymorphs 1−5†

Saikat Roy, Srinivasulu Aitipamula, and Ashwini Nangia*

School of Chemistry, University of Hyderabad, Hyderabad 500 046, India

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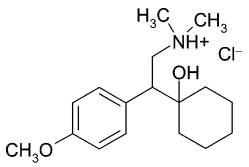
ABSTRACT: Five polymorphs of the antidepressant drug venlafaxine hydrochloride (VenHCl) are reported. Forms 1 and 2 are crystalline modifications, form 3 is obtained by melting, form 4 is a hydrate/alcoholate, and form 5 is an amorphous, glassy phase from sublimation. These five polymorphs of VenHCl are characterized by differential scanning calorimetry (DSC), thermogravimetry analysis (TGA), powder X-ray diffraction (XRD), Fourier transform infrared (FT-IR) spectroscopy, and additionally structures of polymorphs 1 and 2 are confirmed by single-crystal XRD ($Pca2_1$ and $P2_1/n$). The endotherms for the melting transition of forms 1−4 appear at slightly different temperatures in different patents. Moreover, DSC thermograms of forms 1 and 2 (recorded at 10 K/min) are single, sharp peaks, and there is no discussion of phase transition other than melting. Our DSC profiles (recorded @ 2 K/min) show that both forms 1 and 2 undergo a phase transition just after the melting event in the temperature range 210−220 °C. Form 1 transforms to form 3 (phase from melting) and form 5 (phase from sublimation), whereas form 2 converts completely to form 5 in DSC heat−cool−heat cycles. These transitions are also examined under a hot stage microscope. Form 5 is not very stable and converts to form 1 (inert conditions) or hydrate form 4 (open air) in laboratory experiments. In the heating cycle of DSC (30−300 °C), both polymorphs 1 and 2 undergo sublimation to form 5, as characterized by thermogravimetry-infrared (TG-IR) spectroscopy of the evolved vapor. There is no interconversion between polymorphs 1 and 2 in the ambient-to-melting temperature range. Crystal lattice energy of polymorph 2 is lower than form 1 by 2.0 kcal/mol. However, form 1 is stable to ball mill grinding, whereas form 2 partially transforms to hydrate phase 4, suggesting that form 1 is perhaps more suitable in pharmaceutical formulations. With the identification of at least five different solid-state modifications, VenHCl belongs to the category of highly polymorphic drug substances.

Introduction

Venlafaxine, (±)-1-[2(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol, belongs to the class of antidepressant drugs that act by inhibiting the reuptake of norepinephrine and serotonin in the brain (serotonin-norepinephrine reuptake inhibitor, SNRI).[1] This free base is widely used in pharmaceutical formulations as the salt, venlafaxine hydrochloride (VenHCl), sold under the trade name Effexor XR. This extended release capsule is indicated in the treatment of generalized anxiety disorder (GAD). Venlafaxine hydrochloride is a widely prescribed antidepressant drug with sales of US $3.7 billion per annum. Some popular serotonin-enhancing antidepressant drugs are listed in Table 1.



Racemic VenHCl is known to exist in at least five different polymorphic/pseudopolymorphic forms in the patent literature.[2] Two crystalline polymorphic modifications of the drug are the most studied forms (1 and 2). There are also hydrate/alcoholate forms (H_2O/MeOH/EtOH/*i*-PrOH), DMF/DMSO solvated forms, and a phase obtained from the melt. The chronology of VenHCl synthesis and the appearance of its polymorphs are summarized in Table 2. Polymorphs of VenHCl have been given different names (e.g., 1, 2, 3, A, B, C, etc.), some of which are overlapping forms. We use the terminology forms 1−5 for the five polymorphs of VenHCl in this paper. One of the reasons for initiating the present thermal analysis was that differential scanning calorimetry (DSC) experiments of VenHCl in various patents do not show consistently matching endotherm peaks for melting. For example, different melting points are reported for forms 1 and 2, and the thermodynamically stable form is different depending on the patent report (see entries 2, 3, and 5 in Table 2).

Table 1. Antidepressants and Serotonin-Enhancing Drugs

generic name	brand name
fluoxetine	Prozac, Serafem
paroxetine	Paxil
setraline	Zoloft
bupropion	Wellbutrin
venlafaxine	Effexor
nefazadone	Serazone
mirtazapine	Remeron

Polymorphism may be defined as the ability of a substance to exist in two or more crystalline phases that have different arrangements and/or conformations of molecules in the solid state.[3] Polymorphs are relatively common in pharmaceutical solids. Polymorphism is of great current interest because different modifications can have different physical and chemical properties such as melting point, particle size, stability, tableting,

* To whom correspondence should be addressed. Tele-fax: (+91) 40 2301 1338; E-mail: ashwini_nangia@rediffmail.com.

† This paper is dedicated to my teacher Prof. J. Michael McBride on his 65th birthday.

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Table 2. Chronology of Venlafaxine Hydrochloride Polymorphs[a]

no.	patent appl no. publication date	CAS reference	description of melting and DSC endotherm (↓) and exotherm (↑) (°C)	characterization of solid phases and comments	DSC experimental details
1	US 4,535,186 13 Aug 1985	CA 102:5895	preparation of Ven base and its HCl salt mp 215−217	No DSCs are given or polymorphs are mentioned.	NA
2	WO 02/46140 A1 13 Jun 2002	CA 137:20211	Form 1: 211↓, 245↓ (dec)	FT-IR, PXRD, DSC	not provided
			Form 2: 221↓, 255↓ (dec)	single-crystal XRD	
			Form 2 is thermodynamically stable at room temp	Form 1, $Pca2_1$ Form 2, $P2_1/n$	
3	US 2002/0183553 A1 5 Dec 2002	CA 138:8362	Form 1: 210−213↓	DSC and PXRD of polymorphs and solvates	MT DSC821e, 30−250 °C @ 10 K/min
			Form 2: 210−213↓ (major), 219−222↓ (minor)		
	WO 03/048082 A2 12 Jun 2003		Form 3: 219−220↓ (water/alcohol)		
			Form 4: 212−213 (DMF/DMSO)		
4	WO 03/042161 A1 22 May 2003	CA 138:406926	three forms, no melting points are reported	Polymorphs are characterized by PXRD lines.	NA
5	US 2003/0105359 A1 5 Jun 2003	CA 136:355063	Form C: 215−217 (same as entry 1)	characterized by PXRD and FT-IR/Raman. Form B is more stable than C (= form 1 and 2 of entry 2)	NA
			Form A: melt phase from C		
			Form B: more stable than C		
			Form D: hydrate form		
6	US 2003/0109585 A1 12 Jun 2003	CA 139:41803	Form 1: 209↓ (ΔH −125.8 J/g)	DSC and PXRD. Form 3 is more stable.	25−240 °C @ 10 K/min
			Form 2: 211↓ (ΔH −130.3)		
			Form 3: 219↓ (ΔH −116.1)		
7	US 2003/0114536 A1 19 Jun 2003	CA 139:57923	monohydrate form: 80−100↓ (dehydration), 196 (phase transition), 219↓ (melting)	DSC and PXRD reported. Reversible dehydration and rehydration.	25−240 °C @ 10 K/min
8	WO 03/050074 A1 19 June 2003	CA 139:41833	Form 1: mp 210−212	DSC, FT-IR and SS−NMR characterization. Both chiral R/S and racemate.	not provided
			Form 2: mp 215−216		
			Form 3: mp 215−216		

[a] Data extracted from patents listed in ref 2.

bioavailability, dissolution rates, pharmacological activity, and side effects.[4] It is therefore important to produce active pharmaceutical ingredients (APIs) in pure, crystalline form to enable formulation of drug substances in accordance with exacting Food and Drug Administration (FDA) specifications. Thermochemical transformations of existing forms must be properly understood, and new forms must have good stability/solubility characteristics. In this background, we studied the thermal behavior of VenHCl polymorphs to better understand phase transitions and transformations, melting endotherms, degradation, and hydration/dehydration of this drug substance. The five polymorphs of VenHCl are classified according to their main melting endotherm in DSC: form 1 (210−212 °C), form 2 (208−210 °C), form 3 (202−204 °C, phase from melting), form 4 (219−220 °C, hydrate/alcohol solvate), and form 5 (216−218 °C, phase from sublimation). Forms 1 and 2 are numbered according to the appearance of VenHCl crystal structures in the Cambridge Structural Database[5] (ConQuest version 1.7, May 2005 release): form 1 = WOBMUV in space group $Pca2_1$; form 2 = WOBMUV01 in $P2_1/n$ space group. We discuss phase transformations of VenHCl and report a new amorphous, transient glassy (semisolid) phase that is obtained by sublimation under vacuum (form 5). Both forms 1 and 2 undergo phase transformation at 214−218 °C to this transient phase (form 5) that sublimes between 220 and 260 °C. Sublimation of VenHCl in DSC/thermogravimetry analysis (TGA) to the vapor state is confirmed by Fourier transform infrared (FT-IR) analysis of the evolved gas (TG-IR). Recent reviews[6a−d] and two theme issues of *Crystal Growth & Design*[6e,f] highlight the wide scope of polymorphism in drugs and materials and the challenges in understanding this important phenomenon.

Results and Discussion

Venlafaxine hydrochloride was prepared using the procedure of Yardley et al.[1] VenHCl form 1 and 2 were crystallized from hot *i*-PrOH (see Experimental Section).[2g]

DSC thermograms of forms 1 and 2 were recorded at heating rate of 2 K/min (Figure 1). Form 1 shows a major endotherm at 210−211 °C and a minor peak at 214−215 °C. Form 2 shows endotherms at about the same temperature (208−209, 215−216 °C, within 2 °C of form 1), but the size of peaks is reversed: the first endotherm is large in form 1, but the second endotherm is large in form 2. Enthalpy changes in the thermal events are listed in Table 3. There is a broad endotherm

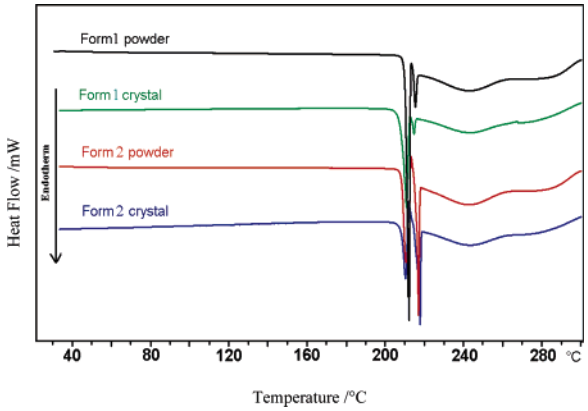


Figure 1. DSC thermograms of bulk powder samples (form 1, black) and (form 2, red) are identical to the thermal profile of orthorhombic $Pca2_1$ (green) and monoclinic $P2_1/n$ (blue) single crystals, respectively. Heating rate is 2 K/min. T_{onset}, T_{peak}, and enthalpy change for each endotherm (↓) are quantified in Figure 5.

Table 3. Thermal Data on Polymorphs 1 and 2 of VenHCl Taken from DSCs in Figure 5

	peak position		
polymorph	T_{onset}/°C	T_{peak}/°C	enthalpy (J/g)
Form 1	210.84	211.27	−119.17
	214.01	215.04	−17.91
	240.88	242.11	−90.82
Form 2	208.11	210.40	−100.00
	215.66	216.42	−45.68
	220.46	242.08	−112.20

at 220−260 °C. Thermograms for forms 1 and 2 (Figure 1) are different from DSCs reported for polymorphs 1 and 2 in patents,[2b,f] which show only one major, sharp peak (see Figure S1, Supporting Information).[7] That we are dealing with pure phases 1 and 2 was confirmed by matching the powder X-ray diffraction (XRD) of our samples with their simulated powder XRDs[8] (Figure 2). X-ray diffraction on single crystals of forms 1 and 2 (Figure 3), obtained from MeCN/DMF and EtOAc/MeOH, have unit cell parameters identical to the orthorhombic and monoclinic forms (see Experimental Section). Furthermore, the DSC profile of powder samples is identical to the thermal behavior of single crystals (Figure 1). Polymorphs 1 and 2 are quite stable and exhibit identical DSCs after one year of storage. When DSCs were recorded at scan rate of 10 K/min (instead of 2 K/min), the peaks are broader and, interestingly, the small endotherm at 215−216 °C in form 1 is barely visible (Figure S2, Supporting Information). Armed with the knowledge that our polymorphic samples 1 and 2 are pure, uncontaminated and stable, we analyzed the peaks in each thermogram below 220 °C.

All subsequent measurements were carried out on powder samples. That the major endotherm in form 1 at 210−211 °C is due to melting was verified by recording its melting point on a Fisher−Johns apparatus (210−212 °C) and observing the phase transition under a hot stage microscope (209−210 °C). The minor endotherm at 214−215 °C is due to phase transformation. In DSC of polymorph 2, the endotherm at 208−210 °C is melting [mp 212−213 °C, hot stage microscopy (HSM) 208−209 °C] after which there is an exo−endo peak. The exotherm is possibly due to solidification/crystallization of melted form 2. The newly

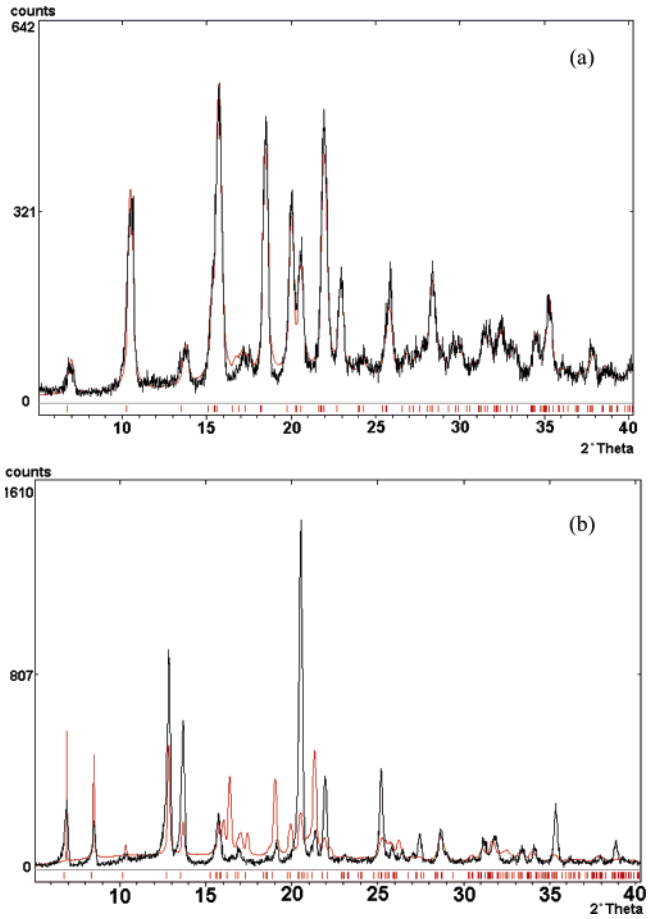


Figure 2. Rietveld refinement of experimental powder XRD peaks (black) with simulated lines (red, from CSD refcodes WOBMUV and WOBMUV01). (a) Form 1 and (b) form 2. The overlay of peaks confirms the identity of forms 1 and 2 with their X-ray crystal structures in $Pca2_1$ and $P2_1/n$ space groups.

transformed solid melts at 215−216 °C. The endotherm at lower temperature in both forms (T_{peak} 210−211 °C) is ascribed to melting. The similarity in melting points of forms 1 and 2 may be rationalized from the hydrogen bonding and molecular packing in their crystal structures. Translation-related molecules are connected by O−H···Cl^- and N^+−H···Cl^- hydrogen bonds in both structures except that this motif is along [010] in form 1 and along [100] in form 2 (Figure 4). Hydrophobic groups close pack to complete the crystal structure with packing fraction of 65.9 and 66.7%, respectively. Correlation of the melting point with crystal packing is difficult because melting is a complex phenomenon that depends both on the enthalpy and entropy of fusion. We have analyzed the enthalpy contribution and assume that the entropy component is similar in both polymorphs.

When TGAs were recorded on forms 1 and 2, there is complete weight loss in the range 220−260 °C (Figure 5a,b). The weight change could be due to decomposition or vaporization of solid in the post-melting phase. Thermal gravimetry-infrared (TG-IR) spectroscopy is a quantitative technique for the characterization and analysis of evolved gases.[9] In this method, the evolved gas from the TG instrument is transferred through a heated transfer line to the FT-IR spectrometer for analysis of its vibration−rotation spectrum. TG-IR of VenHCl forms 1 and 2 show identical infrared spectra

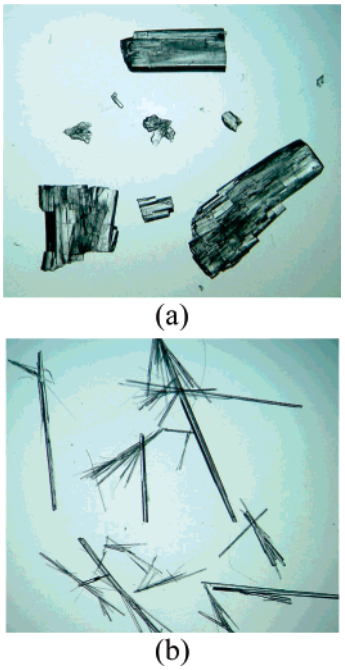


Figure 3. Photomicrographs of form 1 (a) and form 2 (b) crystals of VenHCl. Form 1 crystals of block morphology were obtained from MeCN/DMF and needle-shaped crystals of form 2 from EtOAc/MeOH.

(Figure 5c): a broad peak at 3250 cm^{-1} (OH, NH), an intense peak at 2950 cm^{-1} (aromatic CH), as well as peaks at 1550 cm^{-1} (aromatic C=C) and 1250 cm^{-1} (C−N/C−O stretch). This means that VenHCl vapor is evolved after the phase change at 214−216 °C (peak 2 in Figure 5a,b) in both forms, a phenomenon that is concomitant with sublimation of the solid during the broad endotherm peak 3 at 220−260 °C. The novel form 5 of VenHCl obtained by sublimation and analysis of its vapor phase by FT-IR spectroscopy is not reported in the extensive patent literature on this drug compound.[2] Raman spectroscopy is yet another technique to study multi-polymorphic systems.[10]

The presence of two endotherms at 210−220 °C raises several possibilities. (1) Is the first endotherm due to melting and the second peak for phase transition, or vice versa? (2) Is the endo−exo peak[11] in form 2 a melting−crystallization phenomenon? (3) Which polymorph is more stable? Do they interconvert or transform to a new, different phase? DSCs of forms 1 and 2 were scrutinized to better understand these thermal events. Form 1 was heated @ 2 K/min up to 212 °C, a temperature that is just after the major endotherm peak 1 but before the small peak 2 (see Figure 5a for peak numbering). Then the sample was cooled to room temperature @ 5 K/min in the DSC cell. Reheating @ 2 K/min shows a broad endotherm centered at 212 °C, which means that the solid is still form 1, not a transformed product. The exotherm at 195 °C in the cooling cycle is solidification/crystallization of melted form 1. Therefore, the peak at 210−212 °C in Figure 6a is a melting endotherm and not a phase transition. When the same procedure was repeated up to 219 °C, just past the small peak 2, DSC of reheated form 1 is very different. There is a broad exotherm at 110 °C and an endotherm at 200 °C. The exotherm corresponds to solidification of the transformed phase 3, which is matched with the solid

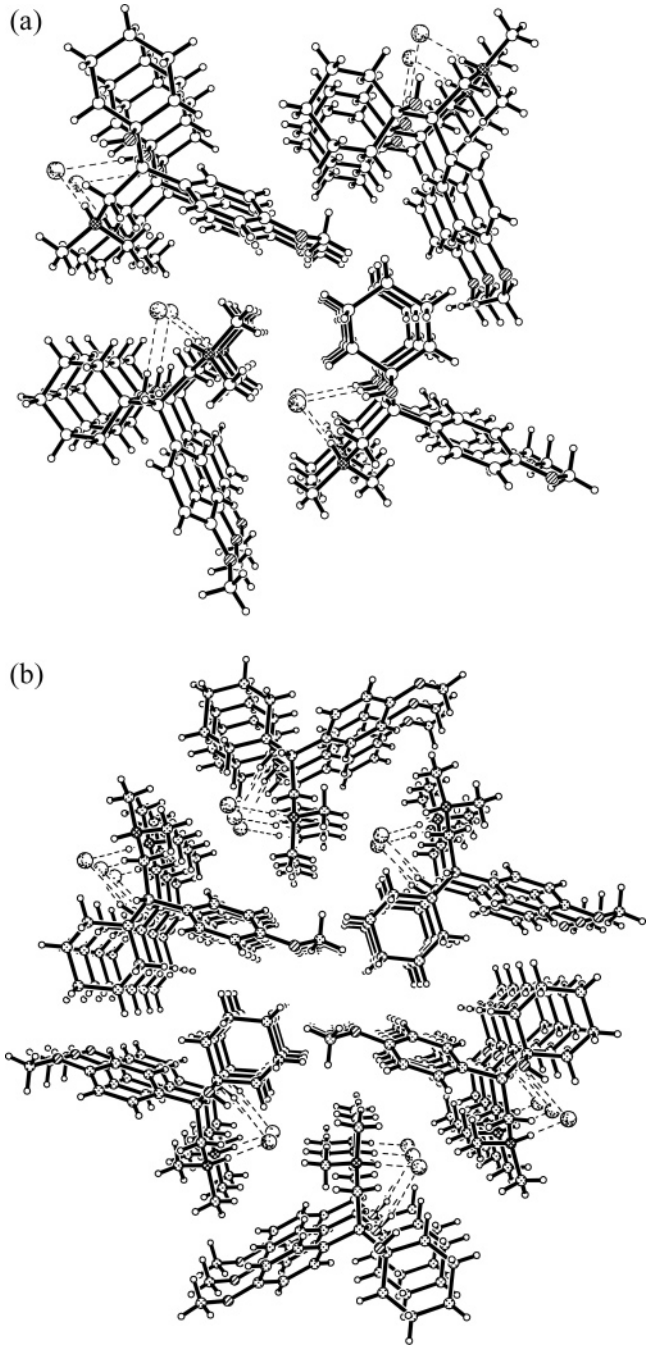


Figure 4. (a) Close packing of helical chains along the *b*-axis in the crystal structure of form 1. (b) Close packing of helical chains along the *a*-axis in form 2. Note the V-shaped O−H···Cl^- and N^+−H···Cl^- hydrogen bond motif in both structures. The void space between hydrophobic groups is slightly larger in (a) compared to (b).

obtained by melting VenHCl based on the endotherm at 200 °C. Thus, form 1 undergoes phase transformation to form 3 upon heating to 218−219 °C, the phase obtained by melting (see next). In a similar procedure, form 2 was heated in DSC @ 2 K/min up to the endo−exo peak at 213 °C (peak 1) and then cooled to room temperature @ 5 K/min. The cooling curve is flat, which means that resolidification of form 2 at the 213 °C exotherm is correctly assigned (Figure 6b). Reheating @ 2 K/min shows a sharp endotherm at 218−220 °C that corresponds to melting of form 5, the phase obtained by sublimation (see next). Upon heating form 2 beyond

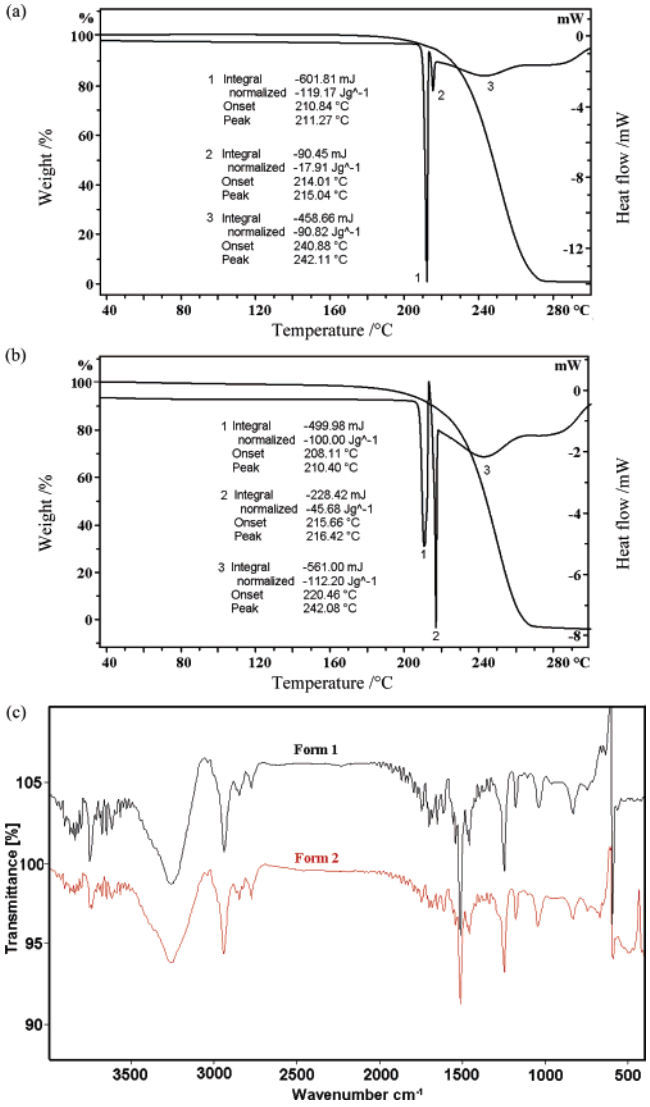


Figure 5. DSC and TGA of VenHCl form 1 (a) and form 2 (b). Note the weight loss concomitant with sublimation. (c) Infrared spectrum of the evolved vapor from form 1 (black) and form 2 (red) are identical. FT-IR spectra as a function of temperature (220−260 °C) are shown in Figure S4 (Supporting Information).

the second endotherm to 220 °C (peak 2), cooling to room temperature, and then reheating shows different peaks. Now, the DSC shows solidification at ∼150 °C and endotherm peaks that resemble form 3. The heat−cool−heat thermograms show that forms 1 and 2 first melt and then phase transform to different solid modifications in the temperature range 210−220 °C. There is no evidence of interconversion between forms 1 and 2. Differences in heating rate can induce crystallization/phase transition of the solid, and this could be a possible reason our DSCs recorded at a slow scan rate show more peaks compared to those recorded at a faster speed.

Powdered samples of form 1 and 2 were gradually heated to 215 °C over 30 min to melt the solid and then slowly cooled to room temperature. DSC of the resulting solid (form 3) shows a single broad peak at 204 °C for melting followed by sublimation (220−260 °C). A hydrate form of VenHCl (polymorph 4) is obtained upon crystallization from MeOH/EtOH, which possibly contains a mixture of water and solvent. This solvated form loses water/alcohol at 70−80 °C and melts at 219−220

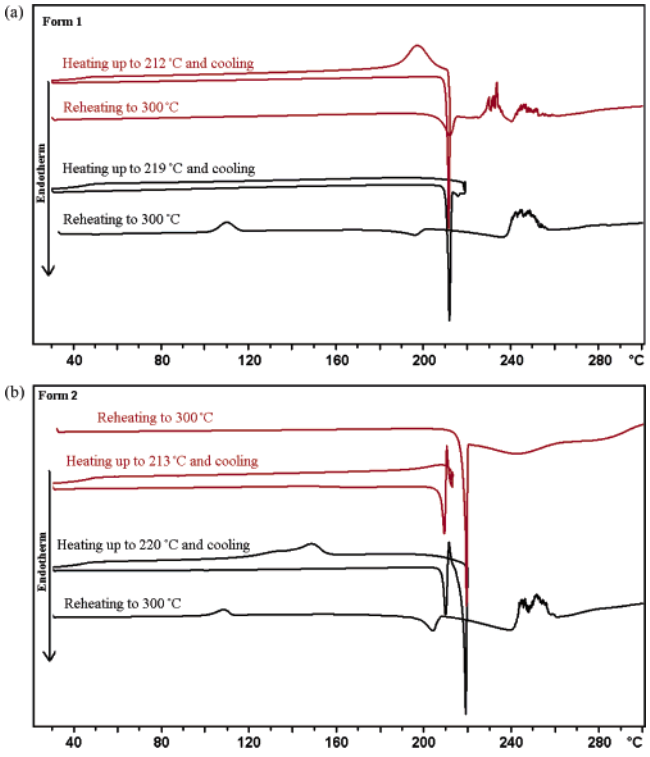


Figure 6. (a) Heating form 1 up to 212 °C (red curve, just after peak 1 of Figure 5a) @ 2 K/min, cooling back to room temperature @ 5 K/min, and then reheating to 300 °C @ 2 K/min. The exotherm at 195 °C is due to solidification of melted form 1, which shows reversible melting at the same temperature as a broad endotherm in the heating cycle. DSC of heating form 1 up to 219 °C (after peak 2 of Figure 5a), cooling to room temperature, and reheating to 300 °C is shown in the black curve. The exotherm at 110 °C is due to solidification of the transformed phase and the broad endotherm at 200 °C is melting of form 3. The exotherms at 220−260 °C are due to decomposition. (b) Heating form 2 up to 213 °C, just beyond the endo−exo melting−solidification peak 1 of Figure 5b, then cooling back to room temperature, and reheating to 300 °C (red curve). Form 2 transforms to form 5, the phase from sublimation, which shows melting endotherm at 218 °C. Heating form 2 up to 220 °C, just beyond exo−endo peak 2, then cooling back to room temperature and reheating to 300 °C is shown in the black curve. The exotherm at 155 °C is solidification of form 3 (phase by melting) based on the endotherm at 200 °C in the reheating curve.

°C. DSC and powder XRD of forms 3 and 4 are in good agreement with literature values[2] (Figures S5 and S6, Supporting Information).

VenHCl was sublimed at reduced pressure (0.2 Torr, ∼160 °C). An amorphous, semisolid material hangs from the coldfinger (Figure 7a). This glassy mass is difficult to handle, but it can be immediately transferred to a glass plate (Figure 7b) as liquidlike droplets. DSC of the sublimed semisolid shows crystallization at 95−100 °C (exotherm) followed by melting at 216−218 °C (endotherm) and a broad endotherm at 220−260 °C for vaporization/sublimation (Figure 8a). Since DSC of the phase from sublimation in Figure 8 is different from that of forms 1−4 and it is obtained under very different experimental conditions, this new form of VenHCl is named form 5. Complete characterization of form 5 is difficult because of its transient, semisolid nature. It transforms to form 1 under inert N_2 atmosphere in a few hours up to a day (Figure 8b). When the sublimed

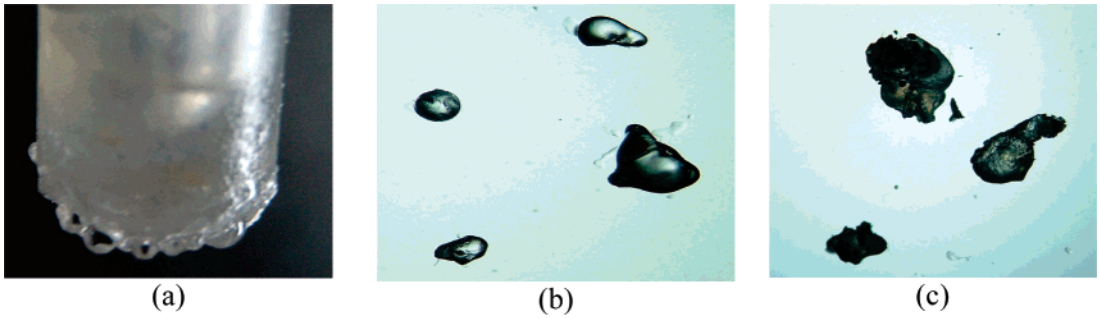


Figure 7. Transient semisolid, glassy phase on the coldfinger of the sublimation apparatus (a) and droplets immediately placed on a glass plate (b). The sublimed material (form 5) transforms to hydrate form 4 (c) after 1 day in Hyderabad climate (25−30 °C, RH 40−50%).

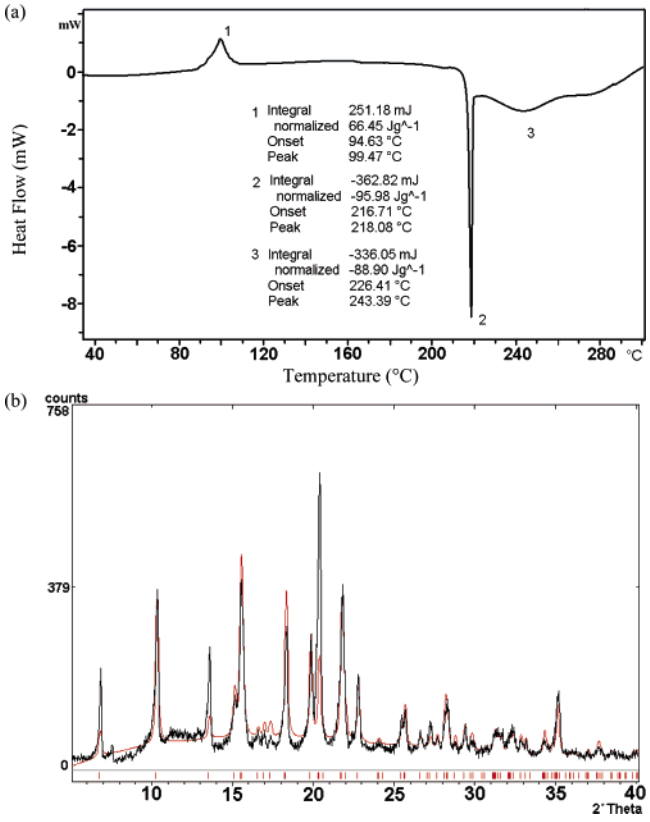


Figure 8. (a) DSC of form 5, the transient phase from sublimation, recorded immediately. The exotherm at 100 °C is due to solidification of the glassy mass, the endotherm at 217−218 °C from melting, and vapor loss occurs at 220−260 °C. (b) The solid kept in dry N_2 solidifies to form 1 after 1 day. Experimental powder XRD (black) fits the simulated powder XRD of form 1 (red).

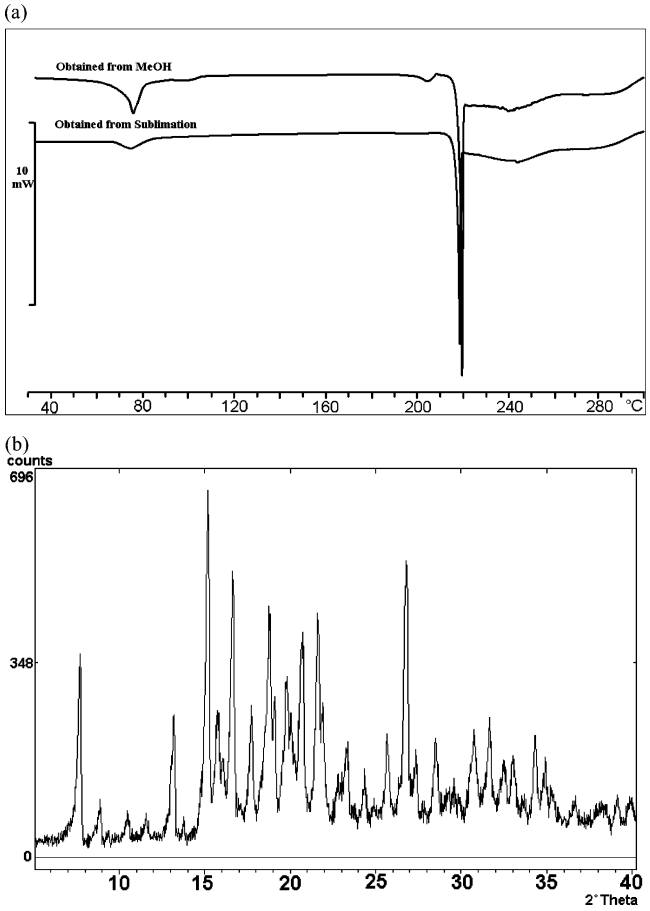


Figure 9. (a) DSC of VenHCl hydrate obtained from form 5 after 1 day in open air (below) and hydrate form 4 prepared by crystallization from MeOH (above). The endotherm at 80 °C is loss of solvent/water. (b) Powder XRD of the lower DSC curve material matches with hydrate form 4.

material is left in open air for 1 day (25−30 °C, RH 40−50%), it turns to hydrate form 4 (Figure 9).

In light of the above results, the controlled heat−cool−heat DSC experiments of Figure 6 may be interpreted as follows. Heating form 1 to 219 °C, beyond the higher temperature small endotherm, results in transformation to form 3, as shown by the solidification exotherm at 110 °C and melting endotherm at 200 °C in Figure 6a. Form 2 transforms to form 5, which shows a sharp melting endotherm at 218−219 °C when it is heated to 213 °C just after the endo−exo peak (Figure 6b). Our interpretation is that form 2 completely transforms to sublimation form 5. On the other hand, part of form 1 converts to form 3 and the balance to form 5, and the latter vaporizes on further heating. Careful examination of the intensity and duration of FT-IR peaks in the 220−260 °C range of TG measurements (see 3D spectra in Figure S4, Supporting Information) shows more intense vibration maxima for form 2 than for form 1. It is clear that the phase from sublimation (form 5) does not have an indefinite lifetime; once it is formed, heating must be continued to evolve the vapor.

Morphological and phase changes in form 1 and 2 and the thermal events leading to sublimation of form 5 were studied by HSM. Photomicrographs in Figures 10 and 11 show snapshots of the transformation of both solids to form 5. While the extent of vaporization is almost complete when starting from form 2, it is partial

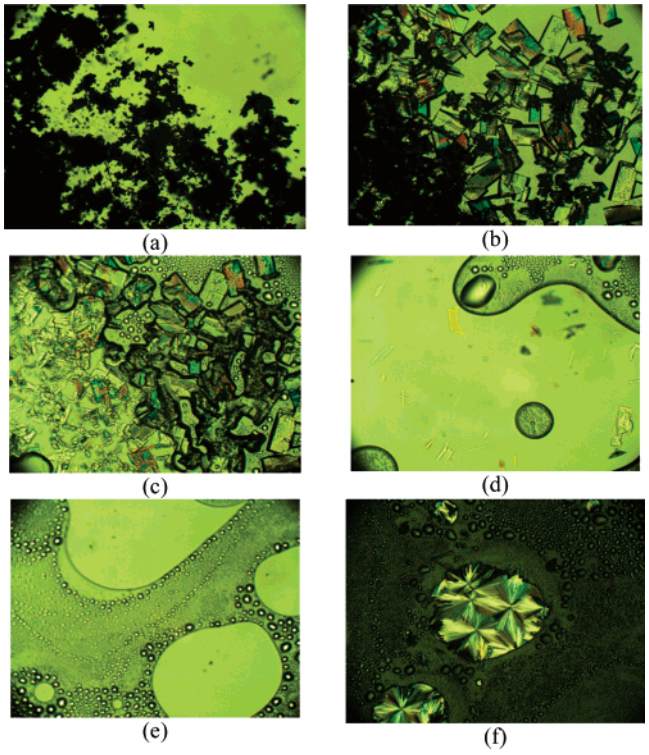


Figure 10. HSM of form 1: (a) 30 °C, microcrystalline and powder sample; (b) 150−190 °C, crystals begin to appear and increase in concentration; (c) and (d) 209−210 °C, melting starts and ends immediately; (e) 215−216 °C, glassy phase appears (form 5); (f) recooled solid shows microcrystallinity under polarized light. Bubbling of droplets indicates vaporization of form 5 between 218 and 230 °C. Selected frames of thermal events between 200 to 220 °C may be viewed in PPT format (see VenlaSI-form1-200-220.ppt file, Supporting Information).

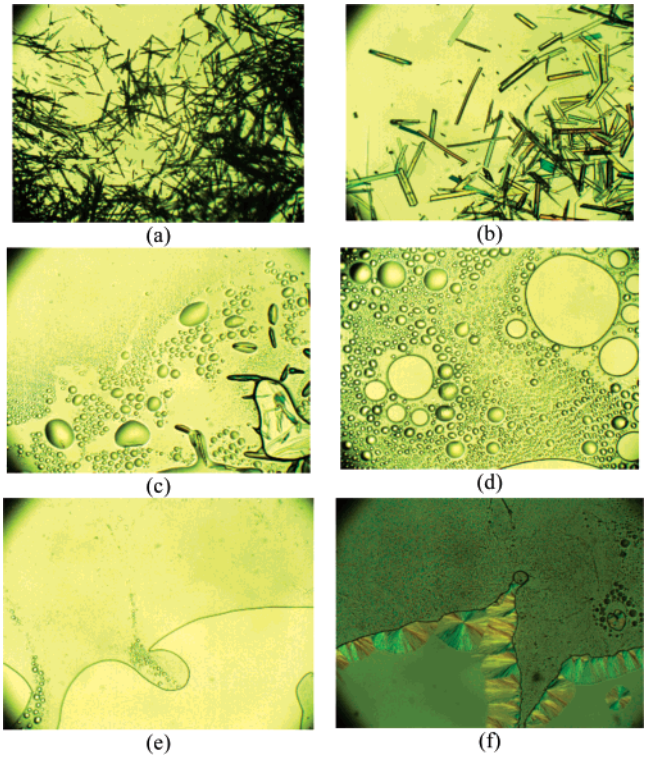


Figure 11. HSM of form 2: (a) 30 °C, needle shaped crystals; (b) 150−195 °C, small crystals begin to appear and become large, flat ones; (c) 208−209 °C, melting starts and ends immediately; (d) 213−217 °C, becomes glassy like droplets (form 5); (e) 217−218 °C, melting of form 5 (endotherm peak 2 of Figure 5b); (f) re-cooled solid shows microcrystallinity under polarized light. Complete vaporization of form 5 between 220 and 240 °C. Selected frames of thermal events between 200−225 °C may be viewed in PPT format (see VenlaSI-form2-200-225.ppt file, Supporting Information).

in case of form 1. The HSM measurements confirm our interpretations of DSC thermograms in Figure 6 and the existence of transient, glassy phase form 5.

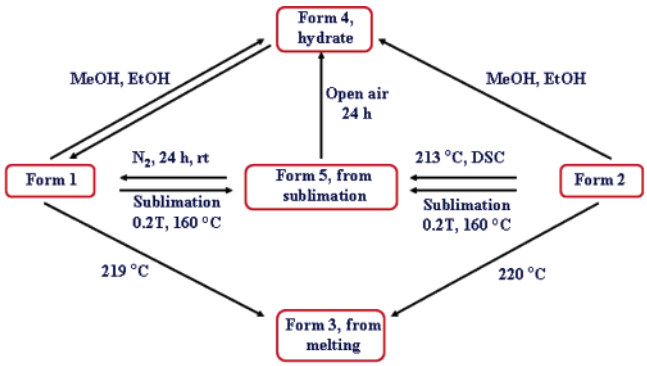
The two main polymorphs of VenHCl used in drug formulations are forms 1 and 2. Which is the kinetic form and which is the thermodynamic one? Melting points of these forms are nearly the same (in the range 210−213 °C on Fisher−Johns and 208−210 °C from HSM), although form 1 has 1 °C higher T_{onset} and T_{peak} values than form 2 (Table 3, Figures 6, 10, and 11). It is difficult to accurately measure the correct melting point because of a ±1 °C variation depending on the method used (T_{onset} or T_{peak} in DSC, visual observation of melting in HSM). We use crystal density and lattice energy as a guide for polymorph stability (Table 4). Crystal lattice energy (Cerius^2, Compass force field) of form 2 ($P2_1/n$) is lower than form 1 ($Pca2_1$) by 2.0 kcal/mol per unit cell, a value that is in agreement with energy differences between polymorphs. Furthermore, form 2 has higher density than form 1. We therefore conclude that form 2 is more stable. Our conclusion is consistent with the same hydrogen bond motif in their crystal structures and the slightly better close packing of hydrophobic groups in form 2 than form 1 (see Figure 4). The "infrared rule"[12] says that in hydrogen-bonded polymorphic structures (with similar hydrogen bond motifs) the structure with the higher frequency in bond stretching modes may be assumed to have the larger entropy. The highest ν_s in the IR spectrum of form 1 is at 3323 cm^{-1} and in form 2 at 3350 cm^{-1} (Table S1, Supporting Information). This means that form 2 has larger entropy or weaker intermolecular hydrogen bonds. Form 1 has stronger O−H···Cl$^-$ and N$^+$−H···Cl$^-$ hydrogen bonds in accordance with its lower bond stretch vibration, an observation that is supported by the hydrogen bond energy component to the crystal lattice (Cerius^2, Dreiding2.21 force field): form 1 = −5.38 and form 2 = −4.72 kcal/mol per molecule. Grinding experiments with forms 1 and 2 point toward the latter modification showing phase transformation. When form 2 was powdered in a ball mill for 20 min, it partially converts to the hydrate form 4 by absorbing moisture from the atmosphere. On the other hand, form 1 does not transform on ball milling (Figure S8, Supporting Information). We have not observed transitions between forms 1 and 2 in our experiments. Given that the melting point of both forms 1 and 2 is a few degrees below the phase transition temperature, it means that these polymorphs are monotropically related in the ambient to 220 °C range.[3c] Accurate calculation of the

Table 4. Calculated Lattice Energies[a] of Forms 1 and 2 of VenHCl[b]

crystal lattice	Form 1	Form 2
total energy	−154.57	−155.09
van der Waals	−13.25	−14.49
Columbic	−141.32	−140.60
density at 298 K (g/cm^3)	1.181	1.198

[a] Cerius^2, Compass force field, in kcal/mol. [b] Per molecule in the unit cell.

Scheme 1. Phase Transformations in VenHCl Polymorphs 1−5



enthalpy and entropy of melting from DSC is complicated by the fact that the melting endotherm in form 2 follows through with an exotherm. Further experiments and more accurate computations are needed to confirm the relative stability of VenHCl polymorphs 1 and 2.

Our results on the preparation, characterization, and phase transformations in VenHCl polymorphs are summarized in Scheme 1. Dehydration of form 4 to form 1 and rehydration is reversible and the structures of these crystalline solids are different based on powder XRD analysis. It would be interesting to study the kinetics of the transient form 5 converting to hydrate form 4, i.e., whether it is a direct transformation or involves form 1 as an intermediate.

During the course of our studies, we crystallized venlafaxine base from several solvents (see Experimental Section). Single-crystal X-ray diffraction afforded structure solution in monoclinic space group $P2_1/c$.[13] Our preliminary inference is that polymorphism in Ven base is not as likely as in VenHCl. The intramolecular O−H···N interaction shown in Figure 12 (1.77 Å, 145.8°) ties up the molecule in a single conformation. Crystalline polymorphs 1 and 2 of VenHCl are conformational polymorphs.[8]

Conclusions

We describe thermal, spectral, and structural analysis of five polymorphs of VenHCl by manual screening, which puts this substance into the category of highly polymorphic drug compounds. Compounds exhibiting more than three polymorphs are classified as "highly polymorphic".[4d] High-throughput survey of crystal polymorphs in another SSRI drug, setraline hydrochloride,[14] shows the presence of amorphous glass, metastable phase, transient hydrate, melt phase, solvates, and dehydrated phases. Although several polymorphs of VenHCl are disclosed in patents, their interrelationships, phase transitions, and relative stability have not been systematically examined. Furthermore, DSC thermograms and melting points of forms 1 and 2 in the patent literature are not consistent (Table 2). Polymorphs were incompletely characterized, at times using only a single technique, which makes it difficult to assign the modification confidently and to confirm its phase purity. Ideally, multi-instrument measurements (e.g., DSC, TGA, FT-IR, Raman, powder XRD, SC-XRD, SS-NMR) should match the signature of a particular polymorph to establish its identity and purity. Our analysis of VenHCl polymorphs is based on combined data from DSC, TGA, HSM, FT-IR, and XRD measurements. Our thermochemical analysis highlights the importance of slow scan rates in DSC because the small endotherms are observed only at 2 K/min but are not noticeable at 10 K/min. In addition to confirming the presence of four reported forms 1−4 of VenHCl with better characterization, we also show that there is a new phase, form 5, obtained by sublimation. Form 5 is short-lived (stable for few hours up to 1 day) under inert conditions. It transforms to hydrate form 4 in open air and to form 1 upon keeping in dry conditions. All four polymorphs of VenHCl, forms 1−4, show vaporization to the sublimation phase at 220−260 °C as confirmed by TG-IR. Whereas TG-IR has so far been used to analyze vapors evolved from solvated crystals (host−guest compounds),[15] we show that this coupled technique may also be used to identify sublimation of a polymorphic substance. Crystal lattice of form 2 is more stable than form 1, but it is the former modification that transforms partly to hydrate form 4 on ball milling. Form 1 is kinetically stable to further transformation under induced pressure. Hence form 1 VenHCl is the preferred solid modification for formulation in caplets and capsules. Our conclusions are based on results from 3−4 consistent measurements. Phase transitions of forms 1 and 2, search for new polymorphs of VenHCl, and further studies using HSM and VT-PXRD are the subject of continuing investigations in our group.

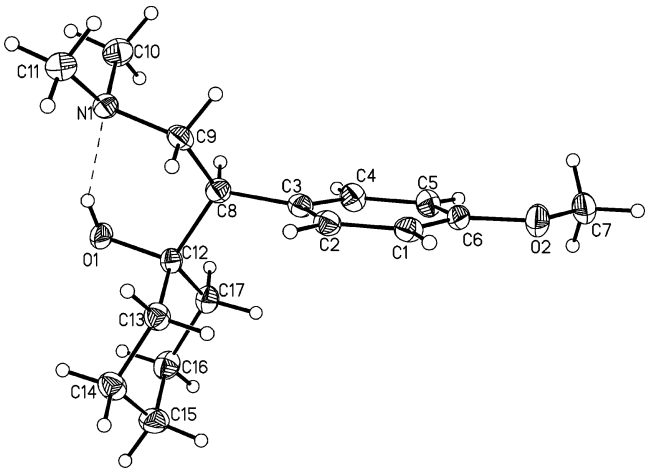


Figure 12. ORTEP diagram of venlafaxine free base to show the intramolecular O−H···N (1.77 Å, 145.8°) hydrogen bond. Thermal ellipsoids are drawn at 50% probability level.

Experimental Section

Thermal Analysis. DSC was performed on a Mettler Toledo DSC 822e module and TGA was performed on a Mettler Toledo TGA/SDTA 851e module. Samples were placed in open alumina pans for the TG experiments and in crimped but vented aluminum sample pans for DSC experiments. The typical sample size is 4−6 mg for DSC and 9−12 mg for TGA. Temperature range was 30−300 °C @ 2 K/min. Samples were purged by a stream of nitrogen flowing at 150 mL/min for DSC and 50 mL/min for TG. The TG instrument is coupled to a Bruker Tensor FT-IR spectrometer for evolved gas analysis. The evolved vapors from TGA instruments were passed through a coupled heated transfer line at 120 °C and characterized with a DlaTGS detector. For TGA-IR analysis, the sample size is 9−12 mg, the heating rate is 10 K/min, and the N_2 flow @ 50 mL/min.

HSM was performed on a PolythermA hot stage and Heiztisch microscope supplied by Wagner & Munz. A Moticam

1000 (1.3 MP) camera supported by software Motic Image Plus 2.0ML is used to record images and videos. About 1−2 mg of the sample was heated @ 5 K/min up to 205 °C and then @ 2 K/min from 205 to 230 °C.

Crystallization Experiments. Form 1: VenHCl form 2 was dissolved in 8 times i-PrOH at 65 °C. The clear solution was seeded with 10% form 1 crystal and cooled to 25 °C over 5−6 h. The product was filtered and dried under reduced pressure to get form 1 (form 2 of US 2003/0109585 Al[2g]).

Form 2: VenHCl was dissolved in 16 times *i*-PrOH at 65 °C to get a clear solution and then cooled to 5 °C in 1 h. The product was filtered and dried under reduced pressure to get form 2 (form 1 of US 2003/0109585 A1[2g]).

Phase from melting (form 3): 100 mg of VenHCl was taken in a test tube and heated to 215 °C in an oil batch until the compound melted (∼1 h). Upon slow cooling, the melt phase was obtained.

Hydrate form 4: 100 mg of VenHCl was dissolved in 5 mL of MeOH or EtOH and left at ambient temperature. The precipitated solid material after 3 days is form 4. The hydrated form is also obtained from the sublimed material when it is left in open air for 1 day.

Phase from sublimation (form 5): 100 mg of VenHCl was taken in a sublimation apparatus and heated to 140−160 °C at reduced pressure (0.2 Torr) for 1 h. The sublimed material was obtained as a glassy, amorphous mass. The semisolid compound was collected and stored in inert N_2 atmosphere. The sublimed material is unstable and transforms to hydrate form 4 after 1 day in open atmosphere (25−30 °C, RH 40−50%).

Crystals of form 1 (orthorhombic) were obtained from MeCN/DMF solvent mixture and form 2 (monoclinic) was crystallized from EtOAc/MeOH at room temperature. Their cell parameters match with refcodes WOBMUV and WOBMUV01 in the CSD, and their structures were established by single-crystal X-ray diffraction.[8] Form 1: 5.905(2), 26.385(4), 11.491(2) Å. Form 2: $a = 5.793(1)$, $b = 26.10(1)$, $c = 11.727(4)$ Å, $\beta = 100.67(2)°$. Crystals of form 2 were ground in a ball mill for 15 min. The resulting powder pattern is a mixture of form 2 and hydrate form 4 (see peaks at $2\theta = 15.05, 26.74°$ in Figure S8, Supporting Information). Powder XRD of form 1 is unchanged after ball mill grinding.

Venlafaxine base was crystallized from various solvents to obtain single crystals, e.g., MeOH, EtOH, EtOAc, CH_2Cl_2, MeCN, dioxane, THF, DMSO, and $CHCl_3$. Single crystals suitable for X-ray diffraction were obtained from EtOAc and DMSO. The unit cell of Ven base is (crystallized from DMSO/EtOAc): $a = 8.2778(17)/8.2688(24)$, $b = 8.8436(17)/8.8134(23)$, $c = 21.479(4)/21.4604(43)/92.228(25)$ Å, $\beta = 92.438(30)/92.228(25)°$. These cell values match the recently reported crystal structure of venlafaxine base (CSD refcode OCALAG).[13]

X-ray Diffraction. Single-crystal XRD measurements were carried out on an Bruker SMART APEX CCD area detector using Mo−Kα radiation. The unit cell for form 2 was determined at 298 K and for venlafaxine free base at 100 K.

Powder XRD of all samples were recorded on a PANlytical 1830 (Philips Analytical) diffractometer using Cu−Kα X-radiation at 35 kV and 25 mA. Diffraction patterns were collected over 2θ range of 5−50° at scan rate of 1 °/min. The program Powder Cell[2.3] was used for Rietveld refinement[16] (see Tables S2 and S3 for the coordinates of refined structures, Supporting Information).

Lattice Energy Calculations. The minimized lattice energy of polymorphs 1 and 2 was calculated in Cerius[2] with Compass and Dreiding2.21 force fields.[17] Crystal lattice energies in Table 4 are calibrated for the number of molecules in the unit cell (per molecule).

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Supporting Information Available: Figures S1−S8, Tables S1−S3, and thermal transformation of forms 1 and 2 on HSM are available free of charge via the Internet at http://pubs.acs.org.

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