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Solid-state evaluation and polymorphic quantification of venlafaxine hydrochloride raw materials using the Rietveld method

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ABSTRACT

Venlafaxine hydrochloride (VEN) is an antidepressant drug widely used for the treatment of depression. The purpose of this study was to carry out the preparation and solid state characterization of the pure polymorphs (Forms 1 and 2) and the polymorphic identification and quantification of four commercially-available VEN raw materials. These two polymorphic forms were obtained from different crystallization methods and characterized by X-ray Powder Diffraction (XRPD), Diffuse Reflectance Infrared Fourier Transform (DRIFT), Raman Spectroscopy (RS), liquid and solid state Nuclear Magnetic Resonance (NMR and ssNMR) spectroscopies, Differential Scanning Calorimetry (DSC), and Scanning Electron Microscopy (SEM) techniques. The main differences were observed by DSC and XRPD and the latter was chosen as the standard technique for the identification and quantification studies in combination with the Rietveld method for the commercial raw materials (VEN1–VEN4) acquired from different manufacturers. Additionally Form 1 and Form 2 can be clearly distinguished from their ^{13}C ssNMR spectra. Through the analysis, it was possible to conclude that VEN1 and VEN2 were composed only of Form 1, while VEN3 and VEN4 were a mixture of Forms 1 and 2. Additionally, the Rietveld refinement was successfully applied to quantify the polymorphic ratio for VEN3 and VEN4.

1. Introduction

Since pharmaceutical solids can have different crystalline structures, polymorphism is a major concern for the pharmaceutical industry in the development of new drugs and in relation to the stability of drugs, since different structures may have different properties that can influence the performance of the drug product [1–3].

Polymorphism is defined as the possibility for a substance to have two or more crystalline forms. The polymorphs differ in terms of their internal solid-state structure and the arrangement and/or conformation of the molecules in the crystalline lattice. Thus, they have significant commercial and industrial implications in various fields [2].

The different polymorphs can show distinct physical properties, such as melting point, solubility, dissolution rate and stability (physical and chemical), which may affect their pharmaceutical processing, therapeutic efficacy, bioavailability, performance, and quality. These concerns have led to increased regulatory requirements by the Food and Drug Administration (FDA) in order to avoid problems related to polymorphism [3–5].

Understanding the differences in the physical properties of the polymorphs and their relative stabilities is therefore essential for the pharmaceutical manufacturers in relation to the selection of a particular form that has the desirable characteristics for the administration of the medicines [6,7].

Venlafaxine hydrochloride (VEN), Fig. 1, chemically known as ±1-[2-(dimethylamino)-1-(4-methoxyphenyl)-ethyl] cyclohexanol hydrochloride, is an antidepressant drug that acts by simultaneously blocking the re-uptake of neuronal norepinephrine and serotonin [8–10]. VEN is a widely prescribed antidepressant drug with sales of US $3.7 billion per annum [11,12].

The recrystallization of VEN can yield crystals with two different morphologies, that is, blocks (Form 1) and needles (Form 2). The crystal structure of Form 1 lies in the orthorhombic space group $Pca2_1$ according to Vega et al. [13] while Form 2 lies in the monoclinic space group $P2_1/n$, as reported by Sivalakshmidevi et al. [14]. Although the polymorphs do not show significant differences *in vivo*, Roy et al. [7] have reported that Form 2 is preferable for the formulation because it has a larger particle size with better filtration and drying characteristics. However, Form 2 is under patent and some countries do not

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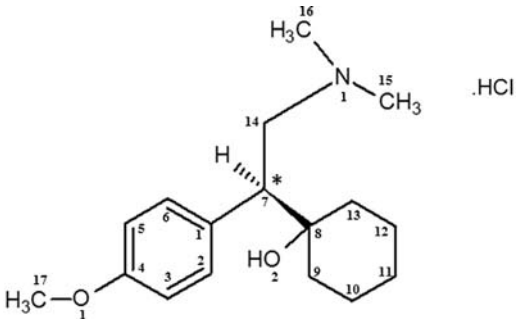

Fig. 1. Chemical structure of venlafaxine hydrochloride.

allow the use of this patented form in pharmaceutical formulations [7,15,16].

To ensure the ideal polymorphic form for the development of new formulations and to guarantee the reproducibility and the reliability of the quality control test procedures applied to the final products, the raw material needs to be well characterized prior to use [5,17]. Different strategies for a systematic study of polymorphism can be applied and usually involve a combination of different techniques [18].

X-ray powder diffraction (XRPD) is one of the most commonly used techniques for studying polymorphs. It is the "standard" procedure for differentiating polymorphs, since each crystal form produces a diffraction pattern that can be used as its fingerprint and can thus be employed to screen polymorphs during drug discovery, formulation development, and manufacturing [19]. Differential scanning calorimetry (DSC), Raman spectroscopy (RS), diffuse reflectance infrared Fourier transform spectroscopy (DRIFT), solid state nuclear magnetic resonance (ssNMR) and scanning electron microscopy (SEM) are, among other techniques, also applied in the characterization of polymorphs [19–22].

The aim of this study was to carry out the preparation and solid state characterization of the pure VEN polymorphs (Form 1 and Form 2) through different techniques: XRPD, DRIFT, RS, ssNMR, DSC and SEM. Additionally, the evaluation of VEN raw materials purchased from various suppliers was carried out employing XRPD followed by the Rietveld refinement method in order to identify the presence and the amount of each polymorphic form.

2. Materials and methods

2.1. Materials

Venlafaxine hydrochloride (CAS 99300-78-4) raw materials were obtained from different suppliers and were identified as VEN1–VEN4. All chemicals used were of pharmaceutical analytical grade.

2.1.1. Preparation of polymorphs

To obtain the monoclinic form (Form 2), approximately 50 mg of VEN1 was dissolved in 4 mL of methanol:ethyl acetate (1:8, v:v) and the solution was subjected to low temperature (3–8 °C) until VEN crystallization was complete [14]. To obtain the orthorhombic form (Form 1), an amount corresponding to around 50 mg of VEN was dissolved in 2 mL of dichloromethane and allowed to slowly evaporate under ambient conditions for 5 weeks until all of the solvent had evaporated. The pure phases 1 and 2 were confirmed by comparing their XRPD patterns with those calculated from Refs. [13,14].

2.2. Methods

2.2.1. Scanning electron microscopy (SEM)

The morphological characteristics of VEN Forms 1 and 2 and the four raw materials were observed by scanning electron microscopy (Phillips XL30). Samples were mounted on metal stubs using double-side adhesive tape, vacuum-coated with gold (350 Å) in a Polaron E 5000 sputter coating unit and directly analyzed by SEM (2000 ×).

2.2.2. Assay of VEN raw material by HPLC

The assaying of the VEN raw materials was carried out by a previously validated stability-indicating HPLC method [23].

2.2.3. Powder X-ray diffractometry (PXRD)

The diffraction patterns for VEN were obtained on a Stoe STADI-P powder diffractometer using Cu $K\alpha_1$ radiation selected by a Ge (111) curved monochromator, with a tube voltage of 40 kV and current of 40 mA, and the signals were detected on a multistrip silicon detector (Mythen 1 K). The samples were loaded into 0.7-mm borosilicate glass capillaries that were kept spinning during the data collection in the range of 5–50° (2θ) with step sizes of 0.015° and 60 s of integration time for every 1.05°.

2.2.4. Polymorphic quantification methodology—Rietveld refinements

The polymorphic quantification of the raw materials VEN3 and VEN4 was carried out by means of the Rietveld method using the software program Topas Academic v.4.1 [24] and the published structural data [13,14] for venlafaxine hydrochloride. The background was fitted using a 12-term Chebyschev polynomial. The peak asymmetry was fitted applying the simple axial divergence model of Cheary and Coelho [25,26]. The peak profiles were modeled by the Double–Voigt approach with anisotropic peak profiles adjusted using the 4-term preferred orientation spherical harmonics of the crystals. Both the peak asymmetry and the peak profiles were kept fixed during the refinement of the VEN samples. The values were obtained from the refinement of a Si (SRM-640c) standard reference material distributed by National Institute of Standards and Technology (NIST, USA). Only the terms describing the preferred orientation of the crystallites were then refined. An analytical correction was applied in order to reduce aberrations affecting data collected with 1D position-sensitive detectors in the Debye–Scherrer capillary geometry [27].

2.2.5. Differential scanning calorimetry (DSC)

DSC curves were recorded using a Shimadzu DSC-60 cell under dynamic atmosphere with a 50 mL min^{-1} nitrogen flow rate. Approximately 2 mg of each sample of VEN powder were weighted out and placed in a sealed aluminum pan; an empty aluminum pan was used as the reference. A heating rate of 2 °C min^{-1} was employed over the temperature range of 30–250 °C.

2.2.6. Diffuse reflectance infrared Fourier transform spectroscopy (DRIFT)

The DRIFT spectra were acquired on a Shimadzu spectrophotometer (Prestige) in the range of 400–4000 cm^{-1} (average of over 32 scans) at a spectral resolution of 4 cm^{-1} in KBr. A background spectrum was obtained for each experimental condition.

2.2.7. Raman spectroscopy (RS)

Raman spectra were collected in a backscattering geometry using an Agiltron PeakSeeker 785 PRO Raman system (Woburn, MA, USA) with a diode laser of 785 nm and 300 mW at the source. The Raman radiation collected was dispersed with a grating and focused on a Peltier-cooled charge-coupled device (CCD) detector obtaining a spectral resolution of 6 cm^{-1}. The laser was focused on the sample by the 20 × objective lens of a microscope. All spectra were recorded in the spectral window of 200–2000 cm^{-1} with the same acquisition time (15 s). The powders were analyzed on glass slides at room temperature.

2.2.8. Solid-state ^{13}C nuclear magnetic resonance (ssNMR)

High resolution ^{13}C solid state spectra for both Forms 1 and 2 were recorded using the ramp CP/MAS sequence with proton decoupling during acquisition. The solid state NMR experiments were performed at room temperature in a Bruker Avance II spectrometer operating at 300.13 MHz for protons and equipped with a 4 mm MAS probe. The operating frequency for carbon was 75.46 MHz. Adamantane was used as an external reference for the ^{13}C spectra and to set the Harmann–Hahn matching condition in the cross-polarization experiments. The spinning rate was 10 kHz. The values for the number of transients were 512 and 1024 for Forms 1 and 2, respectively, in order to obtain an adequate signal to noise ratio. The recycling time was 10 s for Form 1 and 6 s for Form 2, the contact time during CP was 3 ms and the acquisition time was 41 ms for the two samples. The SPINAL 64 sequence was used for decoupling during acquisition with a proton field H_{1H} satisfying $\omega_{1H}/2\pi = \gamma H$ $\omega_{1H}/2\pi = 78.2$ kHz. Quaternary carbon spectra were recorded for the two samples. These spectra were acquired with the non-quaternary suppression (NQS) sequence, where the ^{1}H and ^{13}C radio-frequency (rf) fields are removed for 40 μs after CP and before the acquisition. This delay allows the carbon magnetization to decay because of the ^{1}H–^{13}C dipolar coupling, resulting in spectra where CH and CH_2 are substantially removed. This experiment thus allows quaternary carbon signals and methyl groups to be identified.

3. Results and discussion

3.1. Solid state characterization of venlafaxine hydrochloride Forms 1 and 2

In order to obtain a pure sample of each different crystalline forms of VEN recrystallization experiments were carried out. The pure Forms 1 and 2 were confirmed by comparing their X-ray powder diffraction (XRPD) patterns with the powder patterns calculated from crystal structures deposited in the Cambridge Structural Database (CSD) (Fig. 2) [28,29].

The assay results for the polymorphic forms and commercial samples of VEN were > 99.8%, when evaluated by the stability-indicating HPLC method [23].

During the crystallization of a substance, external factors can induce the formation of a particular crystalline habit. The crystal morphology plays an important role in pharmaceutical processing and the development of solid dosage forms. Differences in the crystal habit may strongly influence the particle orientation and modify the flowability, packing, compaction, compressibility and dissolution characteristics [30,31].

The SEM analysis (Fig. 3A) showed two different morphologies in agreement with the blocks (Form 1) and needles (Form 2) reported in the literature. The crystal of Form 1 exhibited an irregular surface with the appearance of overlapped non-ordered plates. On the other hand, the larger crystals of Form 2 exhibited a regular acicular habit with a well-defined surface. Fragments of crystals were deposited on the surface and the smaller acicular crystals showed a tendency to agglomerate. Roy et al. [7] have reported that Form 2 has a larger particle size, being preferable for this formulation; however, the particle sizes of VEN Forms 1 and 2 were not measured in this study.

The fundamental frequency positions in the DRIFT spectra (Fig. 4A) of both polymorphic forms showed the characteristic vibrations of VEN, a broad peak related to O–H vibrations at 3450–3200 cm^{-1}, stretching vibrations of C=C at 1513 cm^{-1}, followed by C–O–CH_3 stretching at 1246 cm^{-1} and the resonance band at 1183 cm^{-1} for N–C vibrations [32].

The DRIFT spectra of VEN Forms 1 and 2 did not reveal significant differences that could be used to distinguish the two forms. The main difference was observed only in the large broad peak related to the O–H vibrations of Form 2. On the basis of the OH vibrations, a broadening of this band is related to the formation of hydrogen bonds due to the position of the molecules in the crystalline cell, conferring higher stability to the structure of Form 2. These results are in agreement with the DSC data, which revealed a higher melting point for Form 2.

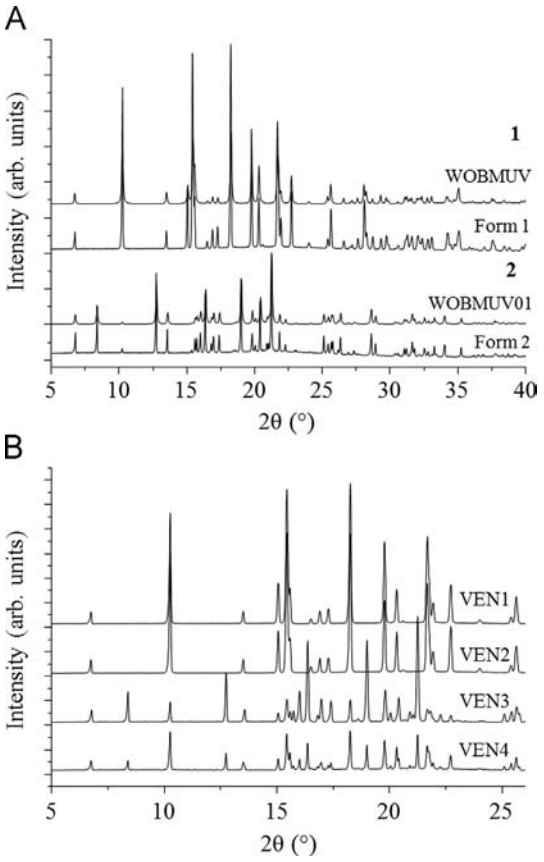

Fig. 2. (A) XRPD patterns (1) Form 1 experimental and calculated (WOBMUV) and (2) Form 2 experimental and calculated (WOBMUV01); and (B) XRPD patterns of VEN polymorphs: raw material (VEN1–VEN4).

The Raman spectra of the pure Forms 1 and 2 in the range of 200–2000 cm^{-1} are presented in Fig. 4B. The features in the spectra for Forms 1 and 2 are basically the same, although the former presented slightly sharper peaks with different relative intensities between 800 and 880 cm^{-1} and a higher baseline. The baseline increase is attributed to fluorescence effects from an undefined source, since no degradation was observed. Also, it could be related to a photo-induced phenomenon. The relative intensities between 800 and 880 cm^{-1} and the peaks at 1470, 1300, 1250, and 980 cm^{-1} may be used to develop a probe to distinguish between Forms 1 and 2.

The DSC curves for Forms 1 and 2 of VEN obtained at 2 °C min^{-1} are shown in Fig. 5A and Table 1. The DSC curve for Form 1 revealed a single sharp endothermic peak even at 208.34 °C (T_{onset}=207.77 °C; $\Delta H_{fusion} = -106.14$ J g^{-1}), corresponding to the VEN melting point. The DSC curve for Form 2 showed a single endothermic event at 214.09 °C (T_{onset}=213.61 °C; $\Delta H_{fusion} = -131.52$ J g^{-1}) also corresponding to the melting point.

The characterization of VEN polymorphs using DSC has been previously described in the literature. However, in the related papers and patents the DSC curves and melting points reported for Forms 1 and 2 are not always consistent [7,13,14,16].

Roy et al. [16] described that the DSC curves for both forms showed two endothermic events. The DSC curve for Form 1 exhibited a

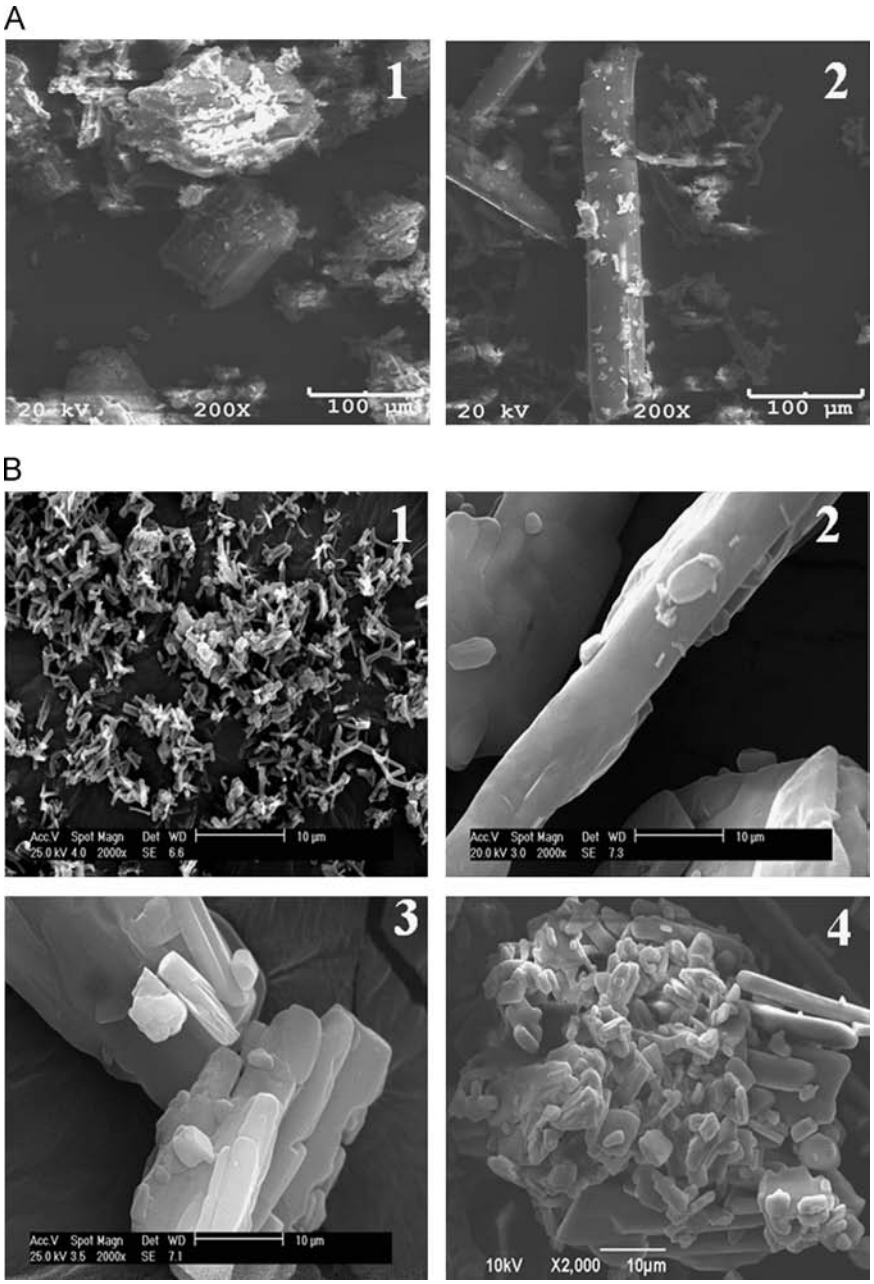

Fig. 3. (A) SEM photomicrographs of the two polymorphic forms of VEN. (1) Blocks (Form 1) and (2) needles (Form 2) at 200 × magnification; and (B) SEM photomicrographs of (1) VEN1; (2)—VEN2; (3)—VEN3; and (4)—VEN4; at 2000 × magnification.

major endothermic peak at 210–211 °C and a minor peak at 214–215 °C, and the DSC curve for Form 2 displayed an endothermic peak in the same temperature range observed on the curve for Form 1 (208–209 °C and 215–216 °C) but with the relative size of the peaks reversed [7,16]. Thus, our results are not in agreement with those obtained by these authors. In order to confirm the identity and purity of our polymorphs, the Rietveld method was applied and the results revealed that the recrystallized Forms 1 and 2 were 100% pure forms.

The two polymorphs of VEN were also studied by ssNMR. The ^{13}C NMR spectra for VEN Forms 1 and 2 are shown in Fig. 6. The assignments for the ^{13}C spectra (see carbon numbering in Fig. 1) were carried out taking into account the quaternary carbon spectra and by comparing with the solution ^{13}C spectra and simulations obtained from the commercial software. The ^{13}C ssNMR chemical shifts for both forms are displayed in Table 2 together with the solution NMR ^{13}C chemical shifts. The two solid forms can be clearly distinguished based on their high resolution ^{13}C ssNMR spectra. The ^{13}C spectra for Forms 1 and 2 showed distinct resonances for each carbon in the molecule and the two polymorphs have a single molecule in the asymmetric unit. Despite their distinct ^{13}C spectra, the difference in the chemical shifts for the two cases indicates that the molecular conformations of the two polymorphs are very similar or that crystal packing effects have equally large effects, compensating for conformational differences in the chemical shifts. These finding are in agreement with the X-ray results [13,14], verifying the physical purity of the forms.

Polymorphic Forms 1 and 2 were readily distinguishable from their XRPD patterns (Fig. 2A). The XRPD pattern for Form 1 exhibited two characteristic peaks with diffraction of significant intensity at 10.3° and 20.3° (2θ). In addition, peaks at 15.1°, 18.31° and 22.75° (2θ) are present only in the case of Form 1. The pattern for Form 2 showed three Bragg peaks at 2θ (8.4°, 12.78° and 16.41°), which are not present in the case of Form 1. These angles were used for the polymorphic characterization of the commercial samples.

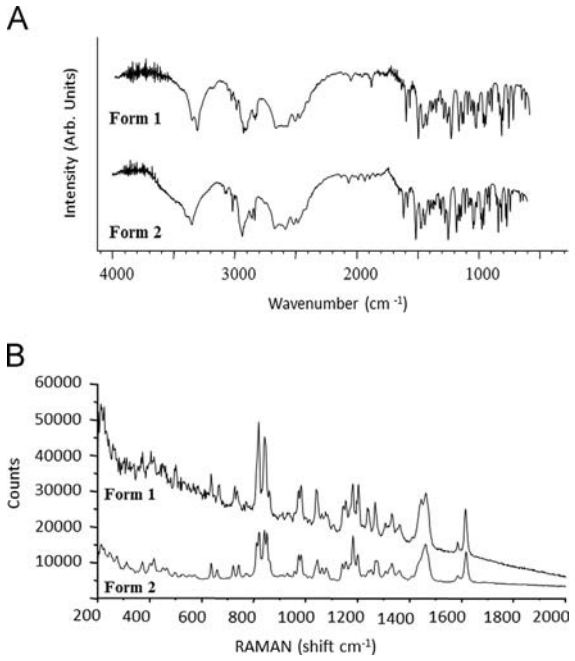

Fig. 4. (A) DRIFT spectra: VEN Forms 1 and 2 and (B) Raman spectra: VEN Forms 1 and 2.

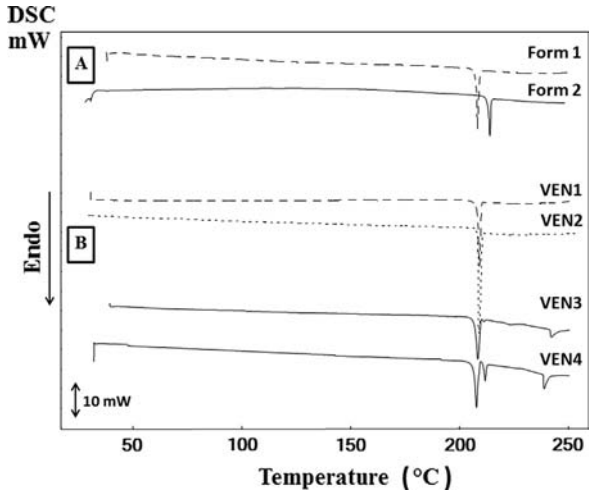

Fig. 5. DSC curves of VEN: (A) Form 1 (dashed lines) and Form 2 (solid lines); and (B) VEN1–VEN4 obtained with heating rate of 2 °C min^{-1}.

3.2. Solid state characterization of venlafaxine hydrochloride commercial raw materials

The SEM images of the VEN raw materials (Fig. 3B) confirmed the differences in the crystalline habit, morphology and particle size of Forms 1 and 2. The VEN2, VEN3 and VEN4 samples showed mixtures of particles in the shape of rods and irregular plates (with the particle size and frequency of aggregates differing between samples). VEN2 showed large dispersed plates with regular surfaces. The surfaces of the VEN3 crystals presented rough and uneven edges and the crystals of VEN4 exhibited irregular surfaces with fissures and a tendency to form agglomerates. VEN1 contained the smallest particles (rod-like) with well-defined smooth surfaces, which also showed a tendency to agglomerate.

The DRIFT and Raman spectra of VEN1–VEN4 showed the same characteristic vibrations for Forms 1 and 2. No significance differences were observed that could distinguish the pure phases or a mixture of VEN polymorphs in the raw materials.

Table 1
Data related to the DSC curves for venlafaxine hydrochloride raw materials (VEN1–VEN4) obtained at a heating rate of 2 °C min^{-1}.

Sample	T_{onset} (°C)	T_{peak} (°C)	ΔH (J g^{-1})
Form 1	207.76	208.34	−106.14
Form 2	213.61	214.09	−131.52
VEN1	208.60	209.40	−78.57
VEN2	208.70	209.00	−169.85
VEN3	207.15	208.60	−110.97
	210.60	211.37	−3.24
VEN4	206.90	207.95	−119.8
	211.26	211.96	−33.88

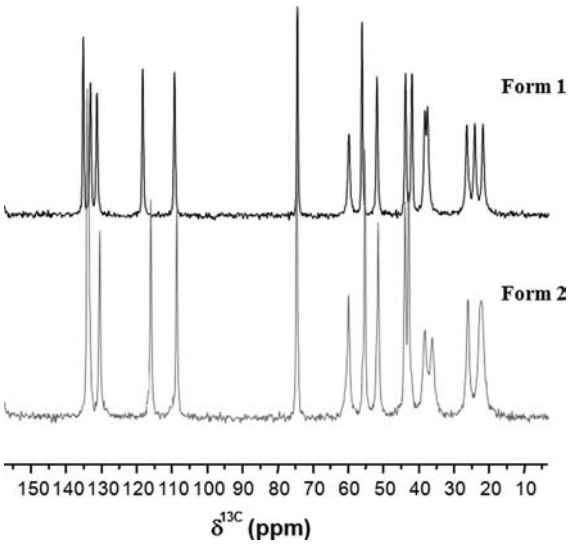

Fig. 6. ssNMR spectra of VEN Forms 1 and 2.

Table 2
^{13}C ssNMR chemical shifts for Form 1 and Form 2.

Chemical shift (ppm)			
Carbon	ssNMR		NMR ($CDCl_3$)
	Form 1	Form 2	
1	135.3	134.3	130.0
2, 6	131.4, 133.3	130.7, 133.8	130.0
3, 5	118.4, 109.4	116.1, 108.8	113.8
4	158.4	158.6	158.6
7	52.0	51.7	52.2
8	74.6	74.7	73.4
9, 13	37.8, 38.6	36.3, 38.4	31.1, 36.4
10, 12	22.0, 24.3	22.1, 22.8	21.0
11	26.6	26.2	25.1
14	60.0	60.0	59.8
15, 16	42.1, 43.9	43.0, 44.0	42.4, 44.8
17	56.3	55.4	55.0

The DSC curves for VEN1–VEN4 were obtained at 2 °C min^{-1} and the results can be observed in Fig. 5B and Table 1. On comparing the DSC curves for the polymorphic forms VEN1 and VEN2 were found to be associated with Form 1, due to the unique single sharp event at 209.1 °C, while VEN3 and VEN4 were associated with a mixture of the two polymorphic forms since two endothermic events can be observed.

The XRPD patterns of the VEN raw materials (Fig. 2B) confirmed that VEN1 and VEN2 were composed only of Form 1, whereas VEN3 and VEN4 were a mixture of the two polymorphs. It is worth highlighting that, although our experiments were performed using

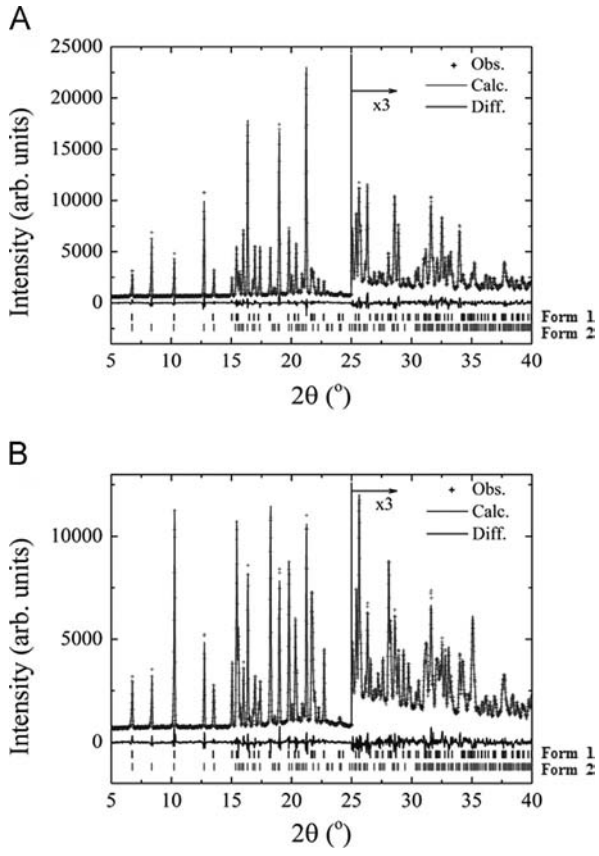

Fig. 7. Rietveld refinement plot of VEN3 (A) and VEN4 (B). *y*-axis increased three times at range 25–40° for better viewing of peaks. Obs = observed; Calc. = calculated; and Diff. = difference.

borosilicate glass capillaries, we observed a slight influence of preferred orientation effects. The XRPD technique is a quick tool able to confirm the presence/absence of the polymorphic forms in the samples, verifying that XRPD analysis should be included in routine laboratorial methods.

3.3. Polymorphic quantification using the Rietveld method and XRPD

The Rietveld method, originally developed for the refinement of crystal structures, proved to be very efficient in quantitative phase analysis, as the Rietveld scale factor of a phase relates to its relative amount in a multiphase mixture. The method has been successfully applied to the quantitative application of pharmaceutical solids in recent years [33–35]. Previous studies have demonstrated that some parameters, such as the type of sample holder, sample spinning, particle size, powder packing and preferred orientation effects, are critical in relation to acquiring XRPD patterns appropriate for use in the Rietveld analysis [33,35,36].

Initially our experiments were performed in a zero background holder and strong preferential orientation effects were observed. Therefore, the phase quantification procedure was performed using XRPD patterns collected in 0.7-mm borosilicate glass capillaries in order to minimize the preferred orientation effect. The fitting of the Rietveld refinements for samples VEN3 and VEN4 is shown in Fig. 7. The results revealed 17.5% of Form 1 and 82.5% of Form 2 (± 0.3) in VEN3, while VEN4 contained 57.5% of Form 1 and 42.5% of Form 2 (± 0.8). The goodness of fit indicator and R-factors [37] obtained for the VEN3 and VEN4 samples were: VEN3–$\chi^2 = 1.83$, $R_{wp} = 0.0600$, $R_p = 0.0422$, $R_{Bragg\_Form\_1} = 0.0198$, and $R_{Bragg\_Form\_2} = 0.0237$; and VEN4–$\chi^2 = 1.76$, $R_{wp} = 0.0542$, $R_p = 0.0408$, $R_{Bragg\_Form\_1} = 0.0191$, and $R_{Bragg\_Form\_2} = 0.0178$.

4. Conclusions

The two pure polymorphs of VEN (Form 1: orthorhombic and Form 2: monoclinic) were obtained from VEN1 through solvent recrystallization methods. The pure polymorphs and the raw materials (VEN1–VEN4) were characterized using structural, thermal and spectroscopic techniques. Forms 1 and 2 were clearly distinguished by XRPD, DSC and ssNMR. DSC and XRPD analyses showed that VEN1 and VEN2 raw materials were comprised purely of Form 1, while VEN3 and VEN4 were a mixture of the two forms. The Rietveld refinement procedure using XRPD data collected by capillary showed that VEN3 has a lower content of Form 1 and VEN4 has a higher content of Form 1. The XRPD technique is a powerful tool which can be used to confirm the presence/absence of the polymorphic forms in the samples and even quantify them, demonstrating that it should be included in routine laboratorial methods. Finally, this study showed the diversity in the solid state properties of VEN available in the market, providing information on the solid state characterization of the samples in order to improve the quality control and the reproducibility of the formulations.

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