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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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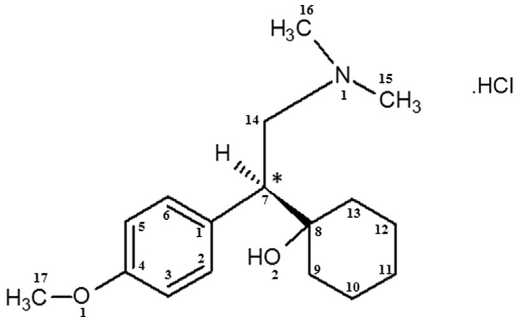

Fig. 1. Chemical structure of venlafaxine hydrochloride.

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 Kα_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.