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Characterization of venlafaxine hydrochloride and compatibility studies with pharmaceutical excipients

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Abstract The thermal analytical study of venlafaxine hydrochloride, a third generation antidepressant, was investigated using thermogravimetry (TG) and differential scanning calorimetry (DSC). The DSC curves have shown a sharp endothermic event at 211 °C and TG demonstrated a single stage of mass loss between 254 and 283 °C. Solid-state characterization was carried out by DRIFT, SEM, and XRPD demonstrating the drug physicochemical properties including crystallinity. Drug-excipient compatibility studies investigated by DSC have shown a possible physical interaction of the drug with magnesium stearate, microcrystalline cellulose and starch. Nevertheless, these results where not confirmed by DRIFT and SEM analyses.

Keywords Venlafaxine hydrochloride · Solid-state characterization · Compatibility studies

Introduction

Venlafaxine hydrochloride (VEN), (1-[2-(dimethylamino)-1-(4-methoxyphenyl) ethyl]cyclohexanol) (Fig. 1), a third generation antidepressant, inhibits the reuptake of serotonin, norepinephrine and to a lesser extent dopamine [1, 2]. VEN has been shown to be effective for treatment of major depression in a broad range of patients [3, 4].

Thermal analyses are routine methods for analysis of drugs and substances of pharmaceutical interest [5, 6]. These methods include differential scanning calorimetry (DSC) and thermogravimetry (TG), in which physical properties of a substance and/or its reaction products are measured as function of a controlled temperature program [5–7].

Studying the drug-excipient compatibility during the formulation of products is an important process to know any physical and chemical interaction between the compounds [8]. Thermal techniques have been increasingly used for evaluating possible incompatibility quickly through comparison of thermal curves of pure substances with curve obtained from a 1:1 mixture [9].

The characterization of solid-state properties at an early stage by using appropriate analytical methodologies is an essential pre-requisite in the development of solid dosage forms both from scientific and regulatory points of view [10]. Variations in physicochemical properties of the pharmaceutical active ingredient may have an impact on the therapeutic, manufacturing, commercial, and legal levels [11]. In this work, the VEN characterization and compatibility studies have been investigated by using a variety of techniques including thermal analysis (TG/DTG and DSC), diffuse reflectance infrared Fourier transform spectroscopy (DRIFT), scanning electron microscopy (SEM), and X-ray powder diffraction (XRPD).

Experimental

Materials

Venlafaxine hydrochloride bulk material was obtained from DEG (lot: VH06/0106/07). The tested pharmaceutical excipients in the compatibility studies were: starch (snow flake® 3400), sodium starch glycolate; microcrystalline

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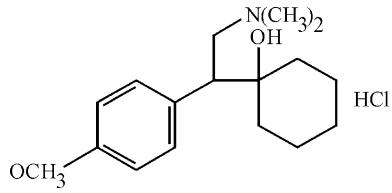

Fig. 1 Chemical structure of venlafaxine hydrochloride

cellulose (Microcel® 200); magnesium stearate; lactose monohydrate, and talc.

Preparation of physical mixtures

The interaction study was performed by using a physical mixture of VEN and excipients of equal weights (1:1 *mass/mass*). The physical mixtures were prepared through simple mixing, kept into an amber glass vials, and submitted to the analysis.

Methods

Differential scanning calorimetry

The DSC curves were obtained using a Shimadzu DSC-60 cell under dynamic nitrogen atmosphere with the flow rate of 50 mL min^{-1}. Approximately 2 mg of samples were weighted out and placed in a sealed aluminum pan. The analysis was carried out from 30 to 400 °C at a heating rate of 10 °C min^{-1}.

Thermogravimetric analysis

The TG/DTG measurements were performed in the thermobalance TGA-50 (Shimadzu), under dynamic nitrogen atmosphere with flow rate of 50 mL min^{-1}. Approximately 6 mg of the samples were placed in platinum crucibles and heated from 30 to 600 °C at a heating rate of 10 °C min^{-1}.

X-ray powder diffraction

The powder diffraction pattern of VEN was obtained in the Siemens diffractometer D5000 model, with a Cuk_α 40 kW tube and current of 40 mA, in the range of 3–65 (2θ) with a pass time of 1 s.

Diffuse reflectance infrared Fourier transform spectroscopy

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

Scanning electron microscopy

The photomicrographs were taken with a Phillips scanning electron microscope, model XL30. The sample was placed on metal stubs by using double-sided adhesive tape, vacuum-coated with gold (350 Å) in a Polaron E 5000 sputter coating unit and directly analyzed by SEM (5000× and 20,000×).

Results and discussion

Characterization of venlafaxine hydrochloride

The TG/DTG and DSC curves obtained for VEN are shown in Fig. 2. The DSC curve has shown a sharp endothermic event (T_{peak} = 211 °C; T_{onset} = 209 °C; ΔH_{fusion} = −96.75 J g^{-1}), corresponding to the melting point followed by decomposition. The TG/DTG curve has shown a single stage of mass loss between 254–283 °C (Δm = 98.5%; DTG_{peak} = 274.30 °C). The DSC data combined with TG allow evidencing a thermal stability up to 200 °C.

The DRIFT spectrum of VEN has shown a characteristic stronger band of the O–H at 3200–3420 cm^{-1}, stretching vibrations of C=C at 1513 cm^{-1}, followed by C–O–CH_3 stretching at 1243 cm^{-1} and the resonance band at 1179 cm^{-1} for N–C.

X-ray powder diffraction has been used for qualitative and quantitative identification of crystallinity [12, 13]. The XRPD patterns of VEN (Fig. 3) revealed several diffraction peaks which indicate its crystalline character. The

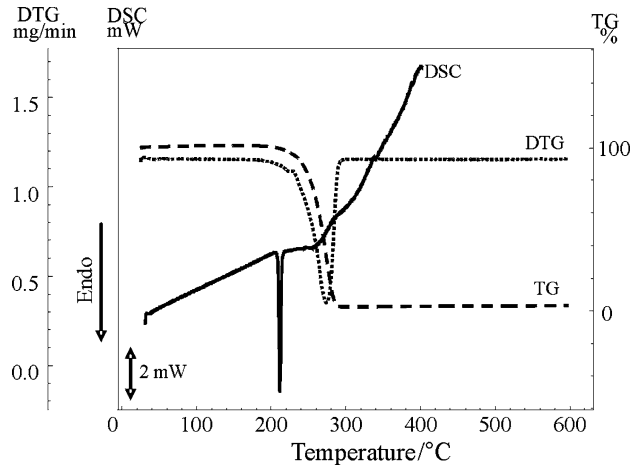

Fig. 2 DSC and TG/DTG curves of pure venlafaxine hydrochloride obtained in nitrogen atmosphere (50 mL min^{-1}) and heating rate of 10 °C min^{-1}

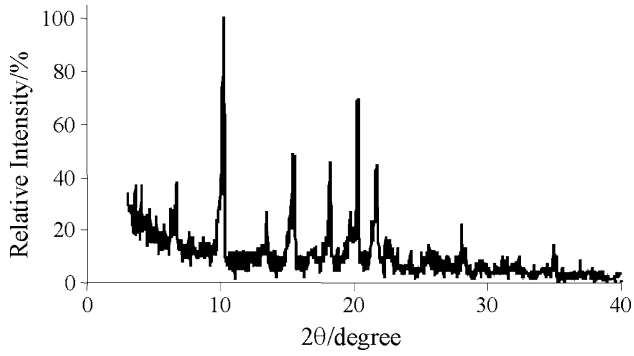

Fig. 3 X-ray powder diffraction of venlafaxine hydrochloride

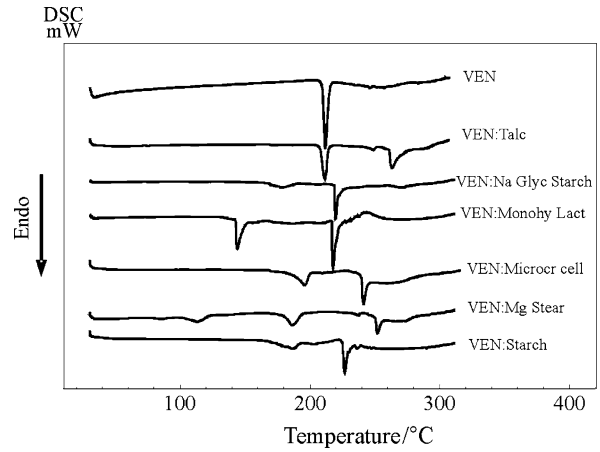

Fig. 5 DSC curves of venlafaxine hydrochloride and excipients obtained in dynamic nitrogen atmosphere (50 mL min^{-1}) and heating rate of 10 °C min^{-1}

relative crystallinity (X_c^{rel}) of VEN was calculated based on the Ruland method, in which the area of the crystalline diffraction relative to the total area of the diffractogram is taken as a measure of crystallinity [14]. The X_c^{rel} index calculated for VEN was 60.01%.

The SEM photomicrographs taken at magnification 5000× and 20,000× are given in Fig. 4. It was observed that VEN is characterized by regular shaped crystals.

Compatibility study with excipients

In fact, DSC has been proposed to be a rapid method for evaluating physicochemical interactions between components of the formulation through the comparison of thermal curves of pure substances with the curve obtained from a 1:1 physical mixture and therefore select adequate excipients with suitable compatibility [8–10].

The thermal profiles of the mixtures venlafaxine/talc, venlafaxine/sodium glycolate starch, and venlafaxine/monohydrate lactose (Fig. 5) can be considered as a superposition of the curves of VEN and excipients, demonstrating the absence of interaction.

The DSC curve of venlafaxine/talc has shown the characteristic endothermic event of VEN melting point at 211 °C and successive endothermic and exothermic events from 240 °C, which can be related to chemical and/or physical reactions in the thermal degradation of the mixture. In venlafaxine/sodium glycolate starch mixture a small endothermic event was observed in the range of 164–187 °C, followed by melting of VEN at 219 °C. The DSC curve of venlafaxine/monohydrate lactose has shown an endothermic event at 146 °C, corresponding to dehydration of lactose bound water; an exothermic event in the range of 157–170 °C due to the lactose crystalline transition [15, 16]; and an endothermic event at 217 °C corresponding to the simultaneous melting of lactose and VEN, followed by exothermic degradation events.

Differences were observed in the DSC curves of venlafaxine/microcrystalline cellulose, venlafaxine/magnesium stearate, and venlafaxine/starch mixtures (Fig. 5), in which the melting point of the drug shifted to a higher temperature of T_{peak} = 241, 252 and 226 °C, respectively. These results indicated the occurrence of a strong interaction in the solid state with temperature, but not necessarily corresponding to incompatibility.

The results of venlafaxine/microcrystalline cellulose have shown one endothermic event at 195 °C, which can be attributed to the rupture of the cellulose glycosidic bonds, and the melting of VEN at 241 °C. DSC curve of venlafaxine/magnesium stearate has shown three endothermic events. The first in the range of 100–122 °C corresponding to the dehydration process of magnesium stearate; the second at 186 °C, which might be due to palmitate impurity or salts of other fatty acids [17, 18]; and the third event at 252 °C corresponding to the melting point of VEN. DSC curve of venlafaxine/starch has shown an endothermic event in the range of 167–191 °C that could be related to a delayed polymer dehydration [19] or melting point of the starch snow flakes® 3400. The endothermic event of VEN melting was shifted to 226 °C, confirming the interaction between the two compounds.

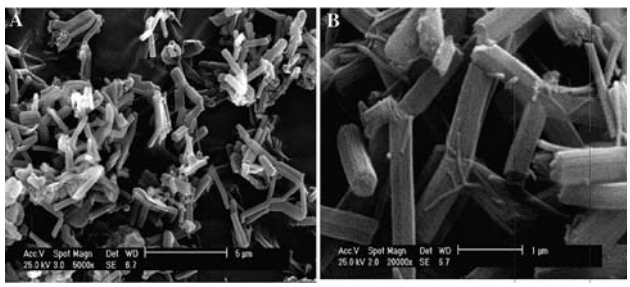

Fig. 4 SEM photomicrograph of Venlafaxine hydrochloride: **a** 5000× magnification; **b** 20,000× magnification

One possible reason can be a Maillard reaction between the hydroxyl groups of starch and the amine group of VEN [20].

DRIFT has been applied as a supplementary technique to investigate drug-excipient interaction and to confirm the results obtained from the thermal analysis. It is the most suitable technique of the non-destructive spectroscopic methods and has become an attractive method in the analysis of pharmaceutical solids, since the materials are not subject to thermal or mechanical energy during sample preparation, therefore preventing solid-state transformations [12]. The appearance of new absorption band(s), broadening of band(s) and alteration in intensity is the main characteristics to evidence interactions between drug and excipients.

The spectra of the drug and all excipients used in this study were obtained for pure compounds as well for binary mixtures (1:1 *mass/mass*) in order to identify a possible chemical interaction between them (Fig. 6). The DRIFT spectra did not show evidence on chemical interaction in the solid state. Moreover, the spectra of binaries mixtures can be considered as the superposition of the individual ones without absence, shift or broadening in the vibration bands of VEN. It demonstrated the absence of chemical interactions between VEN and microcrystalline cellulose, magnesium stearate and starch, suggesting that the modification showed by DSC curves can be related to a possible physical interaction.

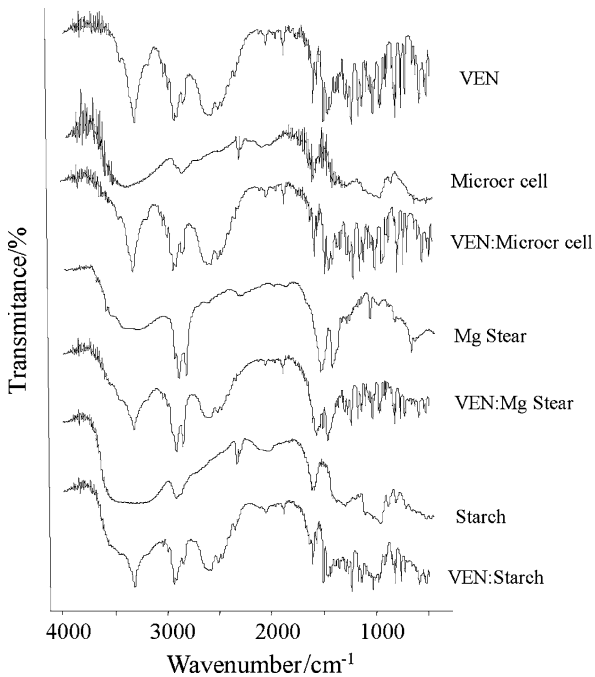

Fig. 6 DRIFT spectra of physical mixtures venlafaxine hydrochloride and excipients

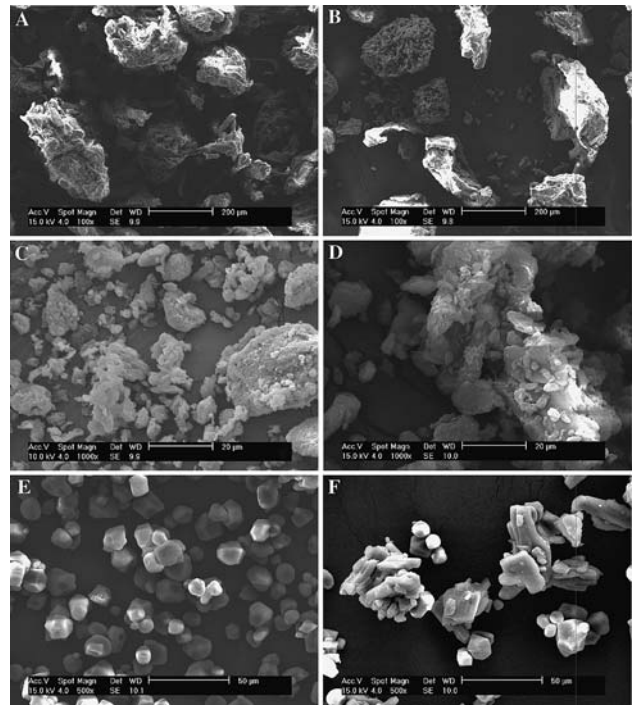

Fig. 7 SEM Photomicrograph of **a** microcrystalline cellulose (100×), **b** VEN:microcrystalline cellulose (100×), **c** magnesium stearate (1000×), **d** VEN:magneium stearate (1000×), **e** Starch (500×), and **f** VEN:starch (500×)

The photomicrographs obtained by SEM (Fig. 7) did not evidence any interaction between VEN and the excipients, providing visual support for the DRIFT results. The SEM images have shown that both VEN and excipients particles maintained their morphology and the drug crystals appeared dispersed on the surface of excipients particles.

Conclusions

The thermal analysis provided information about the thermal stability and decomposition of pure VEN and the binary mixtures which can be used in the quality control. The characterization was obtained by DRIFT, SEM, and XRPD, which, in turn, demonstrated VEN physicochemical properties including the crystallinity. In the compatibility studies, the modifications found in the DSC curves suggested a possible physical interaction of VEN with magnesium stearate, starch and microcrystalline cellulose. Additional DRIFT and SEM analyses were carried out and no evidence of solid-state interaction or incompatibility was observed.

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References

1. Andrews JM, Ninan PT, Nemeroff CB. Venlafaxine: a novel antidepressant that has a dual mechanism of action. Depression. 1996;4:48–56.
2. Olver JS, Burrows GD, Norman TR. Third-generation antidepressants: do they offer advantages over the SSRIs? CNS Drugs. 2001;15:941–54.
3. Lecrubier Y, Bourin M, Moon CAL, Schifano F, Blanchard C, Danjou P, et al. Efficacy of venlafaxine in depressive illness in general practice. Acta Psychiatr Scand. 1997;95:485–93.
4. Gutierrez MA, Stimmel GL, Aiso JY. Venlafaxine: a 2003 update. Clin Ther. 2003;25:2138–54.
5. Giron D. Contribution of thermal methods and related techniques to the rational development of pharmaceuticals—Part 1. Pharm Sci Technol Today. 1998;1:191–9.
6. Giron D. Applications of thermal analysis and coupled techniques in pharmaceutical industry. J Therm Anal Cal. 2002;68:335–57.
7. Ozawa T. Thermal analysis—review and prospect. Thermochim Acta. 2000;355:35–42.
8. Verma RK, Garg S. Compatibility studies between isosorbide mononitrate and selected excipients used in the development of extended release formulations. J Pharm Biomed Anal. 2004;35:449–58.
9. Araújo AAS, Cides LCS, Storpirtis S, Matos JR, Bruns RE. Effects of experimental conditions on the estimation of kinetic parameters of the thermal decomposition of AZT using factorial design. J Therm Anal Cal. 2005;79:697–701.
10. Gandhi R, Pillai O, Thilagavathi R, Gopalakrishnan B, Kaul CL, Panchagnula R. Characterization of azithromycin hydrates. Eur J Pharm Sci. 2002;16:175–84.
11. Tomassetti M, Catalani A, Rossi V, Vecchio S. Thermal analysis study of the interactions between acetaminophen and excipients in solid dosage forms and in some binary mixtures. J Pharm Biomed Anal. 2005;37:949–55.
12. Stephenson GA, Forbes RA, Reutzel-Edens SM. Characterization of the solid state: quantitative issues. Adv Drug Deliv Rev. 2001;48:67–90.
13. Phadnis NV, Cavatur RK, Suryanarayanan R. Identification of drugs in pharmaceutical dosage forms by X-ray powder diffractometry. J Pharm Biomed Anal. 1997;15:929–43.
14. Ruland W. X-ray determination of crystallinity and diffuse disorder scattering. Acta Crystallogr. 1961;14:1180–5.
15. Cides LCS, Araújo AAS, Santos-Filho M, Matos JR. Thermal behaviour, compatibility study and decomposition kinetics of glimepiride under isothermal and non-isothermal conditions. J Therm Anal Cal. 2006;84:441–5.
16. Araújo AAS, Storpirtis S, Mercuri LP, Carvalho FMS, Santos-Filho M, Matos JR. Thermal analysis of the antiretroviral zidovudine (AZT) and evaluation of the compatibility with excipients used in solid dosage forms. Int J Pharm. 2003;260:303–14.
17. Sharpe SA, Celik M, Newman AW, Brittain HG. Physical characterization of the polymorphic variations of magnesium stearate and magnesium palmitate hydrate species. Struct Chem. 1997;8:73–84.
18. Marini A, Berbenni V, Moioli S, Bruni G, Cofrancesco P, Margheritis C, et al. Drug-excipient compatibility studies by physico-chemical techniques. The case of indomethacin. J Therm Anal Cal.. 2003;73:529–45.
19. Mura P, Faucci MT, Manderioli A, Bramanti G, Ceccarelli L. Compatibility study between ibuproxam and pharmaceutical excipients using differential scanning calorimetry, hot-stage microscopy and scanning electron microscopy. J Pharm Biomed Anal. 1998;18:151–63.
20. Santos AFO, Basílio ID Jr, Souza FS, Medeiros AFD, Pinto MF, Santana DP, et al. Application of thermal analysis of binary mixtures with metformin. J Therm Anal Cal. 2008;93:361–4.