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ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF VILAZODONE BY LYOPHILIZATION TECHNIQUE

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ABSTRACT

The aim of the present investigation was to enhance the aqueous solubility and therapeutic efficacy of the drug by formulating solid dispersions (SDs) of vilazodone (VZD) with a hydrophilic carrier Poloxamer 188(PXM) by lyophilization technique. Phase solubility study with increasing PXM concentrations (0.5 to 2 % w/v) was done to study the influence of polymer concentration on solubility of VZD. SD's of VZD and PXM in 1:1, 1:3 and 1:5 w/w ratios were prepared by physical mixing and lyophilization technique, followed by dissolution studies. Evaluation of the properties of the SDs was performed by using dissolution, Fourier-transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC) and X-ray diffraction (XRD) studies. The SDs of VZD with PXM exhibited more enhanced dissolution rate than physical mixture and pure drug, and the rate increased with increasing concentration of Poloxamer 188 in SDs. The FTIR spectroscopic studies showed the stability of VZD and absence of well-defined VZD–PXM interaction. The DSC and XRD studies indicated that the transformation of VZD from crystalline to amorphous state by lyophilization technique. These results demonstrate that the use of a suitable hydrophilic carrier like PXM to formulate SDs by the lyophilization technique can rapidly accelerate the solubility and in vitro dissolution of a lipophilic drug like vilazodone

INTRODUCTION:

Vilazodone is approved for treatment of acute episodes of major depression (Major Depressive Disorder (MDD). It acts as a serotonin reuptake inhibitor and 5HT1A receptor partial agonist [1-3]. It increases serotonin levels in the brain by inhibiting the reuptake of serotonin while acting as a partial agonist on serotonin-1A receptors. It has therefore been coined by scientists as a selective partial agonist and reuptake inhibitor (SPARI). Because of its partial agonist activity for serotonin-1A, vilazodone helps to reduce anxiety [4-7]. It is a *BCS Class - II* drug, offer challenges in developing a drug product with adequate bioavailability [8]. Oral administration is the most common route for therapy of many diseases, however poorly soluble drugs have low bioavailability thereby decreasing treatment efficacy. For any active substance, aqueous solubility and intestinal permeability are key determinants that

govern dissolution, absorption and oral bioavailability. The solid dispersion technique was introduced in the early 1970s. Solid dispersion is one of the most successful strategies to improve the release of poorly soluble drug. This can be defined as dispersion of poorly water soluble drugs in hydrophilic carriers [9]. The present study aimed to develop solid dispersions by lyophilization technique containing poloxamer 188 as a hydrophilic carrier in order to evaluate increased VZD solubility and dissolution rate [10, 11]. The physicochemical characteristics and dissolution were assessed using Fourier transform infrared, differential scanning calorimetry, X-ray powder diffraction and *in vitro* dissolution profiles.

2. MATERIAL AND METHODS

2.1 Materials

Vilazodone was gifted by Dr. Reddy's Laboratories Ltd., Hyderabad, poloxamer 188 purchased from S.D. Fine Chemicals Ltd. All other chemicals used were of analytical grade and procured from commercial sources.

2.2 Phase solubility analysis

The solubility of vilazodone was determined in distilled water and pH 6.8 phosphate buffer medium. The effect of concentrations of Poloxamer 188 on the equilibration solubility of vilazodone in distilled water and pH 6.8 phosphate buffer medium at room temperature was carried out by adding an excess quantity of drug (20 mg) into a screw-capped glass vial containing 20 ml of solvent with various concentrations of the carrier. The suspension were shaken for 24hrs on a rotary bath shaker & filtered through Whatman no.1 filter paper. The filtrate so obtained was diluted & analyzed spectrophotometrically at 240 nm [9-11]. For determination of spontaneity of the process, the values of Gibbs free energy (ΔGtr) were calculated for each carrier in accordance with equation [12].

2.3 Preparation of physical mixtures

Physical mixtures were prepared by mixing of vilazodone and poloxamer 188 in mortar and pestle according to 1:1, 1:3, 1:5 ratios by geometrical dilution method and coded as VZD-PXM 188 Pm 1:1, VZD- PXM 188 Pm 1:3, VZD -PXM 188 Pm 1:5 respectively. The geometric mix blends passed through sieve no#60 and kept in the desiccator [13].

2.4 Preparation of SDs by lyophilization technique

Vilazodone and the hydrophilic polymer PXM 188 were weighed according to 1:1, 1:3, 1:5 ratios and coded as VZD-PXM 188 Lyo 1:1, VZD- PXM 188 Lyo 1:3 VZD-PXM 188 Lyo 1:5 respectively. Specified quantity of drug was weighed and dispersed into 100 ml poloxamer solution. The dispersion being stirred with the help of magnetic stirrer, to this 25% liquid ammonia added drop wise and stirred until a clear solution was obtained. Then the samples were transferred into glass vials and incorporated into the ports of lypholizer with closed mode of valves and frozen at a temperature of -40°C for 3 hours. Then the valves of lypholizer were opened slowly and the samples were sublimed under a pressure of 0.09 mbar and with a condenser temperature of -40°C for 12 hours followed by a secondary drying at 25°C for 2 hours using YSI–250 Yorco Freeze Dryer-Lypholizer. The frozen dried mass was passed through sieve no. #60 to get fine powders and kept in desiccator [13-16].

2.5 Analysis of drug content in solid dispersions

The drug content of vilazodone in each physical mixtures and solid dispersions were determined using UV-spectroscopy. Accurately weighed quantity of solid dispersion or physical mixture equivalent to 10 mg of vilazodone was transferred to 100 ml of volumetric flask and volume was made up to 100 ml with methanol and 1 ml of this solution was taken and it was diluted to 10 ml with methanol and absorbance was noted at 240 nm, concentration of vilazodone was

determined using calibration curve of vilazodone in methanol [15].

2.6 Percentage yield value:

The Percentage yield value of solid dispersions and physical mixtures were measured by the following formula. Percent yield value= (Practical yield value/ Theoretical yield value) X 100

2.7 Characterization of solid dispersion

2.7.1 Fourier transform infrared spectroscopy (FT-IR)

The FT-IR spectra were obtained using FT-IR spectrometer (Shimadzu).The samples were previously grounded and mixed thoroughly with potassium bromide, an infrared transparent matrix in 1:5 (sample : KBr) ratio, respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. Forty five scans were obtained at a resolution of 4 cm^{-1} from 4500 to 400 cm^{-1}.

2.7.2 Differential Scanning Calorimetry

The DSC measurements were performed on a Pyris Diamond TG/DTA differential scanning calorimeter with thermal analyzer. All accurately weighed samples (about 5 mg) were placed in sealed aluminum pans. An empty aluminum pan was used as reference.

2.7.3 X-ray diffraction

The X-ray powder diffraction patterns were obtained by using Philips Holland PW 1710 with Cu Kα (λ = 1.54056A^o) radiation and a crystal monochromator, voltage: 45 mv and current: 20 amps. The diffraction patterns were run at 2^0/min in terms of 2θ angle.

2.7.4 In-*vitro* Dissolution rate studies

The in vitro dissolution studies of physical mixtures and solid dispersions of vilazodone were carried out on USP type II dissolution apparatus and the results were compared with those for pure vilazodone. The dissolution vessels contained 900 mL of phosphate buffer pH 6.8 maintained at 37 °C ± 0.5 °C and paddle speed set at 50 rpm. Solid dispersions equivalent to 20 mg of vilazodone were added to the dissolution medium in a powder form. Then, 5 mL samples were withdrawn at 5, 10, 20, 30, 45 and 60 min from the dissolution medium. The withdrawn sample was replenished with 5 mL of fresh media. The withdrawn samples were analyzed for vilazodone content by measuring the absorbance at 240 nm using UV-visible spectrophotometer (Shimadzu). Dissolution studies for each formulation were performed in triplicates [17-19].

3. Results and Discussion

3.1 Phase solubility study

The phase solubility and free energy curves of pure vilazodone in the presence of Poloxamer 188 at 25 ºC are shown in Figure 1. The apparent solubility of vilazodone increased with increasing carrier concentrations. Using the highest carrier concentration, the solubility increased approximately 5.81 fold in distilled water and 5.97 fold in pH 6.8 phosphate buffer as compared to pure drug. The solubility found in this study for vilazodone at 25 ºC was 0.132 mg/mL in distilled water and 0.141 mg/mL in pH 6.8 phosphate buffer. The values of Gibbs free energy ($\Delta G tr_o$) associated with the aqueous solubility of vilazodone in presence of carrier were all negative for carriers at various concentrations, indicating the spontaneous nature of drug solubilisation. The values decreased with increasing carrier concentration, demonstrating that the reaction became more favourable as the concentration of carrier increased

3.2 Percent Yield and Drug Content

The percent yield of various vilazodone physical mixtures and solid dispersions was within the range of 96.85 % to 99.25 % (Table 1). The percentage drug content in physical mixtures and solid dispersions was within the range of 98.89±0.19 % to

99.51±0.24 % and 97.95±0.24 % to 98.96±0.45 % respectively as reported in Table 1. This indicated that drug was uniformly distributed in all of these prepared physical mixtures and solid dispersions.

3.3 Solid state characterization study

3.3.1 FTIR Spectroscopy Analysis.

FTIR spectroscopy analysis was done to analyze physicochemical interactions between vilazodone and poloxamer 188. FTIR spectra of pure vilazodone, poloxamer 188 and physical mixture are shown in Figure 2. The characteristic peaks of pure vilazodone were found at 3437 cm-1 (NH stretching), 3216 cm-1 (Aromatic C-H stretching), 2939 cm-1 (Aliphatic C-H stretching), 2217 cm-1 (C≡N stretching), 1669 cm-1 (C=O stretching) , 1575&1443 cm-1 (C=C ring stretching). The intensity peaks of vilazodone were found to be present in the spectra of physical mixture with poloxamer 188. This finding reveals the lack of interaction between the drug and the carrier in the sample.

3.3.2 DSC Analysis.

DSC analysis was done for pure vilazodone, physical mixture and lyophilized solid dispersions using poloxamer 188 are shown in Figure 3. The DSC thermogram of pure vilazodone showed a sharp endothermic peak at 202.1 ^{o}C, corresponding to its melting point. The DSC curve of poloxamer 188 showed a sharp endothermic peak at 65.2 ^{o}C. The DSC curve of physical mixture of VZD with poloxamer 188 showed the endothermic peaks at 202.1 ^{o}C and 65.2 ^{o}C which are the corresponding melting point of drug and polymer respectively. The DSC curve of lyophilized solid dispersion showed reduction in melting point of drug to 178.3 ^{o} C with widening of peak. This reduction in melting point and broadening of peak was an indication of conversion of crystalline fraction of drug into amorphous one. We can assume a positive conversion here.

3.3.3 X-ray diffraction

X-ray diffraction spectra of pure vilazodone, physical mixture and solid dispersion are illustrated in Figure 4. The presence of sharp distinct peaks in vilazodone spectra indicated its high crystallinity. The diffraction spectrum showed that the drug in crystalline form as demonstrated by numerous distinct peaks at 2θ of 8.41, 9.007, 12.09, 16.803, 18.899, 20.99, 21.879, 24.54, 25.69, 26.14, 28.16 and 29.52. The spectrum physical mixture prepared with poloxamer 188 showed numerous distinct peaks at 2θ of 8.321, 9.786, 11.042, 16.627, 18.879, 21.45, 22.79, 24.54, 25.65, 26.12, 28.19 and 29.54. The spectrum lyophilized solid dispersion prepared with poloxamer 188 showed a reduction in the total number of peaks at 2θ of 8.023, 9.897, 16.887, 18.989, 21.127, 24.792, 25.632, 27.875 and 29.105, base broadening of appeared peak along with a reduction in peak intensity providing convincing evidence for the formation of amorphous form in solid dispersion. The result indicated that the drug in solid dispersion was in amorphous form.

3.3.4. *In-vitro* Dissolution rate studies

The *in vitro* dissolution profiles of the drug, various solid dispersions using poloxamer 188 and their respective physical mixtures in phosphate buffer (pH = 6.8) are shown in Figures 5(a) and 5(b). All of the physical mixture and solid dispersion samples showed improved dissolution of vilazodone. The enhancement of dissolution is mainly attributed to increased surface area of drug exposed to large carrier molecules and increased wettability. Again, all of the solid dispersion samples showed more improved vilazodone dissolution than their respective physical mixture samples.

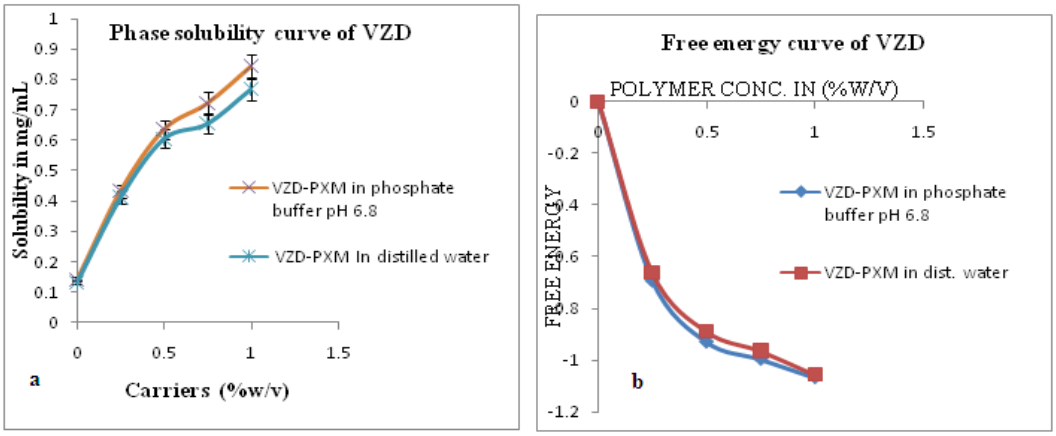

Figure 1. (a) Phase solubility curve of VZD, (b) Free enegy curve of VZD

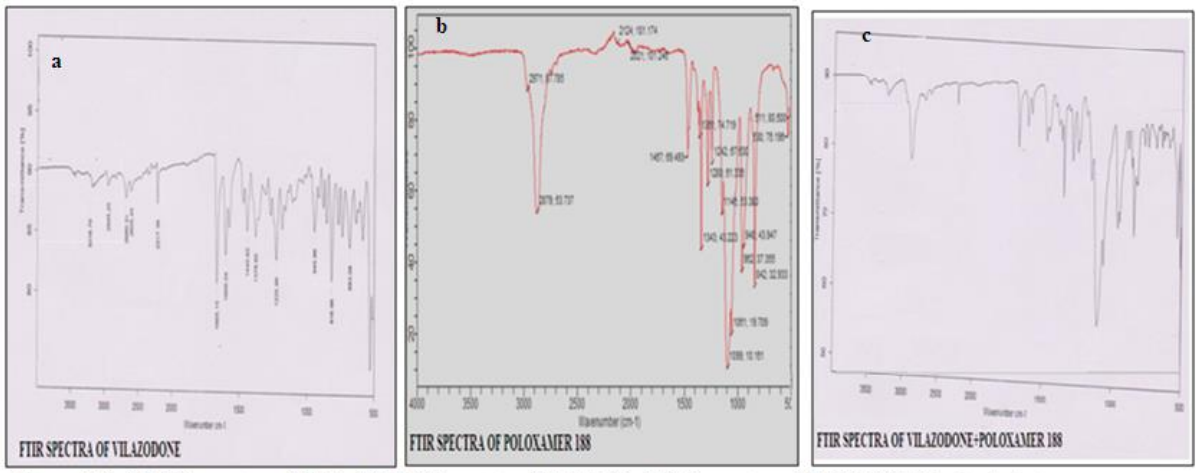

Figure 2. (a) FTIR spectra of VZD, (b) FTIR spectra of PXM, (c) FTIR spectra of VZD-PXM physical mixture

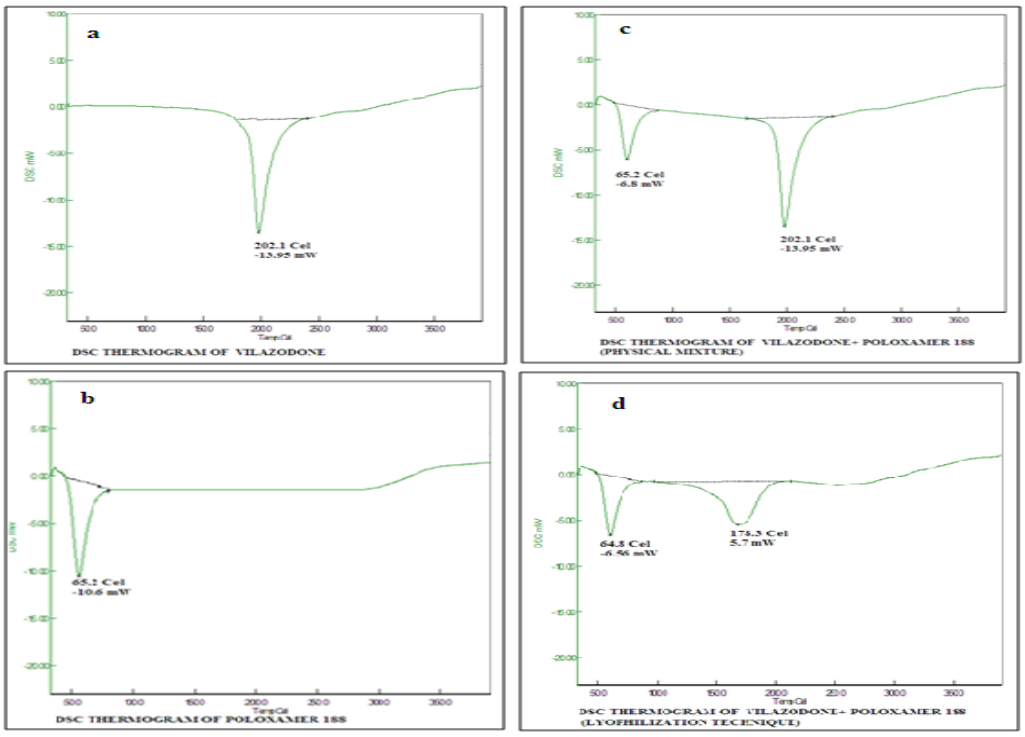

Figure 3. (a) DSC thermogram of VZD, (b) DSC thermogram of PXM,
(c) DSC thermogram of VZD-PXM physixal mixture,
(d) DSC thermogram of VZD-PXM lyophilized SDs

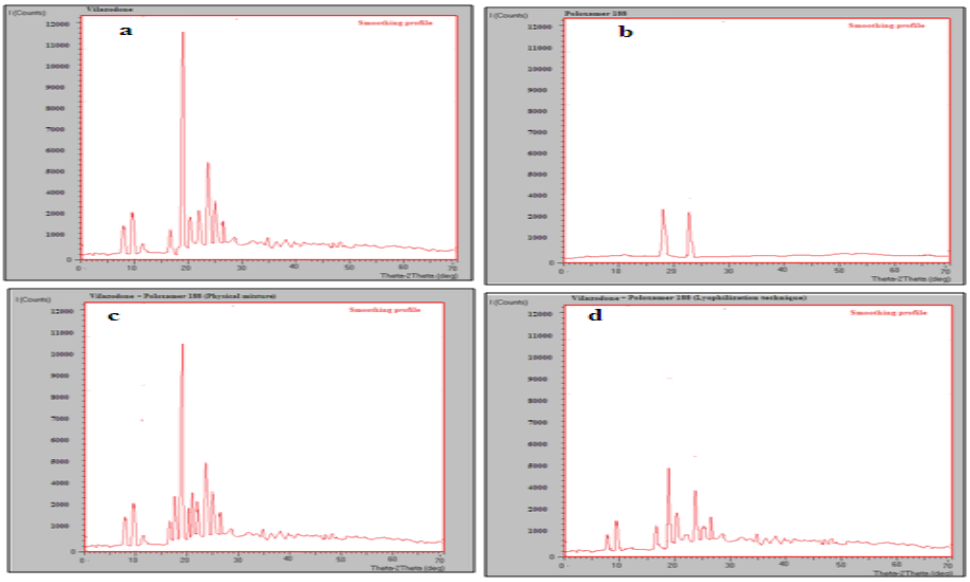

Figure 4. (a) XRD spectra of VZD, (b) XRD spectra of PXM, (c) XRD spectra of VZD-PXM physical mixture, (d) XRD spectra of VZD-PXM lyophilized SDs

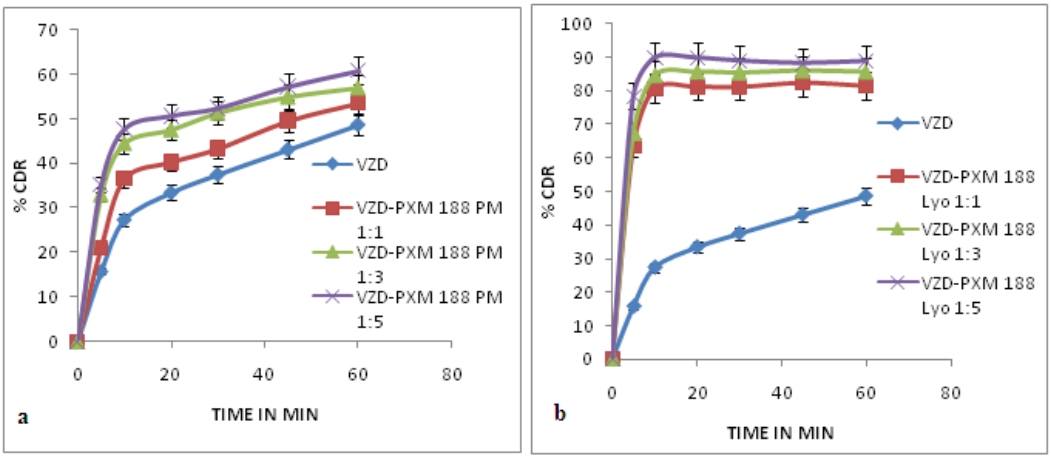

Figure 5(a) In-Vitro release of VZD from physical mixture, (b) From lyophilized SDs

This observation indicated that the increased dissolution of vilazodone from lyophilized solid dispersion due to presence of drug in amorphous state as compared to the physical mixtures and pure drug, where drug is present in crystalline state. The pure drug showed up to 50% dissolution over 60 min, but its solid dispersions prepared by lyophilization with poloxamer 188 (1:3 and 1:5 w/w) showed dissolution of greater than 89% within 10 min (Figure 5).

CONCLUSION

In this work, solid dispersions were prepared with vilazodone and poloxamer 188 by lyophilization technique. In the phase solubility study, the drug showed better solubility in phosphate buffer pH 6.8 than distilled water. The apparent solubility of vilazodone increased with increasing carrier concentrations. Solid dispersions showed better dissolution of vilazodone than physical mixtures. Solid dispersion of VZD-PXM 188 Lyo 1:5 showed the maximum dissolution efficiency among all solid dispersions and physical mixtures. IR spectra indicated no well-defined interaction between the drug and polymer. DSC thermograms of solid dispersion indicated complete miscibility of the drug in carrier. Amorphous nature of the drug in solid dispersion was confirmed by a decrease in enthalpy of drug melting

in solid dispersion compared to the pure drug. XRD analysis indicated a reduction in drug crystalline nature in solid dispersion. In conclusion, these results could be an indication that solid dispersion prepared by the lyophilization technique could be useful for the development of pharmaceutical products containing vilazodone.

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