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OLANZAPINE-PEG 6000 BINARY SYSTEMS: *IN VITRO* DISSOLUTION BEHAVIOR, PHYSICOCHEMICAL CHARACTERIZATION AND MATHEMATICAL MODELING

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Abstract: The objective of the present work is to study the dissolution behavior of olanzapine from its solid dispersions with PEG 6000. Solid dispersions were prepared by melt dispersion method and characterized by phase solubility studies, drug content and *in vitro* dissolution studies. The best releasing dispersions were characterized by X-ray diffraction, differential scanning calorimetry, FT-IR spectroscopy, Near Infrared, Raman analysis and wettability studies. The phase solubility studies and its thermodynamic parameters indicated the spontaneity and solubilization effect of the carrier. The release study results showed greater improvement of drug release from solid dispersions than pure drug and a linear increase in drug release was observed with an increase in carrier content. XRD, DSC, FT-IR, NIR and Raman analysis revealed the crystallinity reduction of olanzapine and its compatibility with the carrier. Wettability studies proved the increased wettability in samples due to water absorbing nature of the carrier. The possible mechanisms for increased release rate are attributed to solubilization effect of the carrier, formation of solid solution, prevention of agglomeration or aggregation of drug particles, change in surface hydrophobicity, increased wettability and dispersability of drug in dissolution medium. The suggested reasons for such release behavior were found to be well supported by results of the evaluation techniques.

Keywords: olanzapine, PEG 6000, solid dispersions, X-ray diffraction, wettability, solid solution

Drug dissolution from solid oral dosage forms depends on the release of drug from the dosage form and subsequent release of drug in physiological fluids. It has been estimated that nearly 35-40% of drugs suffer from poor aqueous solubility and this affects the absorption of drug from gastrointestinal tract that leads to poor oral bioavailability, high intra and inter subject variability, increase in dose, reduction in therapeutic efficiency and finally, failure in formulation development (1). Development of solid dosage forms for water insoluble drugs had been a major challenge for pharmaceutical scientists for decades. Various formulation strategies like micronization, micellar solubilization, complexation, dendrimers for drug solubilization, formation of solid solutions/dispersions with hydrophilic carriers, self emulsifying drug delivery systems, spray drying, nano approaches, pro-drug approaches and salt synthesis have been developed to increase the dissolution rate of these types of drugs (2).

An attractive possibility could be represented by employing simple solid dispersion technique utilizing various hydrophilic carriers. Solid dispersions (SDs) are defined as the dispersion of one or more active ingredients in an inert hydrophilic carrier or matrix in a solid state, prepared by the fusion, solvent or solvent-fusion method. This technique provides a means of reducing particle size to a nearly molecular level, offers a variety of processing and excipients options that allow for flexibility when formulating oral delivery systems of poor water soluble drugs with cost effectiveness and significant dose reduction. It has been widely demonstrated that hydrophilic carrier dissolves rapidly exposing the drug particles to dissolution medium as fine particles for quick dissolution and absorption (3).

The mechanisms for increased dissolution rate may include reduction of crystallite size, a solubilization effect of the carrier, absence of aggregation of drug crystallites, improved wettability and dis-

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persability of a drug from the dispersion, dissolution of the drug in the hydrophilic carrier or conversion of the drug to an amorphous state (3).

Schizophrenia is a severe, non-curable illness of brain with serious consequences if not properly treated and kept under control. Olanzapine (2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno-[2,3-*b*],[1,5]benzodiazepine; OLZ) is a relatively new benzodiazepine atypical antipsychotic which belongs to the class of thienobenzodiazepines and has proven efficacy against the positive and negative symptoms of schizophrenia, bipolar disorder and other psychosis. It is poorly water soluble drug and belongs to BCS class II drug (low solubility and high permeability) and highly bound to plasma protein (about 93%). Following oral administration, C_{max} is reached within 5-6 h of dosing. OLZ undergoes extensive pre-systemic metabolism in liver resulting in relatively very low oral bioavailability (4-6).

MATERIALS AND METHODS

Materials

OLZ was received as a gift sample from Unichem Laboratories, (Mumbai, India). Mannitol was purchased from SD Fine Chemicals Ltd., (Mumbai, India). Sodium hydroxide, potassium dihydrogen orthophosphate, microcrystalline cellulose (DC grade) and magnesium stearate were purchased from SD Fine Chemicals Ltd., (Mumbai, India). All other solvents and reagents used were of AnalaR grade.

Melt dispersion method

SDs containing OLZ were prepared using varying concentrations of PEG 6000 and keeping CLZ concentration constant. The drug : carrier ratios used were 1 : 1, 1 : 2, 1 : 4, 1 : 6, 1 : 8 and 1 : 10. The required amount of carrier was melted in a china dish and weighed amount of the drug was added to molten carrier with constant stirring. The mixture was solidified to get waxy mass and dried in desiccators for 12 h. The hardened mixture was powdered in a mortar, sieved through a 100 mesh screen and the dispersion was wrapped and stored in dessicator (7-10).

Phase solubility studies

Phase solubility studies were carried out by adding excess amount of drug to 25 mL of aqueous solutions containing increasing amounts of carrier (1 : 1 - 1 : 10) in screw capped bottles and shaken in orbital shaker (Remi Ltd., Mumbai) incubated at 25 and 37°C for 24 h. Samples with pure OLZ and water were used as control. After 24 h, the solutions were filtered using filter paper (0.45 µm, 13 mm, Whatman, USA). The filtrate was diluted and analyzed spectrophotometrically at 259 nm (1700 UV-Vis Shimadzu, Japan). The solubility of OLZ in various carriers was calculated using the standard curve [OD = 0.1149 × concentration - 0.0031]. The data were subjected to phase solubility analysis to calculate various thermodynamic parameters like ΔH, ΔS and ΔG (11-13).

Phase solubility analysis

Stability constant (11-13)

The value of apparent stability constant, Ka between drug–carrier combinations were computed from the phase solubility profiles as described below from Eq. (1)

$$Ka = \frac{Slope}{Intercept\ (1 - Slope)} \quad (1)$$

Gibbs free energy, ΔG was calculated from Eq. (2)

$$\Delta G = -RT \ln Ka \quad (2)$$

where R - gas constant, 8.313 J/mol K, T - temperature, Ka - stability constant.

Enthalpy

The enthalpy change in systems was calculated from Eq. (3)

$$\Delta H = \frac{-RT \ln Ka}{dT\ (K)} \quad (3)$$

where, R - gas constant (8.313 J/mol K), Ka - stability constant, dT - difference in temperature (Kelvin).

Entropy

The entropy of the system was calculated from Eq. (4)

$$\Delta S = \frac{\Delta H - \Delta G}{T} \quad (4)$$

where ΔH - enthalpy, ΔG - entropy.

Drug content

Assay of weighed amount of SDs were carried out to determine the drug content. The weighed samples were dissolved in 10 mL of analytical media and stirred by vortex mixer. The solutions were filtered, using Whatman filter paper (0.45 µm, 13 mm, Whatman, USA). Next, the filtrate was diluted suitably and the content was estimated spectrophotometrically (UV-1700, Shimadzu, Japan) at 259 nm using standard curve.

In vitro dissolution studies

Dissolution of olanzapine (20 mg), and all SDs in PEG 6000 (equivalent to 20 mg of OLZ), was car-

ried out using USP dissolution test apparatus (Type II) at a temperature of 37 ± 0.5 °C, at 100 rpm using 900 mL 0.1 M HCL as dissolution medium. Five mL sample was withdrawn at 5.0, 10, 20, 30, 40, 50 and 60 min. The withdrawn sample was replenished with 5.0 mL of fresh media. The withdrawn samples were analyzed for OLZ content by measuring the absorbance at 259 nm using UV-visible spectrophotometer (UV-1700, Shimadzu, Japan). Three such determinations were carried out for each formulation. The content of olanzapine was calculated from the standard curve [OD = 0.1149 × concentration + 0.001 (R^2 = 0.9999; p > 0.001). The *in vitro* dissolution parameters namely, cumulative percent drug release, dissolution parameters like amount released (Q), percent dissolution efficiency (% DE), dissolution rate constant (DRC), relative dissolution rate (RDR), dissolution half life ($t_{50\%}$) and time taken to release 85% of drug ($t_{85\%}$) were calculated by subjecting the release data into various equations given below (12-16).

Dissolution half life ($t_{50\%}$)

Time taken to release 50% of drug was calculated by using Eq. (5)

$$t_{50\%} = \frac{0.693}{K} \quad (5)$$

Relative dissolution rate (RDR)

It is the ratio of the drug released from the samples with respect to pure drug at specific time intervals.

Dissolution efficiency (% DE)

It can be defined as the area under the dissolution curve up to a certain time. It is measured using the trapezoidal method and is expressed as a percentage of the area of the rectangle divided by the area of 100% dissolution in the same time and calculated from the Eq. (6)

$$\%DE = \left(\frac{\int_0^t y\,dt}{y_{100} \times t}\right) 100 \quad (6)$$

Dissolution rate constant (DRC)

A plot of log % drug unreleased *versus* time was drawn and the slope was calculated using MS Excel 2007 computer programme. Dissolution rate constant was calculated from Eq. 7

$$DRC = Slope \times 2.303 \quad (7)$$

Release kinetics

In order to describe the kinetics of drug release from the preparations, various mathematical equations have been proposed (16-18). The zero-order equation (Eq. 8), the first-order equation (Eq. 9), and the Higuchi model (Eq. 10), Hixson-Crowell model (Eq. 11) and Korsmeyer-Peppas (Eq. (12) were used in the present study

Zero order:

$$Q_t = Q_0 + K_o t \quad (8)$$

where Q_t = amount of drug released at time t, Q_0 = amount of drug in solution at time t = 0, (usually Q_0 = 0) and K_o = zero order release constant.

First order:

$$\log Q_t = \log Q_0 \times K_1 \frac{t}{2.303} \quad (9)$$

where Q_t = amount of drug released in time t, Q_0 = amount of drug in solution at time t = 0, (usually Q_0 = 0) and K_1 = first order release constant.

Higuchi model:

$$M_t = K\sqrt{t} \quad (10)$$

where M_t = amount of drug dissolved at particular time "t", K – Higuchi release constant.

Hixson Crowell model:

$$(W_0)^{1/3} - (W_t)^{1/3} = k_{1/3}t \quad (11)$$

where W_0 = weight of the drug taken at time t = 0 and W_t = weight of the drug taken at time "t"

Korsmeyer-Peppas empirical model:

$$\frac{Q_t}{Q_\infty} = k_{KP} \times t^n \quad (12)$$

Where, Q_t/Q_∞ = fractional release of drug at time t, k_{KP} = a constant comprising the structural characteristics of the formulation and "n" (the release component) = a parameter indicative of the mechanism of drug release. For the particular case of delivery system, n = 0.5 corresponds to Fickian release (case I), 0.5 < n < 1.0 to an anomalous (non Fickian) transport, n = 1 to a zero order release kinetics (case II) and n > 1 to a super case II transport (17-19).

Solid state characterization

X-ray diffraction studies (X-RD)

X-ray diffractometer (Philips, Finland) consisting of 40 kV, 30 mA generator with a Cu-Kα radiation tube was used. Diffraction patterns of pure drug (PD), physical mixtures (PM) and selected SDs were scanned over 2θ range from 2° to 50° at the rate of 2° per min at 0.02° at 2θ step size.

Differential scanning calorimetry (DSC) studies

Thermal analysis was carried out using differential scanning calorimeter (Q 10 DSC TA, Instruments, Waters Inc., Newcastle, USA) with liquid nitrogen cooling accessory. The analysis was performed under purge of nitrogen gas (50 mL/min). High purity indium was used to calibrate the heat flow and heat capacity of the instruments. Sample (5-10 mg), placed in flat bottomed aluminum pan,

was firmly crimped with lid to provide an adequate seal. Sample was heated from ambient temperature to 400°C at preprogrammed heating rate of 10°C/min.

Fourier Transform Infrared (FT-IR) spectroscopic studies

FT-IR spectra of pure OLZ, carriers, physical mixtures of drug and carrier (1 : 1) and optimized SDs were carried out using FT-IR spectrophotometer with KBr disc (Jasco - FT-IR 1700 spectrophotometer, Japan). All the samples viz. OLZ, mannitol and physical mixtures (PMs) and SDs were analyzed in similar manner. Physical mixtures were prepared by blending individual component in glass-pestle mortar.

Near infrared (NIR) analysis

NIR spectra of pure drug and selected samples were recorded in FT-IR spectrometer (Jasco FT-IR, Japan) in diffuse reflectance mode (DRS). The samples were scanned in the wavelength range of 800 – 2000 nm and absorbance was measured in transmittance mode.

Raman spectroscopic analysis

The Raman spectra of samples and pure drug were recorded in Confocal Raman spectrophotometer [WITEC Alpha 300, Confocal Raman Nd: YAG laser (532 nm), USA].

Drug polymer miscibility studies

Miscibility of the drug with the polymer can be assessed based upon the shift in melting endotherm or T_g of the drug or can be predicted theoretically using the following Gordon-Taylor equations (Eqs. 13 and 14) based on the T_g, densities, and weight fractions of the components.

$$T_{gmix}(SDS) = \frac{W_1 T_{g1} + \kappa W_2 T_{g2}}{W_1 + \kappa W_2} \quad (13)$$

$$\kappa = \frac{T_{g1}\rho_1}{T_{g2}\rho_2} \quad (14)$$

where, T_{g1} is the glass transition temperature of drug, W_1 and W_2 are the weight fractions of the components, and κ is the parameter calculated from the true densities (ρ_1 of drug and ρ_2 of polymer) and T_{g2} of the amorphous dispersions. The true densities of OLZ and the carrier were determined in a duplicate using a pycnometer (20-22).

Flory-Huggins (F-H) modeling

The Flory-Huggins model can be applied to calculate the interaction parameter (x) by using Eq. 15

$$\frac{1}{T_m\text{mix}} - \frac{1}{T_m\text{pure}} = \frac{-R}{\Delta H_f}\{\ln\phi_{Drug} + (1 - \frac{1}{m})\phi_{Polymer} + \phi^2_{Polymer}\} \quad (15)$$

where, T_m mix is the melting temperature of the drug in the presence of the polymer, T_m pure is the melting temperature of the drug in the absence of the polymer, ΔH_f is the heat of fusion of the pure drug, m is the ratio of the volume of the polymer to OLZ, and ϕ drug and ϕ polymer are the volume fractions of the drug and the polymer, respectively (20-22).

Wetting studies

Formulation of tablets

The tablets of pure OLZ and selected SDs were formulated by using 20 mg of pure drug and SDs equivalent to 20 mg of OLZ and the formulation scheme is shown in Table 1. Sufficient quantity of microcrystalline cellulose (diluent) and magnesium stearate (lubricant) were added and mixed well in a mortar. The mixture was directly compressed in a 10 station rotary tablet punching machine (Rimek, Ltd., Mumbai, India) at a compression pressure of 5 kg/cm^2. Each tablet weighed around 250 mg.

Wetting time studies

Five circular tissue papers were placed in a Petri dish of 10 cm diameter. Ten mL of water containing 0.5% methylene blue, a water-soluble dye, was added to the Petri dish. The dye solution was used to identify complete wetting of the tablet surface. A tablet was carefully placed on the surface of the tissue paper in the Petri

Table 1 Formulation scheme of tablets for wetting studies.

Composition	Olanzapine (mg)	OPEG10 (mg)
OLZ	20	–
Selected SD (OPEG10)	–	= 20 mg of olanzapine (217 mg of SD)
Microcrystalline cellulose	223	26
Magnesium stearate	7	7
Total	250	250

dish at ambient temperature. The time required for water to reach the upper surface of the tablets and to completely wet them was noted as the wetting time. These measurements were carried out in replicates of three. Wetting time was recorded with digital watch (23, 24).

Water absorption ratio (23, 24)

The weight of the tablet prior to placement in the Petri dish was noted (W_b), utilizing a Mettler Toledo digital balance. The wetted tablet was removed and reweighed (W_a). Water absorption ratio R, was then determined using Eq. (16)

$$R = \frac{W_a - W_b}{W_b} \times 100 \qquad (16)$$

***In vitro* dispersion studies**

A tablet was added to 10 mL of phosphate buffer pH 7.4 at 37°C. The time required for complete dispersion was noted. Three such determinations were carried out (25).

Statistical analysis

The relevance of difference in the *in vitro* dissolution profile and pharmacokinetic parameters were evaluated statistically. The data were tested by two way analysis of variance.

RESULTS

Physicochemical characterization

Phase solubility studies

Phase solubility studies were conducted to determine the effect of temperature, solubilization effect of carrier and the spontaneity of solubilizing process when the drugs is physically mixed with PEG 6000. The thermodynamic parameters of OLZ and its PMs are shown in Table. 2. The solubility of OLZ was found to show a linear increase with an increase in amount of carrier and temperature. The thermodynamic parameters like ΔG and ΔH were found to be negative and entropy ΔS of physical mixtures was positive in nature.

Drug content

The assayed drug content in all SDs was in the range of 98-104%.

In vitro dissolution studies

The % cumulative release of pure OLZ was found to be 70% in 1 h while SDs showed a significant improvement in release rate in the same period. The *in vitro* release profiles of the dispersions were compared in Figure 1. The *in vitro* dissolution

Table 2. Thermodynamic parameters of olanzapine physical mixtures with PEG 6000.

	Carrier	Temp °C	Slope	Intercept	Ka (M^{-1})	Δ G (kJ/mol)	Δ H (kJ/mol)	Δ S (J/mol K)
1.	PEG 6000	25	231.37	-7.338	0.137	-2.841	-2.841	2.831
2.		37	191.10	-4.029	0.245	-3.307	-3.308	3.296

Table 3. Dissolution parameters of olanzapine-PEG 6000 solid dispersions.

Code	Composition OLZ : PEG	Q05[a] (mg)	Q30[b] (mg)	%DE[c]	RDR[d] 05	RDR[d] 30	DRC[e]	$t_{50\%}$[f] (min)	$t_{85\%}$[g] (min)
OLZ	1 : 0	9.34 (0.12)	12.15 (0.56)	59.61	-	-	0.020	12.5	> 60
OPEG1	1 : 1	12.03 (0.24)	13.52 (1.24)	65.75	1.29	1.11	0.022	4.5	> 60
OPEG2	1 : 2	12.08 (0.24)	14.09 (0.40)	68.28	1.29	1.16	0.021	4.5	> 60
OPEG4	1 : 4	13.51 (0.20)	14.27 (0.39)	70.10	1.45	1.17	0.021	3.5	> 60
OPEG6	1 : 6	14.48 (0.31)	15.84 (0.28)	76.78	1.55	1.30	0.017	3.5	60
OPEG8	1 : 8	14.61 (0.32)	15.89 (0.57)	77.06	1.56	1.31	0.017	3.5	60
OPEG10	1 : 10	14.95 (0.31)	16.23 (0.54)	79.75	1.60	1.34	0.010	3.0	43.5

Values in parenthesis indicate standard deviation. [a]Q_{05} – Amount released at 05 min (mg); [b]Q_{30} – Amount released at 30 min (mg); [c]% DE – % Dissolution efficiency; [d]RDR - Relative dissolution rate at specific time intervals; [e]DRC - Dissolution rate constant; [f]$t_{50\%}$ - Dissolution half- life; [g]$t_{85\%}$ - Time taken to release 85% of drug from dispersions.

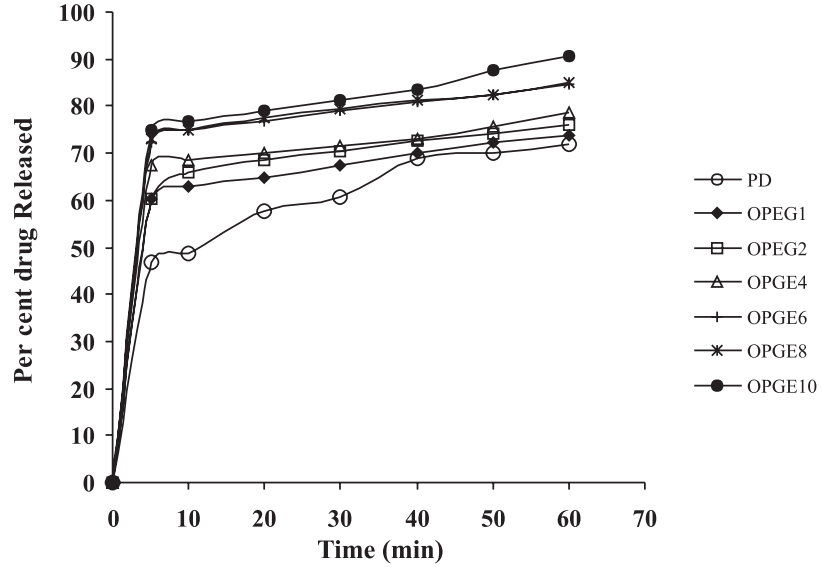

Figure 1. Dissolution profiles of olanzapine-PEG 6000 SDs compared with pure drug. All data points represent the mean of 3 values, n = 3

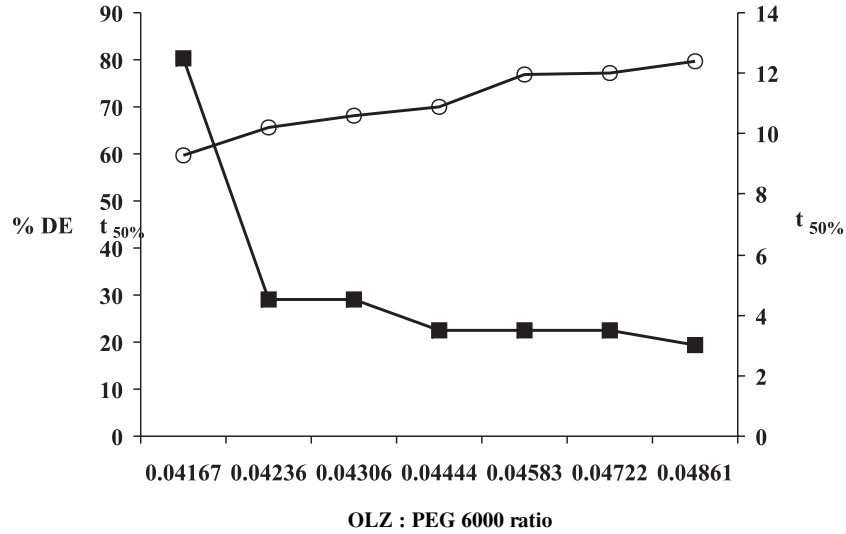

Figure 2. Relationship plot of % dissolution efficiency (% DE) and dissolution half life profiles of olanzapine-PEG 6000 solid dispersions. ■ - t_{50} %, ○ - % DE

parameters of the SDs are presented in Table 3. The relationship plot of % DE and $t_{50\%}$ was shown in Figure 2.

Release kinetic analysis

The release kinetics of the *in vitro* dissolution data (Table 4) and the regression parameters were analyzed to ascertain the type of drug release from SDs.

Solid state characterization

The best releasing dispersions (OPEG10) among the samples were subjected to solid state characterization

X-ray diffraction analysis

X- ray diffraction spectra of pure OLZ, PEG 6000, physical mixture (1 : 1) compared with the best releasing dispersion (Batch OPEG10) are illustrated in Figure 3.

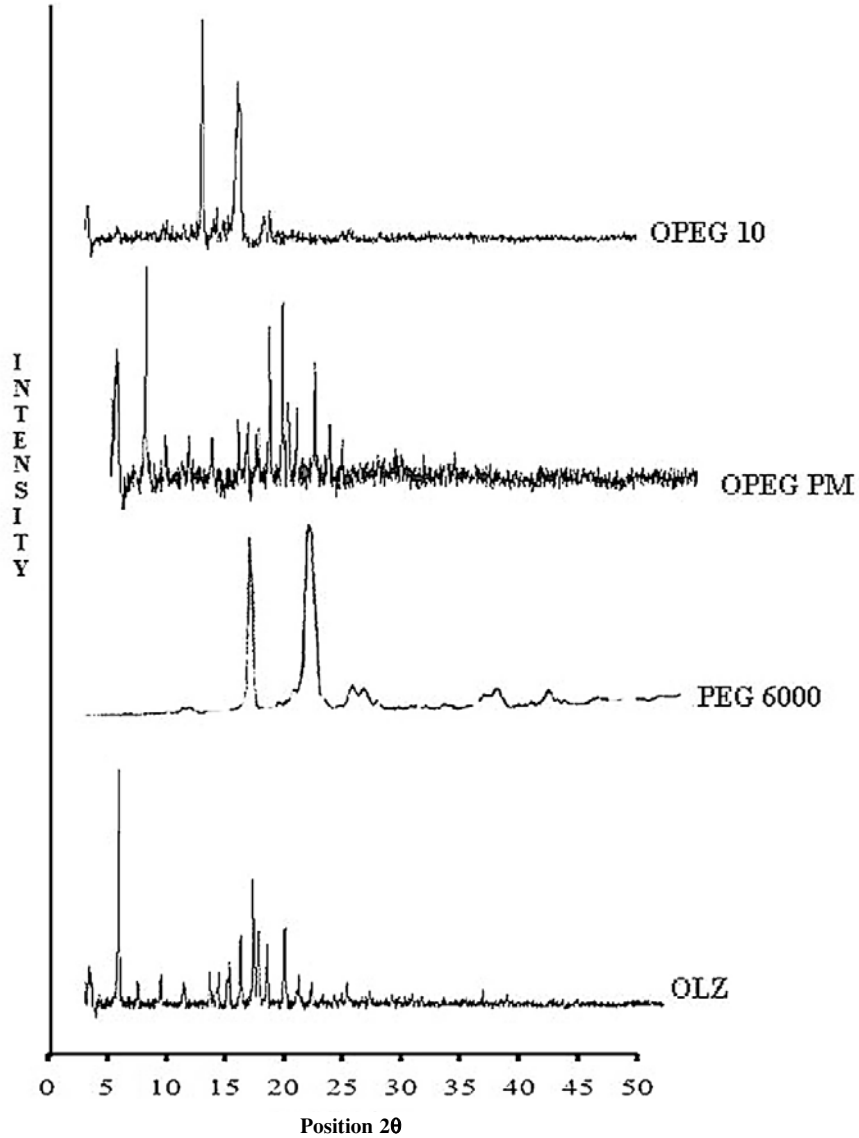

Figure 3. X-RD spectra of pure olanzapine (OLZ), PEG 6000, physical mixtures (PM) at 1 : 1 ratio and solid dispersions (SDs) OPEG at 1 : 1 ratio

Table 4. Release kinetic parameters of olanzapine – PEG 6000 solid dispersions.

Code	Zero order		First order			Higuchi		Hixson Crowell		K-P	
	r^2	K_0	r^2	Slope	K_1	r^2	Slope	r^2	Slope	r^2	"n"
OLZ	0.796	0.998	0.110	0.009	0.020	0.857	8.240	0.751	0.012	0.993	0.257
OPEG1	0.653	0.725	0.154	0.009	0.021	0.677	7.585	0.521	0.010	0.951	0.255
OPEG2	0.650	0.749	0.144	0.009	0.021	0.679	7.880	0.521	0.011	0.953	0.265
OPEG4	0.612	0.720	0.156	0.009	0.021	0.622	7.709	0.460	0.010	0.930	0.265
OPEG6	0.614	0.790	0.114	0.007	0.016	0.630	8.476	0.489	0.012	0.935	0.290
OPEG8	0.610	0.788	0.115	0.007	0.016	0.626	8.476	0.483	0.012	0.933	0.291
OPEG10	0.643	0.866	0.044	0.004	0.009	0.661	9.091	0.586	0.015	0.944	0.307

K-P – Korsmeyer-Peppas model, " n" – release exponent

Table 5. Gordon-Taylor analysis data.

Code	D : C ratio	W_1	T_{g1} (°C)	$W_1 \times T_g$	W_2	T_{g2} (°C)	$W_2 \times T_{g2}$	ρ_1	ρ_2	$T_{g1} \times \rho_1$	$T_{g2} \times \rho_2$	κ	$W_1 \times T_{g1} + W_2 \times T_{g2}$	$W_1 + \kappa_{w2}$	T_g Mix (°C)
OPEG10	1 : 10	1	196.4	196.4	10	14.96	149.6	1.3	1.08	255.32	16.15	15.8	2560.47	159.0.	16.10

T_{g1} - glass transition temperature of drug; W_1 and W_2 -weight fractions of the components; κ - parameter calculated from the true densities (ρ_1 of drug and ρ_2 of polymer); T_{g2} – Experimental glass transition temperature of the dispersions ; T_g Mix – Predicted glass transition temperature of the dispersion

Table 6. Flory-Huggins modeling data.

Code	D : C ratio	T_{pure}	T_{mix}	$1/T_{mix}$	$1/T_{pure}$	ΔH_f	$-R/\Delta H_f$	OLZ	m	ln ϕ drug	(1-1/m) ϕ polymer	ϕ^2 polymer	χ
OLZ	1 : 0	196.4	-	-	0.005	105	-0.079					0	
OPEG10	1 : 10	196.4	14.96	0.066	0.005	9.07	-0.916	1	10	2.718	0	100	-0.0074

R - 8.314; $T_{m\ mix}$ – melting temperature of the drug in the presence of the polymer; $T_{m\ pure}$ – melting temperature of the drug in the absence of the polymer; ΔH_f – Heat of fusion of the pure drug; m – ratio of the volume of the polymer to OLZ; ϕ drug and ϕ polymer are the volume fractions of the drug and the polymer; χ - interaction parameter.

DSC studies

The DSC scans of pure OLZ, PEG 6000 and optimized SDs (OPEG10) are compared in Figure 4.

FT-IR studies

The FT-IR spectra of OLZ, PMs (1 : 1) and SDs in PEG 6000 are presented in Figure 5.

Near infra red analysis

The near infrared spectra of OLZ and optimized SDs (OPEG10) are compared in Figure 6.

Raman analysis

The Raman spectra of pure OLZ and selected SDs (OPEG10) are compared in Figure 7.

Drug polymer miscibility studies

Gordon-Taylor analysis

The results of Gordon Taylor analysis are shown in Table 5.

Flory-Huggins (FH) modelling

The results of the FH modeling analysis are shown in Table 6.

Wettability studies

The wettability data of pure OLZ and optimized SDs (OPEG10) are shown in Table 7.

DISCUSSION

Phase solubility studies

These results were found to be in accordance with the well established formation of weak soluble complexes (11-13). It was also stated that the drug molecules might have transferred from pure water into the aqueous solution of carriers, which was indicated clearly from the negative values. These findings prove the spontaneous nature of the solubilization process. The enhancement of drug solubility in hydrophilic carrier could also be equally well explained by co-solvency effect of the carrier. It was also suggested that the hydrophilic carriers may interact with the drug molecules by electrostatic bonds and other types of forces like Van der Waals forces and this would have lead to the formation of weakly soluble complexes. The slopes of straight linear relationship assumed as indicative of the relative solubilizing efficiency of the carrier (11-13).

Drug content

The drug content values in the SDs indicate the uniform distribution of the drug in formulation and the suitability of the method used for formulation.

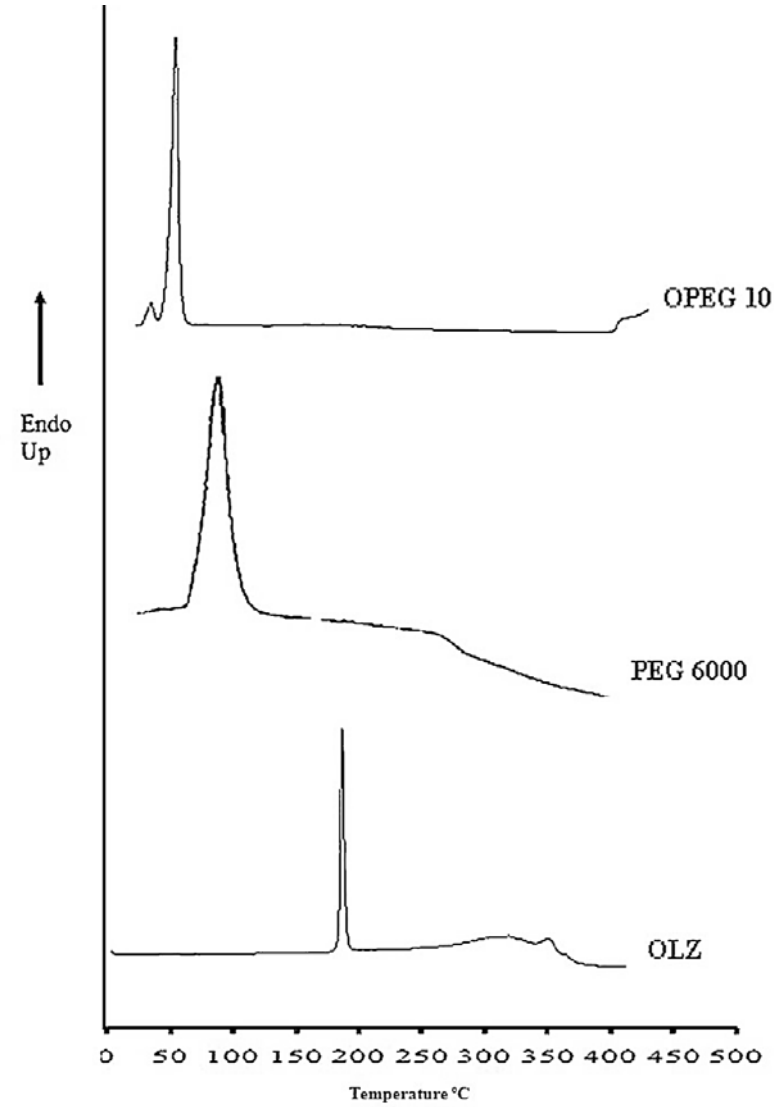

Figure 4. DSC thermograms of pure olanzapine (OLZ), PEG 6000 and solid dispersions (SDs) at 1 : 10 ratio

***In vitro* release analysis**

The percentage of drug release from SDs was found to increase gradually as the amount of carrier in SDs was increased from 1 : 1 to 1 : 10 (Fig. 1). The *in vitro* release data of sample SDs showed significant difference ($p < 0.001$) in release rate in comparison with pure OLZ.

It was found that dissolution parameters like per cent cumulative release, amount of drug released, % DE and RDR values were found to exhibit a linear increase with an increase in the amount of PEG 6000 in SDs. The other parameters like DRC, $t_{50\%}$ and $t_{85\%}$ values tend to decrease with an increase in carrier fraction.

The % DE values were found to increase from 59.61% (for pure OLZ) to 79.75% (for SDs with 1 : 10 ratio). The dissolution half life was found to decrease from 12.5 (pure OLZ) to 3.0 (for OPEG6-10) and $t_{85\%}$ were found to be reduced from 60 min (for pure OLZ) to 43.5 min (for OPEG6-10). Based on these findings, it can be inferred that batch OPEG10 was identified as the best releasing batch than other SDs. The order of OLZ drug release from the SDs could be ranked as: OPEG10 > OPEG8 > OPEG6 > OPEG4 > OPEG2 > OPEG1 > OLZ.

The relevance of difference in $t_{50\%}$ and % DE were evaluated statistically. When examined by two way analysis of variance, the $t_{50\%}$ and % DE data

showed significant difference between the pure OLZ and test products ($p < 0.001$). However, within the tests products a significant difference was not observed indicating that the data of all SDs differ significantly. Hence, it can be inferred that samples are not the same but are different in their formulations.

The possible reasons for enhanced release rate of OLZ from such SDs could be attributed to the modification of hydrophobic surface properties of OLZ due to the formation of film of polyethylene glycol around the drug particles and increased wettability of the powder with the dissolution medium (26).

The factors like decreased particle size, decreased crystallinity and prevention of aggregation and agglomeration of the drug by the carrier,

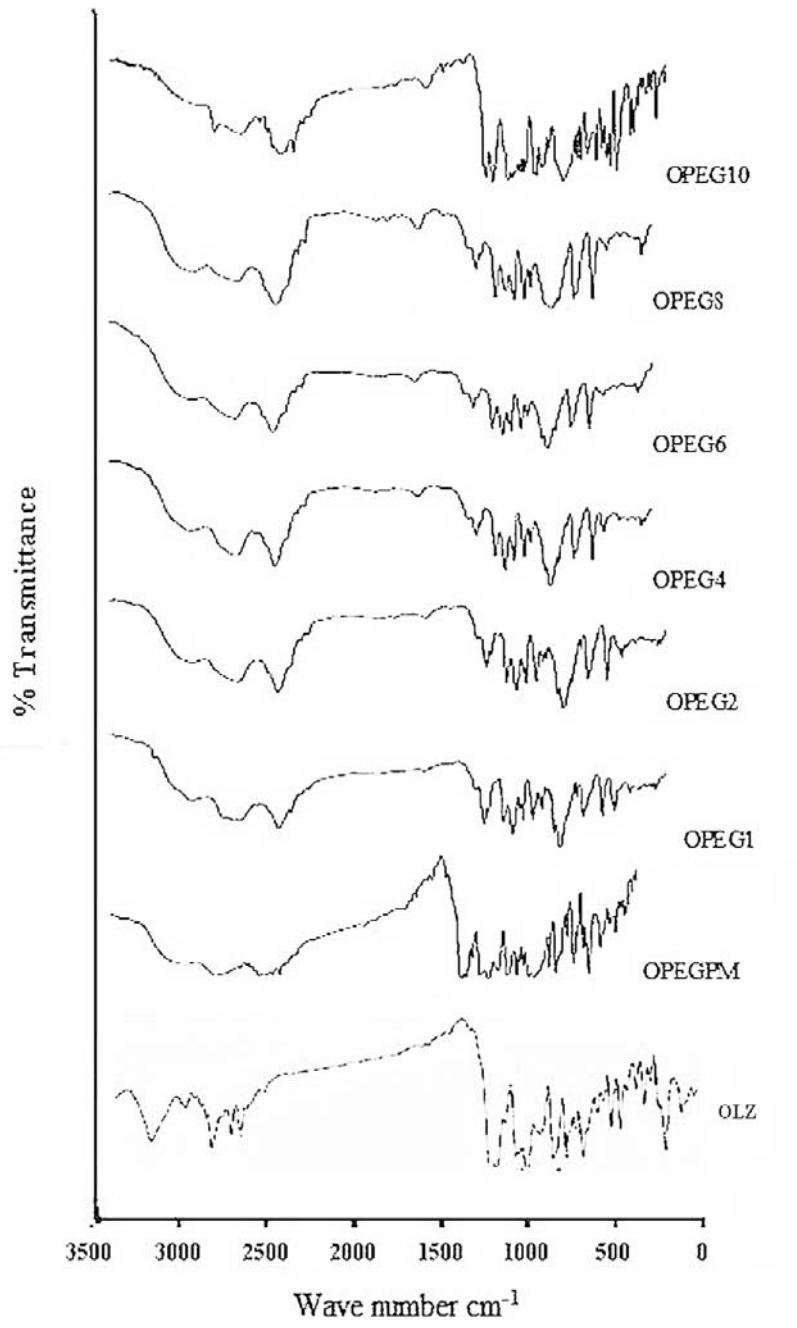

Figure 5. FT-IR spectra of pure olanzapine (OLZ), physical mixtures (PM) at 1 : 1 ratio, solid dispersions (SDs) OPEG1, OPEG2, OPEG4, OPEG6, OPEG8 and OPEG10

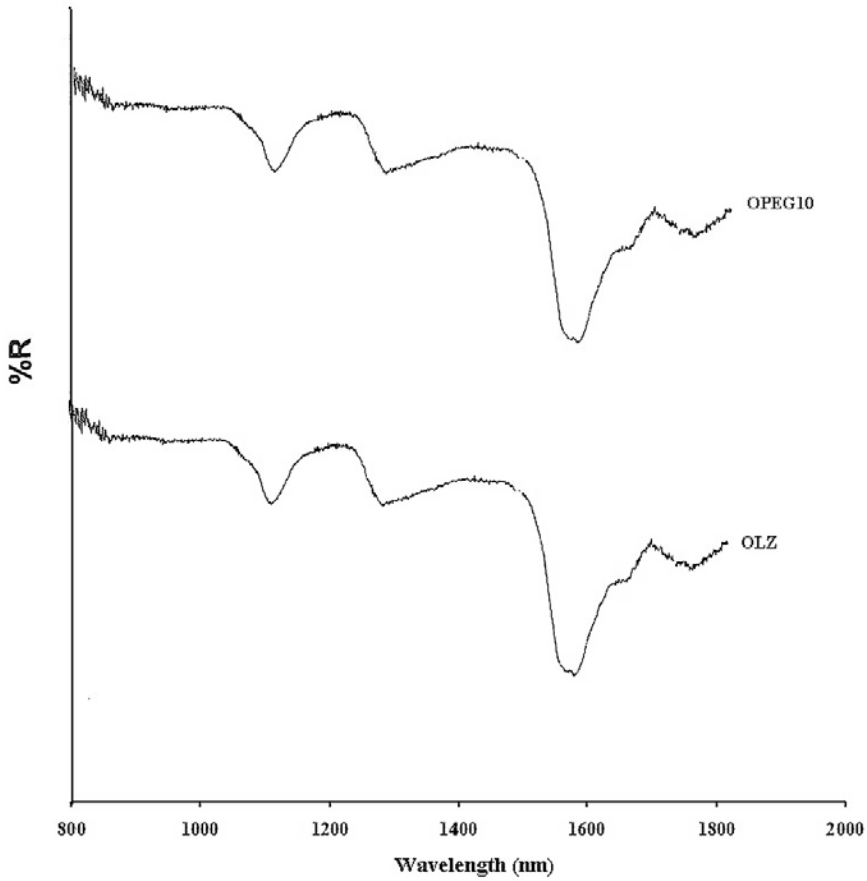

Figure 6. Near infrared spectra of pure olanzapine (OLZ) and solid dispersions (SDs) OPEG10

formation of solid solution are also indicated as the additional factors behind the enhanced dissolution rate from the SDs (8-10, 26-28).

Further, the method of formulation would also decide about the nature of the drug in carrier structure. It was noticed that most of the dispersions formulated by melt solvent or melt dispersion method using PEG as carriers had resulted in formation of a solid solution i.e., drug being molecularly dispersed in the carrier structure. The above said postulations was well supported from the observations made from the results of the *in vitro* wettability and dispersion studies which clearly showed that a polymer rich layer was formed around the tablet and diffusion was clearly observed and tablets surface was found to decrease gradually during the dissolution process (26-28).

Release kinetic analysis

From the release kinetic data of the dispersions it was noticed that the coefficient of correlation "r" value of Korsmeyer Peppas model was found to predominate over the "r" value in other models the release data were found to fit aptly in to Korsmeyer-Peppas kinetic model. Further, the release exponent "n" values were found to be well within 0-0.5, suggesting a Fickian type of drug release from dispersion. The possible mechanisms suggested for high release of OLZ from dispersions was also found to correlate with the findings of release kinetic analysis (14-19).

Solid state characterization

X-ray diffraction analysis

X- ray diffraction spectra of pure OLZ, PEG 6000, physical mixture (1 : 1) and batch OPEG10 are illustrated in Figure 3. The presence of numerous distinctive sharp intense peaks at 2θ of 8.79, 18.48 with peak height of 758.62 and 142.4 in diffractogram of OLZ indicates its high crystalline character (29-31). The carrier (PEG 6000) spectra exhibited a distinct diffraction pattern with two prominent

peaks indicating its nature. The principal peaks of OLZ were found to appear in diffractogram of physical mixture (1 : 1) ratio, suggesting the absence of interaction between drug and carrier.

The peaks present in sample diffractogram are also owed to the carrier PEG 6000. The absence of crystalline peaks of pure OLZ in sample diffractogram indicates that the drug was molecularly dispersed in the carrier structure (26-28).

DSC studies

A sharp single endothermic peak appeared for pure OLZ with the following parameters; Onset at 194.36°C, peak at 196.40°C, area of 262.56 mJ and DH value of 105.023. These values clearly indicate its high crystalline nature (29-31).

A single broad endothermic peak at 65°C in PEG 6000 thermogram denotes its low melting point and its amorphous nature. It was also observed that the prominent peak of OLZ was completely absent in sample (OPEG10) thermogram. Further, the peak parameters (onset at 39.35°C, peak at 45°C, peak area of 28.14 mJ and DH value of 9.078) of samples thermogram in comparison with pure drug may all be related to the nature of carrier. The absence of characteristic peaks of OLZ in sample thermogram clearly reveals that the drug was no more present in its undissolved form and would have resulted in formation of solid solution in dispersions (11, 12, 15). This postulation was also well supported by the method used for preparation of the dispersions with PEG 6000 as carrier, since the drug was added to the molten carrier and solidified. It was also widely reported that many drugs had formed solid solution or dispersed in molecular form, when dispersed in carrier like PEG 6000 (29-31).

FT-IR studies

From the IR spectra of pure drug, carrier and the SDs it was noticed that pure olanzapine showed characteristic absorptions at 3239 cm^{-1} (NH and OH stretching), 2929 cm^{-1} (C-H stretching), 1587 cm^{-1} (C=C stretching), 1421cm^{-1} (C=N stretching) and 1287 cm^{-1} (C-N stretching). The characteristic peaks of pure OLZ were found to be present in the spectra of PM as well as in SDs. This finding reveals the lack of interaction between drug and the carrier in samples. It was also noticed that the significant peaks of pure OLZ at specific wave number (3239 cm^{-1}) was found to be reduced gradually in sharpness and increased in broadness as the amount of PEG 6000 was increased in samples. These findings clearly reveal the possibility of formation of solid solution of drug in the carrier (32).

Near infrared analysis

The characteristic peaks of pure OLZ appeared at 1141 nm and 1581 nm (29, 30). The specific peaks of OLZ were found to be broader in nature and a slight shift in the peak position in spectra of optimized SDs was observed. These findings indicate the reduction of crystallinity of drug present in SDs.

Raman analysis

The sharp peaks of OLZ appeared at 2435, 1594, 1517, 1460, 1224, 1050, 965, 784 and 480 cm^{-1} positions which indicated its high crystallinity (29, 30). The characteristic peaks of pure OLZ were found to be in much reduced form with broadness and slight shift toward their lower wave numbers in sample spectra. These findings clearly suggest that some degree of structural changes had taken place in the drug molecule when dispersed in hydrophilic carriers.

Drug-polymer miscibility studies

Gordon-Taylor analysis

Incomplete miscibility or reduced solubility can result in the formation of concentrated drug spheres that may lead to recrystallization after production and during stability. The T_g of pure OLZ was found to be 196°C and the carrier PEG 6000 showed a T_g of 52°C. A single T_g was observed for the optimized solid dispersions. According to the Gordon-Taylor equation, if the drug and polymer are miscible, the binary mixture will exhibit a single T_g as shown in Table 4. The predicted T_g was found

Table 7. Wettability data of pure olanzapine and selected solid dispersions.

Batch	Wettting time (min)	Water absorption ratio	*In vitro* dispersion time (min)
OLZ	> 60 (2.26)	11.49 (1.14)	> 60 (1.12)
OPEG10	22 (1.24)	15.20 (0.84)	22 (0.96)

Values in parentheses indicate standard deviation n = 3.

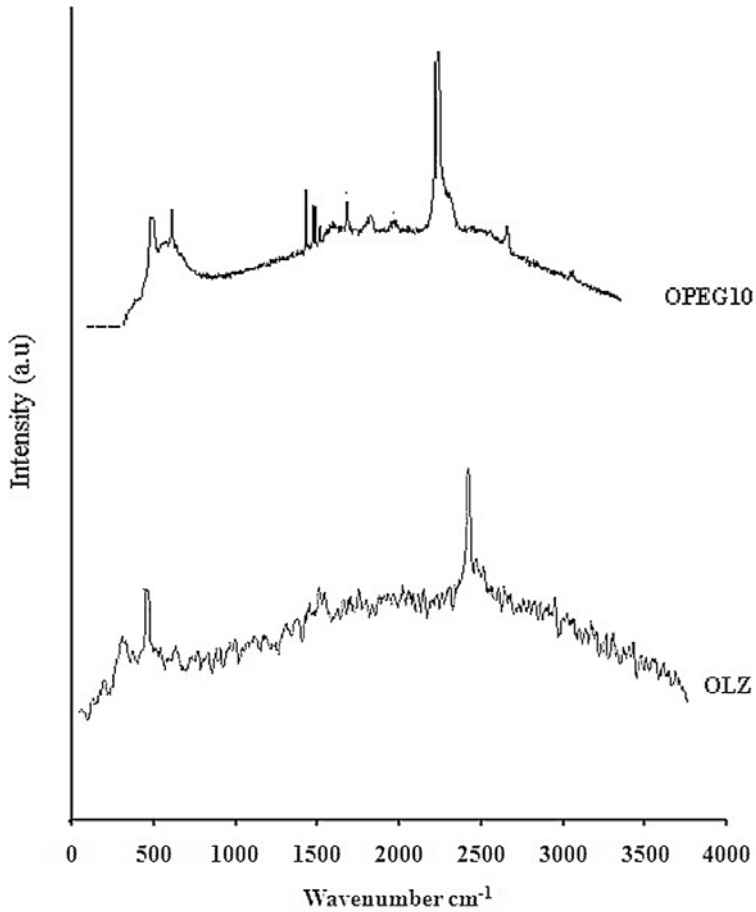

Figure 7. Raman spectra of olanzapine and SDs (OLZ and OPEG10)

to be closely related to the experimental values of the optimized dispersions. These findings were found to correlate well with the earlier reports (20-22).

Flory-Huggins (FH) modeling

FH modeling suggests that if the interaction parameter $\chi \geq 0.5/M$, there are slightest possibility for unfavorable interactions between the drug, polymer and excipient mixture, which may cause phase separation. It was noticed that the calculated value of FH interaction factor (χ) (Table 5) for the optimized dispersions was found to be $\geq 0.5/M$, which signifies higher favorable extent of drug-polymer interactions at micro level. This behavior may be attributed to the reduction of entropy during the formulation of solid dispersion and it also indicated the thermodynamic stability of developed SDs. Adhesive interaction between drug and polymer was favored by the reduction in the T_g of SDs, which implicates the miscibility of drug and polymer (20-22).

Wettability studies

The wetting time and *in vitro* dispersion of pure OLZ was found to be more than 60 min and water absorption ratio of OLZ was found to about 11.49. It was observed that tablets prepared with olanzapine did not show any sign of structural changes after 60 min and it was also found to retain its compactness during the *in vitro* dispersion studies. These results clearly prove the high hydrophobicity, poor wettability and low water absorption potential of OLZ (25-28). The wetting time and *in vitro* dispersion time of sample was found to be 22 min, much less than the pure OLZ (more than 60 min). The water absorption ratio of sample was found to be higher (15.20) than pure OLZ (11.49) indicating the increased water absorption by PEG 6000. It was also observed that tablets prepared with samples of

OPEG10 showed a slow and steady rate of absorption of water and the size of the tablet gradually decreased in size as the time proceeded and it showed the formation of polymer rich layer around the tablet surface resulting in fine powder with smooth appearance. These observations confirm the increased wettability in samples and it also provides a clear insight into the role of hydrophilic carriers in formulations (23-25).

Mechanisms for enhanced release

The possible reasons that might have attributed for increased release rate from SDs are proposed and summarized as particle size reduction, solubilization effect of carrier, change in crystal quality, or formation of solid solution, prevention of aggregation or agglomeration of drug particles in dissolution medium, change in surface hydrophobicity of drug particles, increased wettability due to increased water absorption by the carrier. These postulations were well supported by findings of various physicochemical characterization techniques used for evaluation of SDs. Further, the suggested mechanism for enhanced release was found to be in accordance with the earlier published reports of using such hydrophilic carriers (3, 7-13, 26-29, 33, 34).

CONCLUSION

The findings from this work provide a clear insight into the drug release enhancement process from such systems. The results of the work clearly suggest that SDs formulated with PEG 6000 could be developed in fast release dosage forms with improved oral absorption and therapeutic efficiency. The SDs could be explored further to establish pharmacokinetic and pharmacodynamic profiles to utilize their potential.

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The authors declare that there is no conflict of interest among them.

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