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Article

Physicochemical characterization and *in vitro* dissolution behavior of olanzapine-mannitol solid dispersions

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The objective of the present work is to study the dissolution behavior of olanzapine from its solid dispersions with mannitol. 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 selected from release data, dissolution parameters and their release profiles. Solid state characterization techniques like Fourier transform infrared (FT-IR) spectroscopy, X-ray diffractometry, differential scanning calorimetry, near-infrared and Raman spectroscopy were used to characterize the drug in selected dispersions. The dispersions were also evaluated by wettability studies and permeation studies. The results of phase solubility studies and the thermodynamic parameters indicated the spontaneity and solubilization effect of the carrier. The release study results showed greater improvement of drug release from solid dispersions compared to pure drug, and the release was found to increase with an increase in carrier content. The possible mechanism for increased release rate from dispersions may be attributed to solubilization effect of the carrier, change in crystal quality, phase transition from crystalline to amorphous state, prevention of agglomeration or aggregation of drug particles, change in surface hydrophobicity of the drug, and increased wettability and dispersability of the drug in dissolution medium. The suggested reasons for increased release rate from dispersions were found to be well supported by results of solid state characterization, wettability and permeation studies. The absence of any interaction between the drug and the carrier was also proved by FT-IR analysis.

Uniterms: Olanzapine. Mannitol. Solid dispersions.

O objetivo do presente trabalho é estudar o comportamento de dissolução da olanzapina a partir de suas dispersões sólidas de manitol. As dispersões sólidas foram preparadas por dispersão por fusão e caracterizadas por estudos de solubilidade de fase, conteúdo de fármaco e dissolução *in vitro*. As melhores dispersões quanto à liberação foram selecionadas a partir dos dados de liberação, parâmetros de dissolução e perfis de liberação. Técnicas de caracterização de estado sólido como espectroscopia no infravermelho pela transformada de Fourier (FTIR), difratometria de raios X, calorimetria de varredura diferencial, infravermelho próximo e espectroscopia Raman foram utilizadas para caracterizar os fármacos a partir das dispersões selecionadas. As dispersões foram, também, avaliadas pelos estudos de capacidade de umedecimento e permeação. Os resultados dos estudos de solubilidade de fase e os parâmetros termodinâmicos indicaram a espontaneidade e o efeito de solubilização do transportador. Os resultados dos estudos de liberação mostraram maior aperfeiçoamento da liberação do fármaco das dispersões sólidas, comparativamente à do fármaco puro, e descobriu-se que a liberação aumenta com o aumento do conteúdo de transportador. O mecanismo possível para o aumento da taxa de liberação das dispersões pode ser atribuído ao efeito de solubilização do transportador, mudança da qualidade do cristal, transição de fase cristalina para estado amorfo, prevenção da aglomeração ou agregação das partículas do fármaco, mudança na superfície de hidrofobicidade do fármaco e aumento da capacidade de umedecimento e dispersividade do fármaco no meio de dissolução. As razões sugeridas para o aumento da taxa de liberação a partir das dispersões foram apoiadas pelos resultados da caracterização do estado sólido, capacidade de umedecimento e pelos estudos de permeação. A ausência de qualquer interação entre o fármaco e o transportador foi, também, comprovada pela análise no FTIR.

Unitermos: Olanzapina. Manitol. Dispersões sólidas.

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INTRODUCTION

The dissolution of a drug from its solid oral dosage forms depends upon its release from the dosage form and its subsequent mixing into physiological fluids. It has been estimated that nearly 35-40% of the drugs suffer from poor aqueous solubility, thereby affecting their absorption from the gastrointestinal tract, which leads to poor oral bioavailability, high intra- and inter-subject variability, increase in dose, reduction in therapeutic efficiency and finally failure in formulation development (Lipinski, 2002). The development of solid dosage forms for water-insoluble drugs has been a major challenge for pharmaceutical scientists for decades. Various formulation strategies such as micronisation, micellar solubilization, complexation, dendrimers for drug solubilization, formation of solid solutions or dispersions with hydrophilic carriers, self-microemulsifying drug delivery systems, spray drying, nano approaches, pro-drug approaches and salt synthesis (Pinnameni *et al*., 2002) have been developed to increase the dissolution rate of water-insoluble drugs.

An attractive possibility is employing a simple solid dispersion technique making use of various hydrophilic carriers (Chiou, Reigelmann, 1971; Dhirendra *et al*., 2009; Ansu, Jain, 2011). 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, and are prepared by the fusion, solvent or solvent-fusion method (Chiou, Reigelmann, 1971). This technique enables reducing particle size to a nearly molecular level, offers a variety of processing and excipient options that allow for flexibility when formulating oral delivery systems of poor water-soluble drugs that are cost-effective and significantly reduced in dosage (Serajuddin, 1999; Dhirendra *et al.*, 2009). It has been widely demonstrated that a hydrophilic carrier dissolves rapidly, exposing the drug particles to the dissolution medium as fine particles facilitating quick dissolution and absorption.

The mechanisms for increased dissolution rate may include reduction of crystallite size, solubilization effect of the carrier, absence of aggregation of drug crystallites, improved wettability and dispersability of a drug from the dispersion, dissolution of the drug in the hydrophilic carrier or conversion of the drug to an amorphous state (Craig, 2002; Biswal *et al*., 2008).

Schizophrenia is a severe non-curable illness of the brain with serious consequences if not properly treated and kept under control. It is the most common form of severe mental illness. Olanzapine (OLZ;2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno-[2,3-*b*],[1,5]benzodiazepine) is a relatively new benzodiazepine atypical antipsychotic medication, which belongs to the class of the thienobenzodiazepines and has proven efficacy against the positive and negative symptoms of schizophrenia, bipolar disorder and other forms of psychosis. It exhibits poor water solublility and belongs to Biopharmaceutic Classification System (BCS) class II of drugs (low solubility and high permeability), highly bound to plasma protein (about 93%) (Callaghan *et al*., 1999; Ayala *et al*., 2006). Following oral administration, C_{max} is reached within 5–6 h of dosing. OLZ undergoes extensive pre-systemic metabolism in the liver, resulting in relatively very low oral bioavailability (Cheng *et al*, 2000; Di NunZio *et al*., 2008). The objective of this work is to enhance the aqueous solubility of poorly water-soluble drug OLZ by adopting a solid dispersion approach using mannitol as the hydrophilic carrier and to physico-chemically characterize the *in vitro* dissolution behavior of the solid dispersions.

MATERIAL AND METHODS

Material

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

Methods

Dispersion method

A series of solid dispersions were prepared using a varying ratio of the carrier (mannitol). The level of OLZ was kept constant in all the dispersions. The drug:carrier ratios tried were 1:1, 1:2, 1:4, 1:6, 1:8 and 1:10. OLZ was dissolved in absolute ethanol to get a clear solution. The carrier was powdered well in a mortar. The OLZ solution was then added to the powdered carrier with constant trituration. The wet solid mixture was dried at 60 °C for 6 h. The dried mass was kept in a dessicator for 12 h. Then the dried mass was powdered and sifted through sieve no.100. The samples are then stored in dessicator until further use (Chowdhary, Rao, 2000; Masataka *et al.*, 2002; Markus *et al.*, 2008).

Phase solubility studies

Phase solubility studies were carried out by adding excess amount of OLZ to 25 mL of aqueous solutions containing increasing amounts of carrier (1:1 to 1:10)

in screw-capped bottles and shaken in an orbital shaker (Remi Ltd, Mumbai) and incubated at 25 °C and 37 °C for 24 h. Samples with pure drug and water was used as control. After 24 h, the solutions were filtered using a Whatman 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 used in phase solubility analysis to calculate various thermodynamic parameters such as ΔH, ΔS and ΔG (Higuchi, Connors, 1965; Arias *et al*., 1999; Cirri *et al*., 2004; Biswal *et al*., 2008).

Phase solubility analysis

• Stability constant (Biswal *et al*., 2008; Singh *et al*., 2009)

The value of apparent stability constant (K_a) of drug–carrier combinations were computed from the phase solubility profiles as described below:

$$\text{Ka} = \frac{\text{Slope}}{\text{Intercept}\ (1 - \text{Slope})} \qquad \text{Eq. 1}$$

Gibbs energy (ΔG) was calculated using the formula

$$\Delta G = -RT \ln Ka \qquad \text{Eq. 2}$$

where R is the universal gas constant (8.313 J/mol K), T the temperature, and Ka the stability constant.

• Enthalpy

The enthalpy change in the systems was calculated from Van't Hoff equation:

$$\Delta\text{H} = \frac{-\text{RT ln Ka}}{\text{dT (K)}} \qquad \text{Eq. 3}$$

where R is the universal gas constant (8.313 J/mol K), K_a the stability constant, and dT the difference in temperature (Kelvin).

• Entropy

The entropy of the system was calculated from the equation

$$\Delta\text{S} = \frac{\Delta\text{H} - \Delta\text{G}}{\text{T}} \qquad \text{Eq. 4}$$

where ΔH is the enthalpy and ΔG the entropy.

Drug content

The assay of a weighed amount of solid dispersions was carried out to determine the drug content. The weighed samples were dissolved in 10 mL of analytical media and stirred by a vortex mixer. The solutions were filtered using a Whatman filter paper (0.45 µm, 13 mm, Whatman, USA). Then the filtrate was diluted suitably and the content was estimated spectrophotometrically (UV-1700, Shimadzu, Japan) at 259 nm using the standard curve, applying a validated method (data not shown).

In vitro dissolution studies

The *in vitro* dissolution study of all solid dispersions of OLZ in mannitol was carried out on USP dissolution apparatus (Campbell Electronics, Mumbai) and the results were compared with those for pure OLZ. The dissolution vessels contained 900 mL of 0.1 N HCl maintained at 37 °C ± 0.5 °C and paddle speed set at 50 rpm. Solid dispersions equivalent to 20 mg of OLZ were added to the dissolution medium in a powder form. Then, 5 mL samples were withdrawn at 5, 10, 20, 30, 40, 50 and 60 min from the dissolution medium through a graduated pipette equipped with plastic tube end closed with a cotton plug. The presence of cotton plug allows only the dissolved OLZ to be collected and filters all the carrier components. The withdrawn sample was replenished with 5 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 OLZ was calculated from the standard curve [OD=0.1149 × concentration+ 0.001(R^2 = 0.9999; $p > 0.001$). The *in vitro* dissolution parameters such as cumulative per cent drug release and dissolution parameters such as amount released (Q), per cent 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 applying release data into various equations given below (Cirri *et al*., 2004; Biswal *et al*., 2008; Singh *et al*., 2009).

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

Time taken to release 50% of drug was calculated by

$$t_{50\%} = \frac{0.693}{K} \qquad \text{Eq. 5}$$

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 trap-

ezoidal method and is expressed as a percentage of the area of the rectangle divided by the area of 100% dissolution in the same time:

$$\% DE = \left(\frac{\int_0^t y.dt}{y100 * t} \right) \quad \text{Eq. 6}$$

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 the equation

$$DRC = Slope * 2.303 \quad \text{Eq. 7}$$

Release kinetics

To study the release kinetics of the drug from the solid dispersions, the release data were fitted in to the following equations.

Zero order (K_0)

$$Q_t = Q_0 + K_0 t \quad \text{Eq. 8}$$

where Q_t is the amount of drug released at time t, Q_0 the amount of drug in solution at time t=0 (usually Q_0=0) and K_0 is zero-order release constant.

First order constant (K_1)

$$logQ_t = logQ_0 * K_1 \frac{t}{2.303} \quad \text{Eq. 9}$$

where Q_t is the 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 is the first-order release constant.

Higuchi model

$$M_t = K\sqrt{t} \quad \text{Eq. 10}$$

where M_t is the amount of drug dissolved at particular time t, K the Higuchi release constant.

Hixson Crowell model

$$(W_0)^{\frac{1}{3}} - W_t)^{\frac{1}{3}} = K_{\frac{1}{3}}\, t \quad \text{Eq. 11}$$

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

Further, in order to better characterize the drug release behavior from the dispersions, the Korsemeyer-Peppas empirical model was applied:

$$\frac{Q_t}{Q_\infty} = k_{KP} * t^n \quad \text{Eq. 12}$$

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, $n \leq 0.5$ 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 (Costa, Lobo, 2001; Hamid *et al*., 2006).

Solid State characterization

Fourier Transform Infrared Spectroscopic Studies (FT-IR)

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

X-ray Diffraction Studies (X-RD)

Diffraction patterns (X-ray diffractometer (Philips, Finland), 40 kV, 30 mA generator with a Cu-Kα radiation tube) of the pure drug, physical mixtures and selected solid dispersions were scanned over 2Ø range from 2 °C to 50 °C at the rate of 2 °C per min at 0.02° at 2Ø 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 a liquid nitrogen cooling accessory. The analysis was performed under purge of nitrogen gas (50 cc/min). High-purity indium was used to calibrate the heat flow and heat capacity of the instruments. The sample (5–10 mg), placed in flat-bottomed aluminum pan, was firmLy capped with a lid to provide an adequate seal. The sample was heated from ambient temperature to 400 °C at pre-programmed heating rate of 10 °C min^{-1}.

Near-infrared (NIR) analysis

NIR spectra of the pure drug and selected samples were recorded using a 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.

Confocal Raman spectroscopic analysis

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

Wetting studies

Formulation of tablets

As per the results of the *in vitro* release studies, the solid dispersion that had the highest concentration of mannitol was selected as the best releasing solid dispersion from the samples. The tablets of pure OLZ and selected solid dispersions (OMAN 10) were formulated by using 20 mg of pure OLZ and solid dispersions equivalent to 20 mg of OLZ. Each tablet weighed around 250 mg. Sufficient quantity of microcrystalline cellulose (diluent) and magnesium stearate (lubricant) were added and the resulting product 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. The wetting studies were carried out only on the tablets made from pure drug and the selected solid dispersions.

Wetting time studies

Five circular tissue papers were placed in a petri dish 10 cm in diameter. Ten mL of 0.5% methylene blue solution, 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 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 triplicate. Wetting time was recorded using a digital watch (Gohel, Patel, 2000; Sunilkumar *et al*., 2008; Adel *et al*., 2009).

Water absorption ratio

The weight of the tablet prior to placement in the petri dish was noted (W_b) using a Metler Toledo Digital balance. The wetted tablet was removed and reweighed (W_a). Water absorption ratio (R) was then determined using Eq. 10 (Sunilkumar *et al*., 2007; Adel *et al*., 2009).

$$R = \frac{W_a - W_b}{W_B} \qquad \text{Eq. 13}$$

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 (Adel *et al*., 2009; Shoukri *et al*., 2009).

Permeation studies

Preparation of egg membrane

The outer shell membrane of the egg of *Gallus Domesticus* just located inside the shell exactly under the hard calcified layer was prepared by immersing the egg in 0.01 N HCl for 6 h to dissolve the calcified layer. The membrane was cut cautiously to expel the contents of the egg and washed with normal saline solution. The inner membrane was repeatedly washed with water and stored in distilled water (Mehdi *et al*., 2006; Corti *et al*., 2009).

Preparation of onion membrane

The middle membrane of the *Allium Cepa* L. (onion) was peeled or separated with caution by gradual application of water in filler to avoid damage to the membrane. The stripped membranes (3 cm^2) without any crack or orifice were selected and stored in cold water until further use (Mehdi *et al*., 2006).

Preparation of tomato membrane

Tomatoes were boiled in hot water for about 15 min. The softened outer layer of tomato was removed carefully and repeatedly washed with water to remove the fleshy

TABLE I - Composition of tablets for wetting studies

Composition	Olanzapine (mg)	OMAN 10 (mg)
OLZ	20	–
Selected SD (OMAN 10)	–	≡ 20 mg of olanzapine (217 mg of SD)
Microcrystalline cellulose	223	26
Magnesium stearate	7	7
Total	250	250

parts of tomato. The washed membranes were stored in cold water until further use (Mehdi *et al*., 2006).

Through natural membrane

All the membranes were inspected by a microscope to ensure their integrity and uniformity. Their thickness was measured by a caliper, and membranes that had thickness similar to a cellophane membrane were used for further studies. The required length of egg, onion or tomato membrane was cut and tied or glued to the bottom (grounded) layer of the diffusion cell with a thread to form an inner compartment.

Ten mL of 0.1 N HCl were added to the inner compartment and placed in a beaker containing 100 mL of 0.1 N HCl, which acts as an outer compartment. Care was taken to make sure that the level of media in both compartments is equal. A magnetic bead was added to the outer compartment to stir the contents during the studies. The entire assembly was placed in a magnetic stirrer (Remi Ltd, Mumbai, India) and temperature was maintained at 37 ± 1 °C. The weighed amount of the pure drug was added to the inner compartment of the diffusion cell and the studies were performed for duration of 30 min. At predetermined time intervals, samples were withdrawn and the same volume of media was replenished to maintain the sink volume. The solutions were suitably diluted and the absorbance was measured spectrophotometrically at 259 nm (UV-1700, Shimadzu, Japan). The procedure was repeated with the selected solid dispersions (OMAN10) and with each of the membranes (egg, onion, tomato, cellulose acetate and cellulose nitrate) (Mehdi *et al*., 2006).

Through cellulose nitrate and cellulose acetate

Cellulose acetate and cellulose nitrate membrane were procured as readymade membranes and rinsed in distilled water prior to studies. The cellulose nitrate and acetate membrane were glued to the bottom (grounded) layer of the diffusion cell and the procedure was repeated in the same way as the diffusion studies were performed using egg and other natural membranes (Mehdi *et al*., 2006).

The apparent permeability coefficient (P_{app}) was calculated using the following equation:

$$P_{app} = \frac{dq}{dt} * \frac{1}{A * Co} \qquad \text{Eq. 14}$$

where dq/dt is the linear appearance rates of drug in the receiver solution during sink conditions, A is the surface area of the membrane and C_0 the initial drug concentration in donor compartment (Mehdi *et al*., 2006; Corti, *et al.,* 2005).

Statistical analysis

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

RESULTS AND DISCUSSION

Physico-chemical characterization

Phase solubility studies

Phase solubility studies were conducted to determine the effect of temperature, solubilization effect of the carrier and the spontaneity of solubilizing process when the drug is physically mixed with mannitol. The thermodynamic parameters of OLZ and its physical mixtures are shown in Table II. The solubility of OLZ was found to show a linear increase with an increase in the amount of carrier and temperature. These results were found to be in accordance with the well-established formation of weak soluble complexes (Cirri *et al*., 2004; Biswal *et al*., 2008). It is also known from earlier studies that the drug molecules might have transferred from pure water into the aqueous solution of carriers, which was confirmed in our studies clearly from the negative thermodynamic parameters like ΔG and ΔH and positive entropy ΔS of physical mixtures. These findings prove the spontaneous nature of the solubilization process. The enhancement of drug solubility in the 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 bonding such as van der Waals forces, and this was the likely cause for the formation of weakly soluble complexes. The slopes of straight linear relationship was assumed as indicative of the relative solubilizing efficiency of the carrier (Higuchi, Connors, 1965; Arias *et al*, 1999; Cirri *et al.,* 2004; Biswal *et al*., 2008; Singh *et al*., 2009).

Drug content

The assayed drug content in all solid dispersions was found to be in the range of 98–104%, indicating the uniform distribution of the drug in formulations and the suitability of the method used for the formulation of dispersions.

In vitro dissolution studies

The % cumulative release of pure OLZ was found to be 70% in 1 h while solid dispersions showed a significant improvement in release rate in the same period. The percentage of drug release from SDs was found to increase

TABLE II - Thermodynamic parameters of olanzapine physical mixtures with carriers

S. No	Carrier	Temp. (°C)	Slope	Intercept	K_a (M^{-1})	ΔG (kJ/mol)	ΔH (kJ/mol)	ΔS (J/mol K)
1	MAN	25	–8.46	3.797	–0.236	–1.958	–1.955	1.951
		37	–118.9	10.59	–1.188	–0.787	–0.787	0.784

gradually as the amount of carrier in solid dispersions was increased from 1:1 to 1:10 (Figure 1).The *in vitro* release data of sample solid dispersions showed a significant difference ($p > 0.001$) in the release rate in comparison with pure OLZ. The *in vitro* dissolution parameters of the SDs are presented in Table III. It was found that parameters like % cumulative release, amount of drug released, % DE and RDR values were found to exhibit a linear increase with increase in the amount of carrier in dispersions. The other parameters like DRC, $t_{50\%}$ and $t_{85\%}$ values were found to decrease with an increase in carrier fraction.

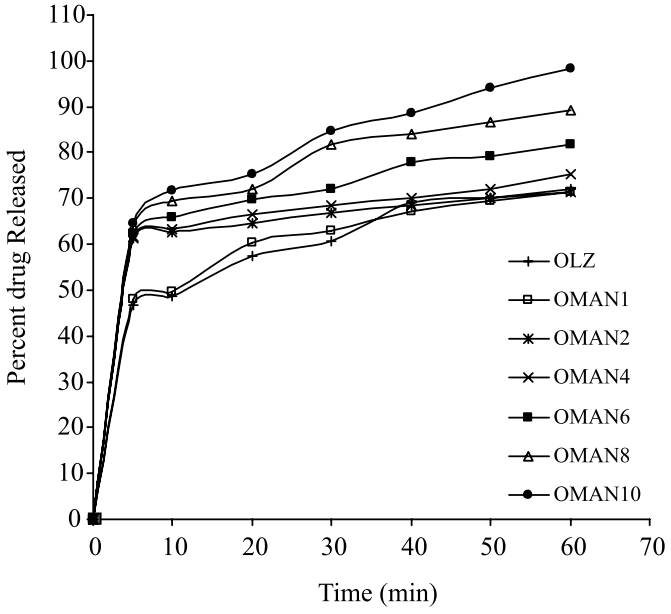

FIGURE 1 - Dissolution profiles of olanzapine–mannitol SDs compared with pure OLZ. All data points represent the mean of 3 values, n=3. ⏐- OLZ, □- OMAN1, ж-OMAN2, X- OMAN4, ■-OMAN6, Δ- OMAN8 and ●- OMAN10.

The correlation plot of % DE and $t_{50\%}$ is shown in Figure 2. The % DE values were found to increase from 59.61% (for pure OLZ) to 80.73% (for solid dispersions) with 1:10 ratio. The dissolution half-life was found to decrease from 12.5 (pure OLZ) to 3.5 (for OMAN10), and $t_{85\%}$ were found to be reduce from 60 min (for pure OLZ) to 30 min (for OMAN 10). Based on these findings, it can be inferred that batch OMAN10 was found to exhibit best release behavior than other solid dispersions. The order of OLZ drug release from the solid dispersions could be ranked as: OMAN10 > OMAN > 8 > OMAN> 6 > OMAN4 > OMAN2 > OMAN1 > OLZ.

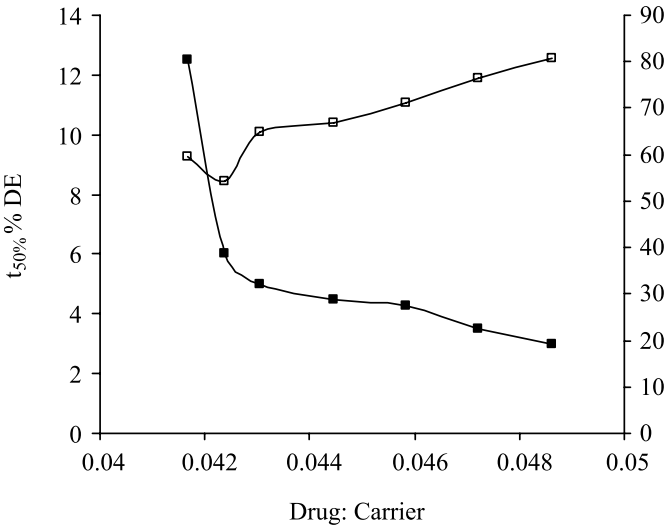

FIGURE 2 - Correlation plot for dissolution efficiency (% DE) and dissolution half-life ($t_{50\%}$). ■- Dissolution half-life and □-% dissolution efficiency.

The difference in $t_{50\%}$ and %DE between the pure durg and solid dispersions was evaluated statistically. When examined by two-way analysis of variance, the $t_{50\%}$ and % DE data showed significant difference between the pure drug and test products (p>0.001).

The possible reasons for enhanced release rate of OLZ from such dispersions could be that hydrophilic carrier mannitol forms a hydrophilic diffusion layer around the drug particles, altering the hydrophobic surface characteristics, which results in an increased wettability of drug within the dissolution medium. The factors like decreased particle size, decreased crystallinity and prevention of aggregation and agglomeration of the drug by the carrier are also indicated as the additional factors responsible for the enhanced dissolution rate from the solid dispersions (Masataka *et al*., 2002; Valizadeh *et al*., 2004; Natalia *et al*., 2005; Nokhodchii *et.al*., 2007). Earlier studies have shown that if the amount of carrier in the dispersion is very

TABLE III - Dissolution parameters of olanzapine–MAN solid dispersion

Code	Composition OLZ:MAN	Q_{05} (mg)	Q_{30} (mg)	DE %	RDR 05	RDR 30	DRC	$t_{50\%}$ (min)	$t_{85\%}$ (min)
OLZ	1:0	9.34 (0.12)	12.15 (0.56)	59.61	–	–	0.020 (0.001)	12.5	>60
OMAN1	1:1	9.63 (0.47)	12.57 (0.24)	54.31	1.03	0.89	0.024 (0.001)	6.0	>60
OMAN2	1:2	12.23 (0.24)	13.36 (0.24)	64.82	1.31	1.10	0.023 (0.001)	5.0	>60
OMAN4	1:4	12.83 (0.21)	13.67 (0.09)	66.95	1.37	1.12	0.022 (0.001)	4.5	>60
OMAN6	1:6	12.44 (0.68)	14.38 (0.16)	70.98	1.33	1.18	0.016 (0.001)	4.25	>60
OMAN8	1:8	12.15 (0.12)	16.36 (0.16)	76.35	1.30	1.35	0.007 (0.003)	3.5	44.5
OMAN10	1:10	12.94 (0.35	16.94 (0.12)	80.73	1.39	1.39	-0.016 (0.031)	3.0	30.0

Values in parenthesis indicates standard deviation:
Q_{05} – Amount released at 05 min (mg)
Q_{30} – Amount released at 05 min (mg)
% DE – Per cent dissolution efficiency
DRC – Dissolution rate constant
RDR – Relative dissolution rate at specific time intervals
$t_{50\%}$ – Dissolution half-life
$t_{85\%}$ – Time taken to release 85% of drug from dispersions

high, there is a possibility of the drug being dispersed in the molecular form in the carrier structure with reduced crystallinity and this phenomenon would have also assisted in increasing the dissolution rate (Arias *et al*., 1996; Masataka *et al*., 2002; Cirri *et al*., 2004; Valizadeh *et al*., 2004; Nokhodichii *et.al*., 2007; Karavas *et al*., 2007).

The release kinetics of the *in vitro* dissolution data (Table IV) and the regression parameters were analyzed to ascertain the type of drug release from solid dispersions. Since the co-efficient of correlation *r* value of Korsemeyer-Peppas model was found to predominate over the *r* value in other models, the release data were found to fit aptly into Korsemeyer-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 the dispersion (Costa, Lobo, 2001; Hamid *et al*., 2006). The possible mechanism suggested for high release of OLZ from dispersions was also found to correlate with the findings of release kinetic analysis.

Solid state characterization

FT-IR studies

The FT-IR spectra of OLZ, physical mixtures (1:1) and SDs are presented in Figure 3. Pure OLZ showed characteristic absorptions at 3239 cm^{-1} (NH and OH stretching), 2929 cm^{-1} (C–H stretching), 1587 cm^{-1} (C=C stretching), 1421 cm^{-1} (C=N stretching) and 1287 cm^{-1}

TABLE IV - Release kinetic parameters of olanzapine–MAN 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	8.24	0.751	0.012	0.993	0.257
OMAN1	0.768	0.819	0.121	0.009	0.021	0.827	8.05	0.703	0.011	0.990	0.258
OMAN2	0.620	0.674	0.177	0.010	0.023	0.637	7.20	0.456	0.009	0.937	0.246
OMAN4	0.646	0.724	0.154	0.009	0.021	0.667	7.60	0.511	0.010	0.947	0.256
OMAN6	0.696	0.845	0.093	0.007	0.016	0.732	8.62	0.629	0.013	0.967	0.284
OMAN8	0.732	0.971	0.021	0.003	0.007	0.778	9.72	0.731	0.017	0.979	0.314
OMAN10	0.775	1.110	0.075	-0.007	-0.016	0.828	10.82	0.877	0.026	0.989	0.342

K_0 – Zero-order release constant, K_1 – First order release rate constant and n – release exponent
K-P – Korsemeyer Peppas model

(C–N stretching) (Ayala *et al*., 2006; 2007; Hiriyanna *et al*., 2008). The characteristic peaks of pure OLZ were found to be present in the spectra of PM as well as in solid dispersions. This finding reveals the lack of interaction between the drug and the carrier in the samples. It was also noticed that the significant peaks of pure drug at specific wave number (3239 cm^{-1}) was found to be in reduced form, with less sharpness and more broadness as the amount of mannitol was increased in the samples. These findings clearly prove the reduction of crystallinity in the drug molecule present in samples (Ayala *et al*., 2006; Ayala, 2007; Hiriyanna *et al*., 2008).

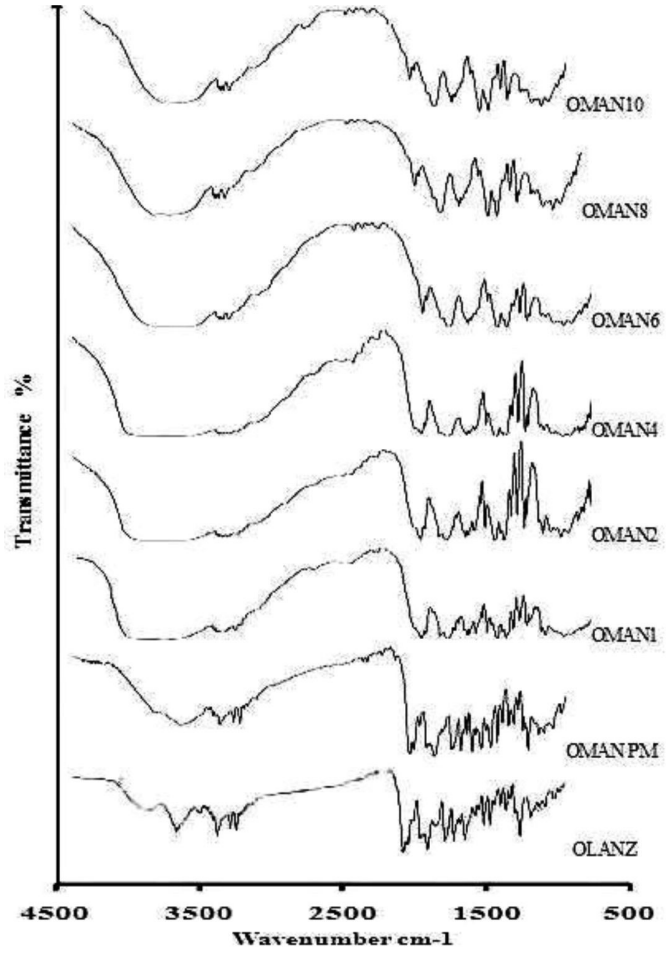

FIGURE 3 -FT-IR spectra of pure olanzapine (OLANZ), physical mixtures (OMANPM) at 1:1 ratio, solid dispersions (SDs) OMAN1, OMAN2, OMAN4, OMAN6, OMAN 8 and OMAN10.

X-ray diffraction analysis

X-ray diffraction spectra of pure OLZ, mannitol, physical mixture (1:1) and batch OMAN 10 are illustrated in Figure 4. The presence of sharp distinct peaks in OLZ spectra indicated its high crystallinity. The carrier (mannitol) spectra exhibited a distinct diffraction pattern with prominent peaks at 2Ø of 18.95, 20 and 22.10º (Valizadeh *et al*., 2004; Manish *et al*., 2007). The principal peaks of the drug were found to appear in diffractogram of physical mixture in 1:1 ratio, suggesting the absence of interaction between the drug and the carrier. The prominent peak of OLZ at 2Ø of 5º was found to be reduced in sharpness in the diffractogram of the sample OMAN10.

Further the peaks in sample diffractogram was also found to possess less peak height, low relative intensity and high full width at half-minimum (FWHM) values than the peaks corresponding to the pure drug. From these observations, it can be concluded that the crystalline nature of the drug was still maintained, but the relative reduction of diffraction intensity of OLZ suggests that the quality of the crystal was reduced. These observations confirm the reduction of crystallinity of OLZ present in dispersions (Arias *et al*., 1999; Cirri *et al*., 2004; Valizadeh *et al*., 2004; Nokodichii *et al*., 2007; Singh *et al*., 2009).

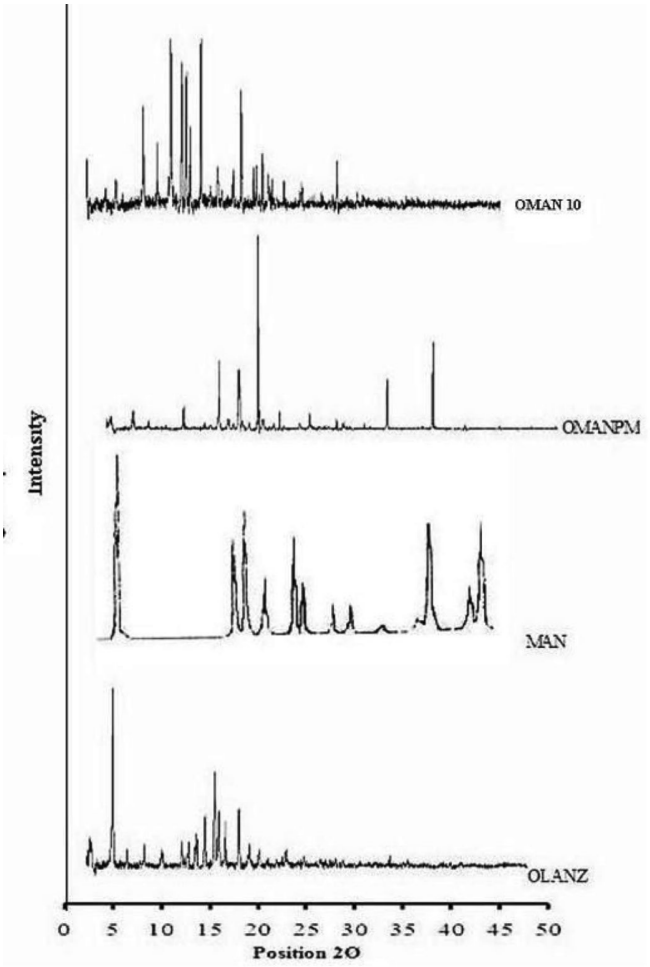

FIGURE 4 - XRD spectra of pure olanzapine (OLANZ), mannitol (MAN), physical mixtures (OMANPM) at 1:1 ratio and solid dispersions (SDs) OMAN 10 at 1:10 ratio.

Differential scanning calorimetry (DSC) studies

The DSC scans of pure OLZ, PGS and optimized solid dispersions (OMAN10) are presented in Figure 5. 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 Δ*H* value of 105.023. These values clearly indicate its high crystalline nature (Ayala *et al*., 2006; Ayala, 2007).

Two peaks were observed in the sample thermogram: one at 165.95 °C (due to carrier) and a very short, reduced endothermic peak at 190.05 °C (of drug) with a peak area of 65.96 mJ and increased Δ*H* value. This variation in thermal behavior of selected solid dispersions can be attributed to the fact that the reduced crystallinity or phase transition (from crystalline to amorphous form) had occurred in the drug molecule during the formulation of solid dispersions. These changes in the structure of the drug molecule might have contributed to the enhanced dissolution rate of OLZ from the dispersions (Arias *et al*., 1999; Valizadeh *et al*., 2004; Nokodichii *et al*., 2007).

Near-infrared Analysis

The near-infrared spectra of OLZ and optimized solid dispersions (OMAN10) are compared in Figure 6.

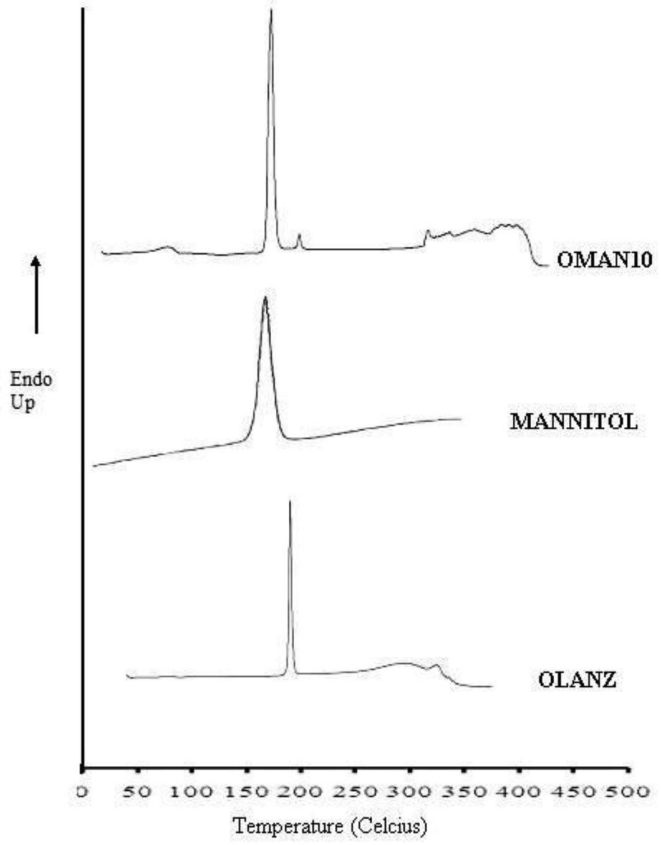

FIGURE 5 - DSC thermograms of pure olanzapine, mannitol and solid dispersions (SDs) at 1:10 ratio.

The characteristic peaks of pure OLZ appeared at 1141 and 1581 nm (Ayala *et al*., 2006; Ayala, 2007). The specific peaks of OLZ in spectra of optimized solid dispersions were found to be broader in nature and a slight shift in the peak position in comparison with the spectra of pure OLZ. These findings indicate the reduction of crystallinity of the drug present in SDs.

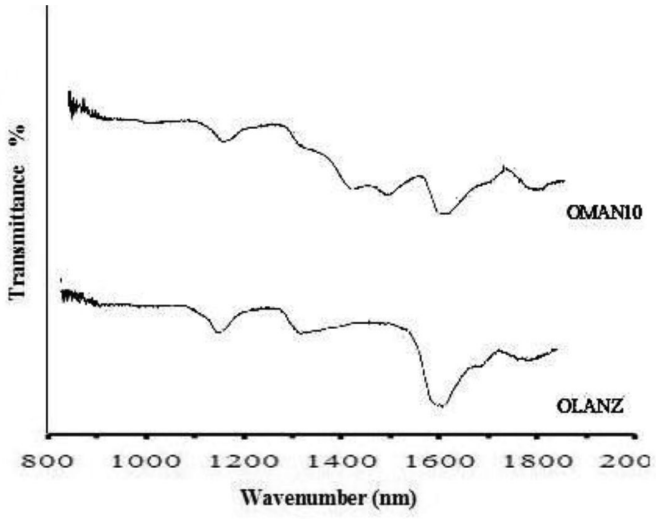

FIGURE 6 - Near-infrared spectra of pure olanzapine (OLZ) and solid dispersions (SDs) OMAN10.

Raman analysis

The Raman spectra of pure OLZ and selected solid dispersions (OMAN10) are compared in Figure 7. The sharp peaks of OLZ appeared at 2435, 1594, 1517, 1460, 1224, 1050, 965, 784 and 480 cm^{-1} positions (Ayala *et al*., 2006; Ayala, 2007) in pure drug spectra, which is indica-

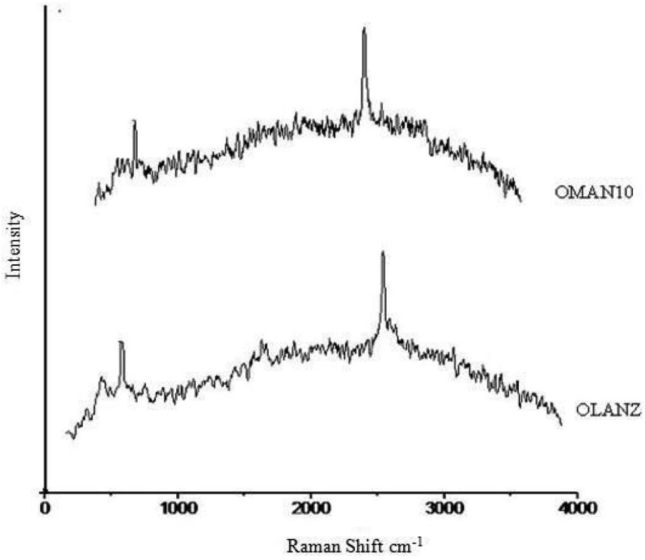

FIGURE 7 - Raman spectra of olanzapine (OLZ) and SDs (OMAN 10).

TABLE V - Wettability data of pure olanzapine and selected solid dispersions

Batch	Wetting Time (min)	Water Absorption Ratio	*In vitro* Dispersion Time (min)
OLZ	>60 (2.26)	11.49 (1.14)	> 60 (1.12)
OMAN10	18 (2.36)	15.86 (0.96)	18 (0.86)

Values in parenthesis indicates standard deviation (n=3).

tive of its high crystallinity. The characteristic peaks of pure OLZ were found to be in much reduced broadness and slight shift towards 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.

Wettability studies

The wettability data of pure OLZ and optimized SDs (OMAN 10) are shown in Table V. The wetting time and *in vitro* dispersion of pure OLZ was found to be more than 60 min and water absorption ratio of olanzapine was found to about 11.49. It was observed that tablets prepared with OLZ 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 (Sunilkumar *et al*., 2007). The wetting time and *in vitro* dispersion time of sample was found to be 18 min, much less than the pure OLZ (more than 60 min). The water absorption ratio of sample was found to be higher (15.18) than pure OLZ (11.49), indicating the water absorption potential of mannitol. It was also observed that the tablets were found to absorb water slowly and get disintegrated into small fragments during the dispersion process. These observations confirm the increased wettability in samples and also provide a clear Insight into the role of hydrophilic carriers in the formulations (Sunilkumar *et al*., 2007; Adel *et al*., 2009).

Permeation Studies

Natural and synthetic membranes

Permeation studies across various natural membranes had been used as a tool to predict the gastrointestinal permeation of drugs. Permeation studies were conducted across natural membranes like onion, tomato, egg membrane and synthetic membranes like cellulose acetate and cellulose nitrate. The apparent permeation coefficient values of pure OLZ and selected solid dispersion batches across the tested membranes are determined and tabulated in Table VI. The permeation coefficient of the optimized solid dispersions across the tested membranes was found to be higher than pure OLZ. These findings prove the permeation efficiency of the selected solid dispersions and the possible reasons attributed to hydrophilic nature of the carrier and increased wettability in samples solid dispersions (Mehdi *et al*, 2006; Corti *et al*., 2006). The possible mechanism suggested for its enhanced aqueous solubility and release rate are particle size reduction, solubilization effect of carrier, change in crystal quality or formation of solid solution, change in surface hydrophobicity of drug particles and increased wettability due to increased water absorption by the carrier. Due to these factors, the drug would dissolve fast in gastric secretions, leading to its higher dissolution and subsequent absorption. Further the membranes in which the permeability studies were conducted were proved to be similar to biological membranes and studies across such membranes have been already reported in literature and it had been suggested that permeation studies across such membranes could be used as predictors for increased permeability of the model drug.

TABLE VI - Apparent permeation coefficient data of OLZ and selected solid dispersions (OMAN10)

Membrane	Apparent permeation coefficient P_{app} (cm s^{-1})	
	OLZ	OMAN10
Egg	0.001	0.002
Onion	0.001	0.002
Tomato	0.001	0.002
CA	0.004	0.016
CN	0.015	0.018

Each value represents the mean of three values.
CA – cellulose acetate, CN – cellulose nitrate.

Mechanisms for enhanced release

The possible reasons that might be attributed to increased release rate from solid dispersions are 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 and increased wettability due to increased water absorption by the carrier. These postulations were well supported by the findings of physicochemical characterization techniques used for evaluation of solid dispersions. Further, the suggested reasons for enhanced release were found to be in accordance with the earlier published reports using hydrophilic carriers (Corrigon, 1985; Leuner, Dressman, 2000; Craig, 2002).

CONCLUSION

The approach of the present work was to characterize the solid dispersion of a BCS Class II drug and study its effect on dissolution. The results of the work clearly suggest that the solid dispersions formulated with mannitol could be developed in fast release dosage forms with improved oral absorption and therapeutic efficiency. The solid dispersions could be explored further to establish pharmacokinetic and pharmacodynamic profiles for realizing their full potential.

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