Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 3, Suppl 5, 2011

Research Article

PHYSICOCHEMICAL CHARACTERIZATION AND *IN-VITRO* DISSOLUTION BEHAVIOR OF OLANZAPINE – CROSCARMELLOSE SODIUM SOLID DISPERSIONS

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Received: 28 July 2011, Revised and Accepted: 21 Nov 2011

ABSTRACT

The objective of the present work is to study the dissolution behaviour of olanzapine from its solid dispersions with croscarmellose sodium (CCS). Solid dispersions were prepared by dispersion method and characterized by phase solubility studies, drug content and *in- vitro* dissolution studies. The best releasing dispersions were selected based on release data, release profiles and dissolution parameters. Solid state characterization techniques like X- ray diffractometry, Differential scanning calorimetry, FT-IR spectroscopy, Near Infrared and Raman spectroscopy and wetting studies were used to characterize the optimized dispersions. The results of phase solubility studies and thermodynamic parameters indicated the spontaneity and solubilization effect of carrier. The release studies results showed greater improvement of drug release from solid dispersions compared to pure drug and the release rate was found to increase with increase in carrier content. Solid state characterization results proved the change in crystal quality or crystallinity reduction in dispersions with compatibility between drug and carrier. The possible mechanism for increased release rate from dispersions may be attributed to solubilization effect of 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 drug, increased wettability and dispersability of 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 and wettability studies

Keywords: OLZ- Olanzapine, CCS- Croscarmellose sodium, Solid dispersions

INTRODUCTION

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 it 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, 2]. Development of solid dosage forms for water insoluble drugs had been a major challenge for pharmaceutical scientists for decades. Various formulation strategies like micronisation, micellar solubilization, complexation, dendrimers for drug solubilization, formation of solid solutions/dispersions with hydrophilic carriers, self micro 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[3]

An attractive possibility could be represented by employing simple solid dispersion technique[4] 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[4]. 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[5-8]. 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.

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 dispersability of a drug from the dispersion, dissolution of the drug in the hydrophilic carrier or conversion of the drug to an amorphous state [6-8]

Schizophrenia is a severe non-curable illness of the brain with serious consequences if not properly treated and kept under control. Schizophrenia is the most common form of severe mental illness. Olanzapine, (2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno-[2, 3-*b*], [1, 5] benzodiazepine) is a relatively new benzodiazepine atypical antipsychotic which belongs to the class of the thienobenzodiazepines and has proven efficacy against the positive and negative symptoms of schizophrenia, bipolar disorder and other psychosis [9,10]. It is poor 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} reaches within 5-6 h of dosing. OLZ undergoes extensive pre-systemic metabolism in liver resulting in relatively very low oral bioavailability [11-12].

The selection of carriers in formulating SDs plays a significant role in development of successful dosage forms without any problems in formulation processing at large scale. Polymers, superdisintegrants, surfactants are extensively studied in recent years for dissolution enhancement in drugs. Superdisintegrants belongs to the recent class of pharmaceutical excipients used widely in food, confectionary and in development of pharmaceutical dosage forms. They owe their function due to their hydrophilic nature. Several insoluble drugs have been shown to exhibit improved aqueous solubility, dissolution rate and oral absorption when incorporated in to SDs utilizing such carriers[13-14].

The aim of this study was to investigate the effect of superdisintegrant like croscarmellose sodium on the dissolution rate of poor water soluble drug OLZ and to provide an insight in to the drug release process from such dispersions thru various evaluation techniques.

MATERIALS AND METHODS

Olanzapine (OLZ) was received as a gift sample from M/s. Unichem Laboratories, (Mumbai, India). Croscarmellose sodium was generously gifted by M/s. Reliance Chemicals, (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.

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 °C and 37 ºC for 24 h.

Samples with pure drug and water was 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=0.1149x concentration-0.0031]. The data was subjected to phase solubility analysis to calculate various thermodynamic parameters like ΔH, ΔS and ΔG[15-18].

Phase solubility analysis [15-18]

Stability Constant

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

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

Gibbs Energy, ΔG was calculated from Eq.2

$$\Delta G = -RT \ln Ka \quad ------ Eq.\ 2$$

Where, R - Gas constant, 8.313 J/mol K

T - Temperature

Ka - Stability Constant

Enthalpy

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

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

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

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

Where, ΔH - Enthalpy

ΔG - Entropy

Dispersion Method

SDs containing OLZ were prepared using varying concentrations of CCS, keeping drug concentration constant. The drug: carrier ratios used 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 poured on 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 dessicator for 12 h. Next, the dried mass was powdered and sifted through Sieve No. 100. The samples are then stored in dessicator till further use [19-21].

Drug content analysis

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**

The *in-vitro* dissolution study of all SDs of OLZ with CCS was carried out on USP dissolution apparatus (Campbell Electronics, Mumbai). 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. Amount of solid dispersions equivalent to 20 mg of olanzapine was added to the 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 to maintain sink conditions. The withdrawn samples were analysed 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 x concentration+ 0.001(R^2 = 0.9999; p > 0.001). The *in-vitro* dissolution parameters namely, cumulative per cent drug release, dissolution parameters like 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 subjecting the release data in to various equations given below [17,18, 22-24]

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

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

$$t_{50\%} = \frac{0.693}{K} \quad ------ Eq.5$$

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 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.

$$\%\ DE = \left(\frac{\int_0^t y.dt}{y_{100} * t}\right) 100 \quad ---------- Eq.6$$

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 Eq. 7

$$DRC = Slope * 2.303 ------ Eq..7$$

Release kinetics [22-24]

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

Zero order (K_o)

$$Q_t = Q_0 + K_0 t ------ Eq.8$$

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 constant (K_1):

$$\log Q_t = \log Q_0 * K_1 \frac{t}{2.303} ------ Eq.9$$

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

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

Where M_t = Amount of drug dissolved at particular time "t", K – Higuchi release constant

Hixson Crowell model

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

Where, Wo= weight of the drug taken at time "t=0 and

Wt = Weight of the drug taken at time "t"

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

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

Where, $Q_t/Q\infty$ 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 systems, 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 [22-24].

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, physical mixtures and selected SDs were scanned over 2Ø range from 2° C -50° at the rate of 2 º per min at 0.02° at 2Ø step size.

Differential scanning calorimetry studies (DSC)

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 (50cc/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 aluminium pan, was firmly crimped with lid to provide an adequate seal. Sample was heated from ambient temperature to 400 at pre programmed heating rate of 10 °C min^{-1}.

Fourier Transform infrared spectroscopic studies (FT-IR)

FT- IR spectra of pure OLZ, carriers, physical mixtures of drug and carrier (1:1) and optimized SDs 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 SDs were analyzed in similar manner. Physical mixtures were prepared by blending individual component in glass-pestle mortar.

Near infra red (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.

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. Sufficient quantity of microcrystalline cellulose (diluent) and magnesium stearate (lubricant) was 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 [25-28]

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 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

Water absorption ratio [25-28]

The weight of the tablet prior to placement in the petri dish was noted (W_b), utilizing a Metler Toledo Digital balance. The wetted tablet was removed and reweighed (Wa). Water absorption ratio R, was then determined using Eq.10.

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

In- vitro dispersion studies [26-28]

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

Statistical Analysis

The relevance of difference in the *in-vitro* dissolution profile and pharmacokinetic 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 carrier and the spontaneity of solubilising process when the drugs is physically mixed with CCS. The thermodynamic parameters of OLZ and its physical mixtures are shown in Table. 1. The solubility of OLZ was found to show a linear increase with increase in amount of carrier and temperature. These results were found to be in accordance with the well established formation of weak soluble complexes [17-18]. It was also stated that, the drug molecules might have transferred from pure water in to the aqueous solution of carriers which was indicated 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 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 Vander Waals forces and this would have lead to the formation of weakly soluble complexes [15-18].

Table 1: Thermodynamic parameters of olanzapine and its physical mixtures with CCS

S. No	Carrier	Temp ° C	Slope	Intercept	Ka (M^{-1})	Δ G (kJ/mol)	Δ H (kJ/mol)	Δ S (J/mol K)
1	CCS	25	172.35	-4.062	0.248	-3.173	-3.174	3.162
		37	-189.06	10.757	-0.092	-2.349	-2.345	2.341

Drug content

The assayed drug content in all SDs was found to be in the range of 97.6- 102 % indicating the uniform distribution of the drug in formulations and the suitability of the method used for formulation of dispersions.

In-vitro dissolution studies

The % cumulative release of pure OLZ was found to be 70 % in 1 hour while SDs showed a significant improvement in release rate in the same period. 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 ($p>0.05$) in release rate in comparison with pure OLZ.

The *in-vitro* dissolution parameters of the SDs compared with pure OLZ are shown in Table 2. It was found that parameters like per cent cumulative release, amount of drug released, % DE and RDR values were found to exhibit a linear increase with increase in amount of the carrier whereas the parameters like DRC, $t_{50\%}$ and $t_{85\ \%}$ values tend to decrease with increase in carrier fraction.

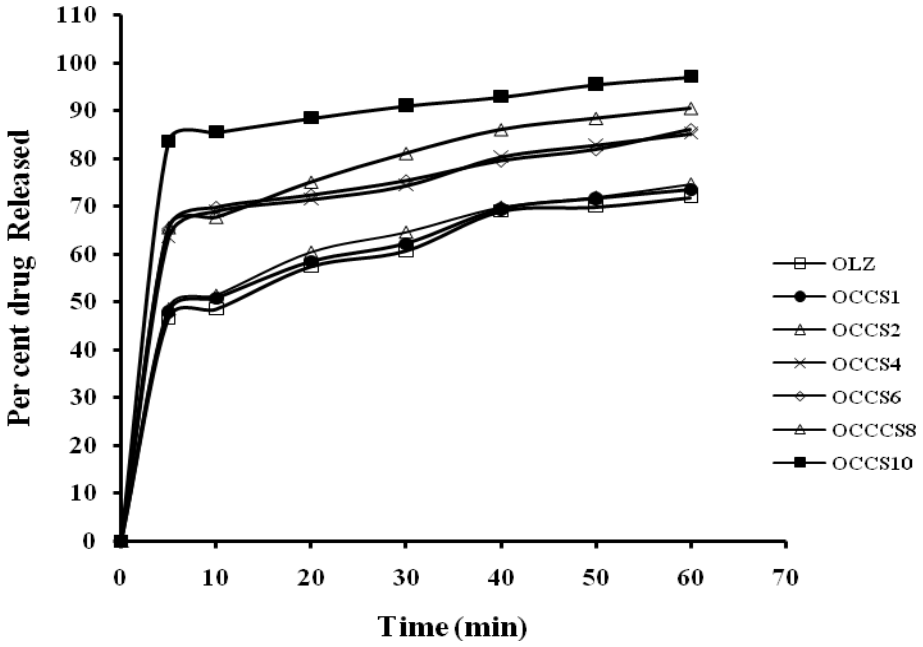


Fig. 1: Dissolution profiles of olanzapine- CCS SDs compared with pure OLZ. All data points represent the mean of 3 values, n=3.

Table 2: Dissolution parameters of olanzapine- CCS solid dispersions

Code	Composition OLZ:CCS	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
OCCS1	1:1	9.6 (0.35)	12.46 (0.32)	49.23	0.94	0.82	0.027 (0.133)	30.0	>60
OCCS2	1:2	9.73 (0.32)	12.93 (0.16)	54.31	1.03	0.89	0.023 (0.001)	10.0	>60
OCCS4	1:4	12.70 (0.65)	14.87 (0.56)	73.57	1.36	1.22	0.013 (0.000)	4.0	60
OCCS6	1:6	13.07 (0.16)	15.08 (0.64)	73.87	1.40	1.24	0.013 (0.002)	4.0	57
OCCS8	1:8	13.12 (0.09)	16.23 (0.24)	77.70	1.41	1.34	0.005 (0.007)	4.0	37
OCCS10	1:10	16.72 0.24	18.22 (0.50)	88.37	1.79	1.50	-0.006 (0.014)	3.0	7

The correlation plot of % DE and $t_{50\%}$ was shown in Fig. 2. The % DE values were found to increase and the dissolution half life was found to decrease from as the carrier content was increased from 1:1 to 1:10 in dispersions. Based on these findings, it can be inferred that batch OCCS 10 was found to exhibit best release behaviour than other SDs. The order of OLZ drug release from the SDs could be ranked as: OCCS 10 >OCCS 8>OCCS 6> OCCS 4> OCCS 2> OCCS 1> OLZ.

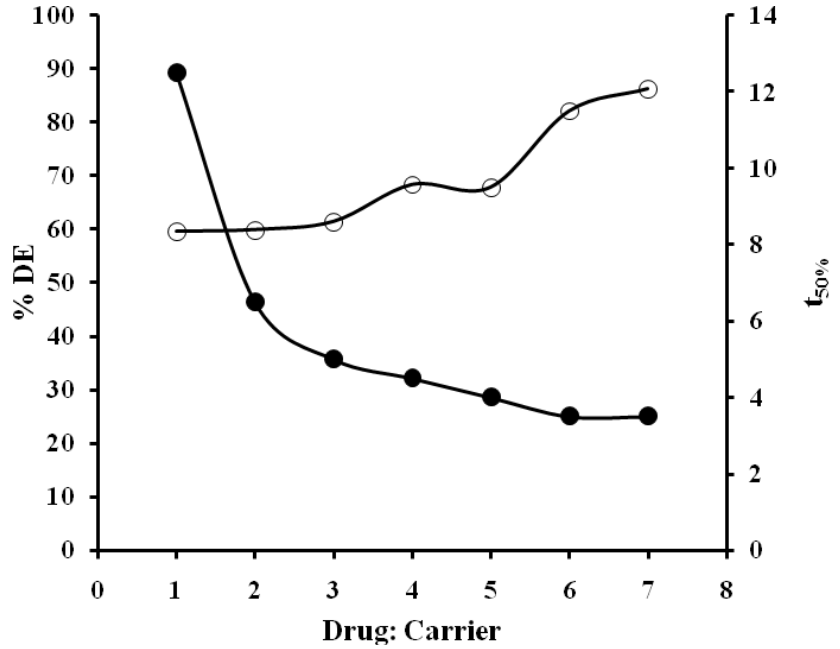


Fig. 2: Correlation plot of % DE and Dissolution half life ($t_{50\%}$)

○ - % DE and ● dissolution half life

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 drug and test products ($p>0.05$). 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 same but are different in their formulations.

The reasons suggested for the dissolution behavior of SDs are mainly related to the nature of carrier. It was stated that the unique fibrous nature of carrier imparts excellent water wicking properties and each fiber acts as hydrophilic channel and it facilitates water uptake in the dispersions. Due to this property, the carrier absorbs the dissolution medium rapidly and increases the total contact area and the wetting property of drug with the medium[27-31]. These suggestions were well supported by the results of water absorption and wettability studies which revealed high water absorption ratio and wettability values. Further, this effect was also visually observed during the wetting and *in-vitro* dispersion studies. The tablets with CCS as carrier was found to absorb water and swells rapidly than pure drug and it get dispersed in to less uniform and fine dispersed particles 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 as the additional factors behind the enhanced dissolution rate from the SDs [30-33].

The release kinetics of the *in-vitro* dissolution data (Table 3) and the regression parameters were analyzed to ascertain the type of drug release from SDs. 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 was found to fit aptly in to 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 dispersion [22-24].The possible mechanism suggested for high release of OLZ from dispersions was also found to correlate with the findings of release kinetic analysis.

Table 3: Release kinetic parameters of olanzapine - CCS 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
OCCS1	0.791	0.864	0.104	0.008	0.018	0.851	8.362	0.751	0.012	0.993	0.262
OCCS2	0.786	0.870	0.101	0.008	0.018	0.847	8.461	0.745	0.012	0.994	0.266
OCCS4	0.705	0.890	0.062	0.005	0.012	0.742	9.031	0.665	0.015	0.970	0.296
OCCS6	0.691	0.873	0.085	0.005	0.012	0.723	8.923	0.642	0.014	0.964	0.294
OCCS8	0.788	0.997	0.008	0.005	0.005	0.787	9.940	0.757	0.018	0.981	0.320
OCCS 10	0.616	0.912	0.021	-0.002	-0.005	0.632	9.771	0.623	0.021	0.935	0.335

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

Solid State Characterization

X-Ray diffraction analysis

X- ray diffraction spectra of pure OLZ, CCS, physical mixture (1:1) and batch OCCS 10 are illustrated in Fig. 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 is indicative of its high crystalline character[34-36]. The absence of sharp peaks in carrier diffractogram indicates the amorphous nature of carrier. 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 prominent peak of OLZ at 2Ø of 5º was found to broader with reduced sharpness in sample (OCCS 10) diffractogram.

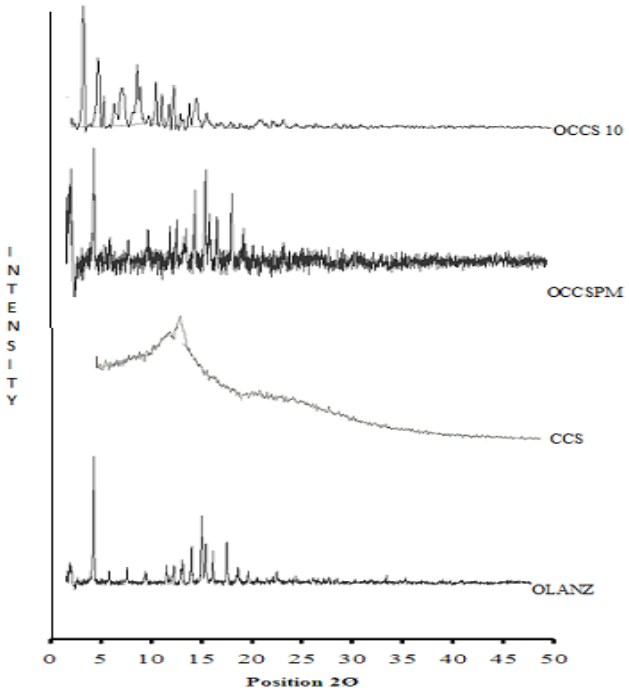


Fig. 3: X-RD spectra of pure olanzapine, CCS, physical mixtures (PM) at 1:1 ratio and solid dispersions (SDs) OCCS 10 at 1:10 ratio

Further the peaks in sample diffractogram was also found to be possess broad base, less peak height, low relative intensity and high FWHM values than the peaks corresponding to pure OLZ. 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.

Differential scanning calorimetry studies (DSC)

The DSC scans of pure OLZ, CCS and optimized SDs (OCCS10) are presented in Fig.4.

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 Delta H value of 105.023. These values clearly indicate its high crystalline nature [34-36]. A broad single endothermic peak at 125.59°C was noticed in carrier (CCS) thermogram proving its amorphous nature. A broad endothermic curve at 80°C (due to carrier) and a short constricted broad endothermic peak with values (Onset -190.27° C, peak -193.03° C, peak area - 12.472 mJ and Delta H value of 5.939) was noticed in sample thermogram. The peak properties were also found to be less than that of pure OLZ. This variation in thermal behavior and peak properties of sample dispersions clearly proves the crystallinity reduction or phase transition in drug molecule present in SDs [17-20, 28-31]. These changes in the structure of the drug molecule might have contributed for enhanced dissolution rate of OLZ from the dispersions.

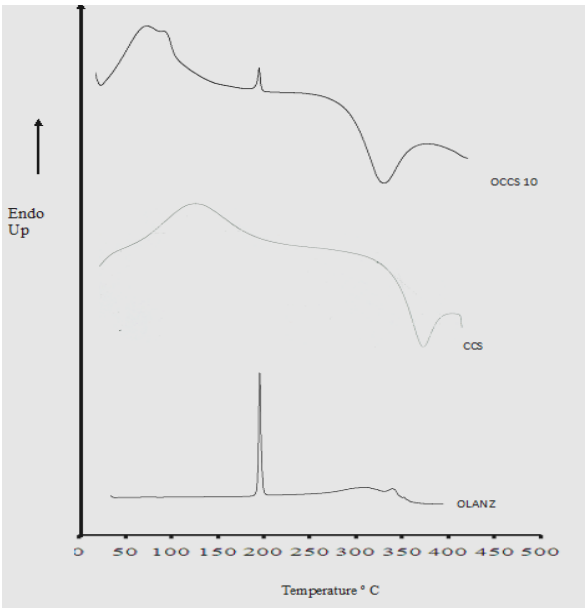


Fig. 4: DSC thermograms of pure olanzapine, CCS and solid dispersions (SDs) at 1:10 ratio

FT-IR studies

The FT-IR spectra of OLZ, PMs (1:1) and SDs were presented in Fig.5. Pure OLZ showed characteristic peaks 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), 1287 cm^{-1} (C-N stretching) [34-37] . The characteristic peaks of pure OLZ were found to be present in spectra of PM as well as in SDs. This finding reveals the lack of interaction between drug and the carrier in SDs. 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 CCS was increased in samples. These findings clearly prove the reduction of crystallinity in drug molecule present in samples [34-37].

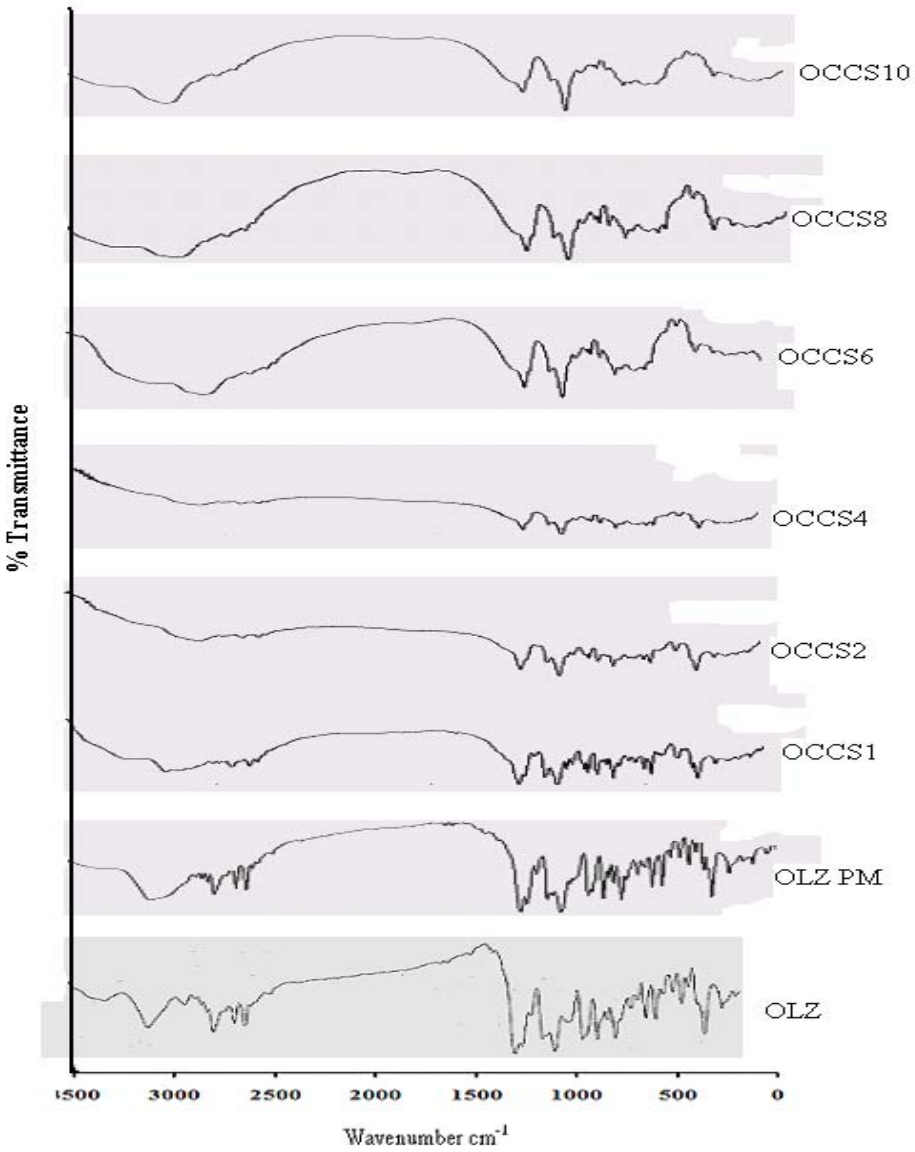


Fig. 5FT-IR Spectra of pure olanzapine, physical mixtures (PM) at 1:1 ratio, solid dispersions (SDs) OCCS1, OCCS2, OCCS4, OCCS6, OCCS 8 and OCCS10

Near infra red analysis

The near infrared spectra of OLZ and optimized SDs (OPEG6 10) are compared in Fig.6. The characteristic peaks of pure OLZ appeared at 1141 nm and 1581 nm [34-37]. The specific peaks of OLZ in spectra of optimized SDs 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 drug present in SDs.

Raman analysis

The Raman spectra of pure OLZ and selected SDs (OCCS 10) are compared Figure.7. The sharp peaks of OLZ appeared at 2435, 1594, 1517, 1460, 1224, 1050, 965, 784 and 480 positions in pure drug spectra which is indicative of its high crystallinity [12, 34-36]. 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.

Wettability Studies

The wettability data of pure OLZ and optimized SDs (OCCS 10) were shown in Table 5. 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 olanzapine did not showed 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. The wetting time and *in-vitro* dispersion time of sample was found to, much less (24 and 21 min) than the pure OLZ (more than 60 min). The water absorption ratio of sample was also found to be higher than pure OLZ confirming the water absorption potential of CCS. The tablets with CCS showed rapid absorption of water, swelling at a rapid pace forming a soft gel like mass reaching the maximum swelling state (Fig.8). Further, the size of the tablets gets doubled due to the absorption process and reaching a constant value and getting disintegrated in to fragments.These observations confirm the increased wettability in samples and it also provides a clear insight in to the role of CCS in dissolution enhancement process [25-28].

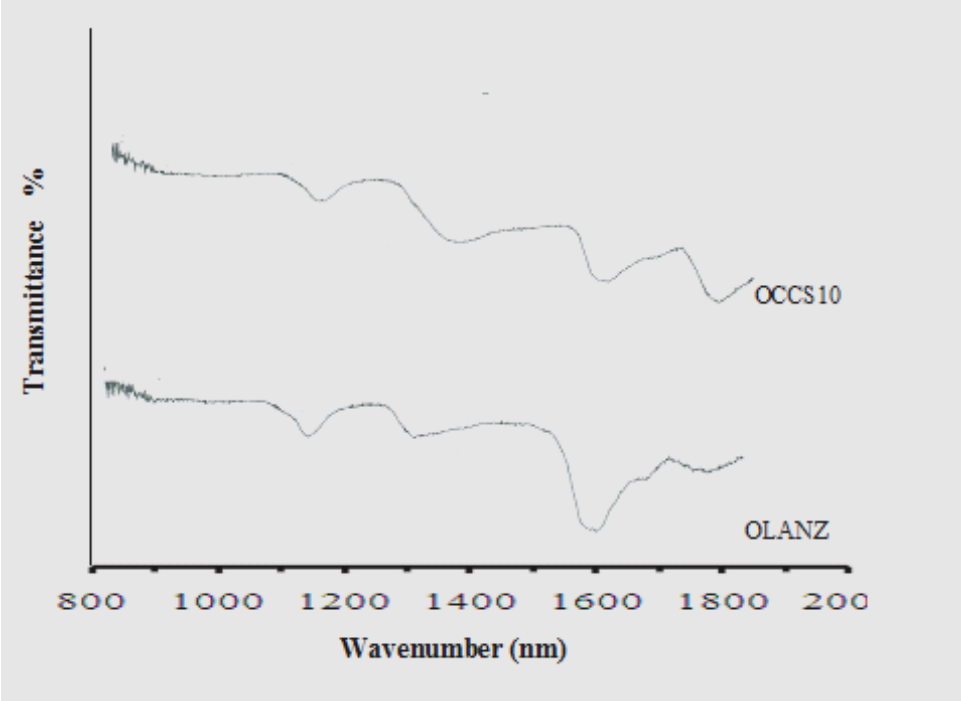


Fig. 6: Near infrared spectra of pure olanzapine and selected dispersions OCCS10

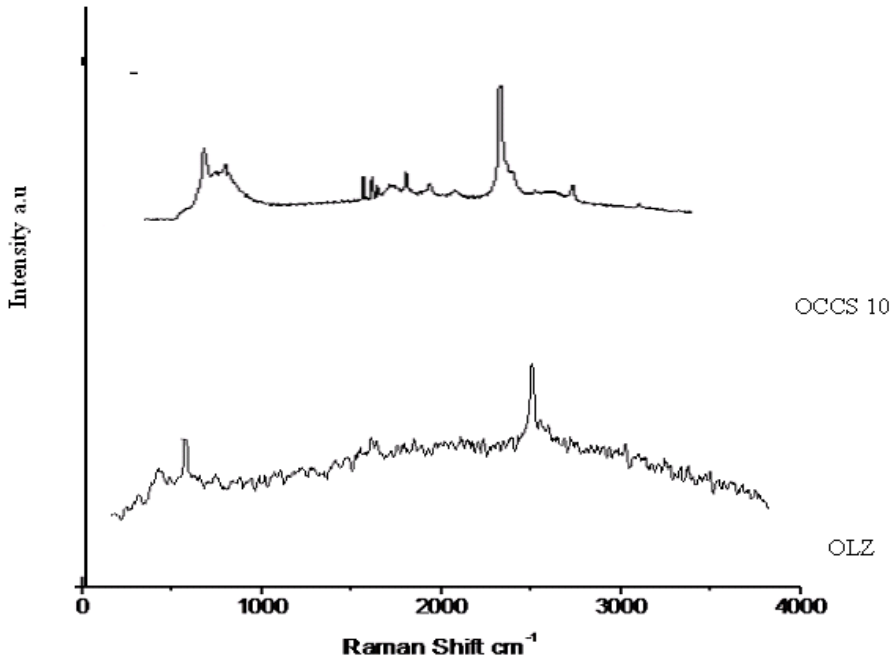
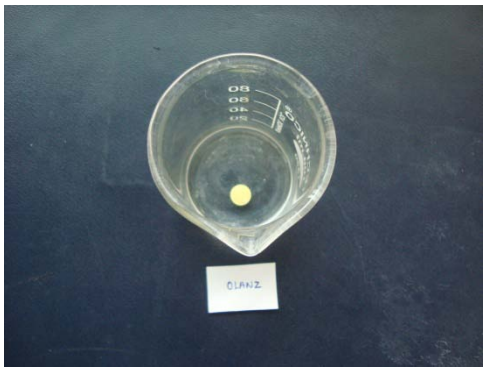


Fig. 7: Raman spectra of olanzapine and selected dispersions (OCCS 10)

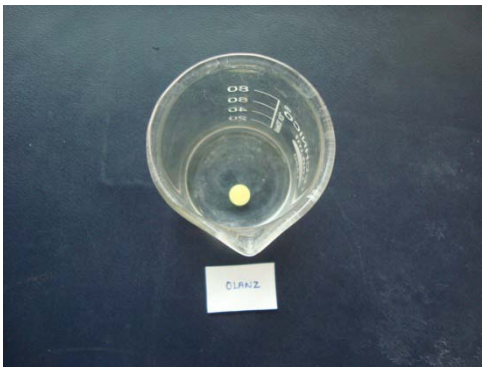
Table 4: Wettability data of pure olanzapine and selected solid dispersion

Batch	Wetting Time (min)	Water absorption ratio	*In- vitro* dispersion time (min)
OLZ	>60	11.49	> 60
	(2.26)	(1.14)	(1.12)
OCCS10	24	15.51	21
	(1.18)	(1.16)	(0.86)

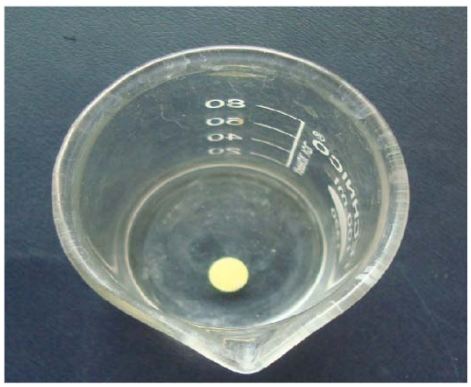
Values in parenthesis indicates standard deviation n=3



a) OLZ - before dispersion



b) after dispersion



c) OCCS 10 - before dispersion

d) after dispersion

Fig. 8: *In-vitro* dispersion photographic images of olanzapine and OCCS 10

Mechanisms for enhanced release

The possible reasons that might have attributed for increased release rate from SDs are summarized as particle size reduction, solubilization effect of carrier, change in crystal quality, or phase transition, 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 the findings of physicochemical characterization techniques used for evaluation of SDs. Further the suggested reasons for enhanced release were found to be in accordance with the earlier published reports using hydrophilic carriers [27-30, 38-41].

CONLCUSION

The approach of the present work was to characterize the solid dispersion of a Class II drug (Biopharmaceutical Classification System) and study its effect on dissolution. The results of the work clearly suggest that the SDs formulated with mannitol 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.

ACKNOWLEDGEMENT

Authors are thankful to M/s. Torrent Pharmaceuticals (P) Ltd, Ahmedabad, India and M/s Colorcon Ltd, Mumbai, India for the gift samples of drug and carrier for the work. We also thank Sophisticated Analytical Instrumentation Centre (SAIF), Indian Institute of Technology (IIT) Chennai for providing the facilities to carry out Near Infra Red and Raman analysis.

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