HYDRATION METHOD: A POTENTIAL PROCEDURE FOR BLENDING OLANZAPINE AND CYCLODEXTRINS IN SEMISOLID CONDITION USING A GREEN SOLVENT

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ABSTRACT

Olanzapine (OLZ) is an antipsychotic drug with low aqueous solubility. Cyclodextrin (CD) complexation is a potential approach employed to improve the solubility of poorly water-soluble drugs belonging to BCS classes II and IV. The solubility of olanzapine was improved using βCD, HPβCD and methyl βCD which was reported in earlier works. In the current study, a combination of βCD and HPβCD in 1:1 molar ratio was used in the preparation of complexes along with βCD and HPβCD. Methods such as slugging, hydration and granulation which are slight modifications of conventional methods like physical mixing and slugging were used. A_L type curves were obtained in phase solubility studies specifying a linear increase in the solubility of drug with increase in concentration of cyclodextrin. The values of slopes calculated for A_L type plots are less than one which suggests that OLZ:CD complexes are formed in 1:1 molar ratio. The stability constants obtained were 188.98 M^{-1}, 140.63 M^{-1} and 157.48 M^{-1} with βCD, HPβCD and βCD+HPβCD and these values indicate that stable OLZ : CD complexes are formed. The drug : cyclodextrin binary complexes demonstrated a 2.27 to 3.67 - fold increment in aqueous solubility when compared to pure drug. The percentage of drug released in 60 minutes was 46 (pure drug), 65 - 89 (OLZ-βCD complexes), 59 - 80 (OLZ-HPβCD complexes) and 61 - 84 (OLZ-βCD+HPβCD complexes). Results of DSC, XRD and SEM indicated partial inclusion complexation. The complexes prepared by hydration method showed higher solubility when compared to other methods. In hydration method, the complexes were prepared using water which does not cause any harm to individual and environment.

Keywords: *direct compression, hydration, inclusion complexes, olanzapine, slugging, wet granulation.*

INTRODUCTION

Among all routes of administration used for obtaining systemic effects, the oral route is the most popular route. The dosage forms designed for oral route have advantages like high patient compliance due to easy and non-painful drug administration and high manufacturer compliance due to easy and cost-effective drug manufacturing. The oral route is unsuitable for patients who are unconscious or uncooperative for some reasons. Some drugs are not stable in the gastric fluids and some drugs suffer from very low bioavailability because of either low solubility or low permeability [1]. However, oral route continues to be the most preferred route of administration of drugs, as its advantages outweigh its major limitations. The bioavailability of a drug is determined by measuring the rate at which it is reaching as well as the amount of drug reaching the systemic circulation [2]. It is influenced by several factors and the most important factors are the solubility, permeability and presystemic metabolism of drug. In gastrointestinal tract, the amount of drug that is present in aqueous solution is only absorbed into the systemic circulation and the quantity of drug that comes into

aqueous solution is influenced by its solubility and dissolution rate. Poor aqueous solubility of new synthetic drugs is a significant challenge for a formulation scientist. Numerous methods are explored to date to augment the drug's solubility in water. These approaches include micronization, inclusion complexation and preparation of micro and nano products like solid dispersions, nanosuspensions and solid lipid nanoparticles.

Cyclodextrins (CD) are versatile additives used as solubilizers by forming inclusion complexes. Cyclodextrins contain six to eight D - glucopyranose units which are linked by α-1,4 bond and hence known as cyclic oligosaccharides. The structure of cyclodextrins resembles a truncated cone with hydrophilic nature externally and hydrophobic nature internally [3]. When the guest molecules are entrapped into the cavity of CDs, the water molecules are removed from it [4]. Weak forces like hydrogen bonds and Vander Waals forces are responsible for the formation of intact complexes. During the process of drug-CD complex formation, there is neither formation nor breaking of any covalent bonds. Thereby, the process of complexation is simply a swapping of water molecules and drug molecules. The inner cavity size of the CDs and the size of guest molecules determine the extent of complexation [5]. The cyclodextrin inclusion complexes of drugs show a multitude of advantages over their pure forms like improved aqueous solubility, increased chemical and physical stability [6].

Olanzapine (OLZ) is a benzodiazepine used for reducing the positive as well as negative symptoms of schizophrenia [7]. It causes less extra pyramidal side effects. It is included in Class II of Biopharmaceutics Classification System (BCS) as it is not soluble in water. It is highly bound to plasma proteins (93 %) and undergoes extensive pre-systemic metabolism [8]. Its low aqueous solubility and its susceptibility to first pass metabolism are the reasons for its low oral bioavailability. The drug's solubility and thereby, the dissolution rate were enhanced by formulating into solid dispersions [9 - 13], nanosuspensions [14], self-nanoemulsifying drug delivery systems [15, 16] co-amorphous systems [17, 18] and cocrystals [19]. The research work was planned to study the influence of type of cyclodextrin i.e., βCD, HPβCD and a mixture of βCD + HPβCD on the solubility enhancement of the drug. Although preparation of cyclodextrin complexes of olanzapine using βCD [20, 21], HPβCD [22] and methyl βCD [23] were reported earlier, preparation of cyclodextrin complexes using a mixture of βCD and HPβCD is not reported. In the current work, the potential of methods such as slugging, hydration and granulation, variants of traditional methods physical mixing and kneading was evaluated for their effect on dissolution enhancement of OLZ.

EXPERIMENTAL

Materials

A gift sample of olanzapine was provided by Dr. Reddy's Laboratories located in Hyderabad. βCD, HPβCD and Avicel PH 102 were procured from Yarrow Chem Products, Mumbai, starch, and magnesium stearate were obtained from Oxford Laboratory, Mumbai and Talc was purchased from Qualikems Fine Chemicals Pvt. Ltd., New Delhi.

Phase solubility studies

The complexation ability of different types of cylcodextrins was investigated by conducting phase solubility studies [24]. To each 20 mL of different concentrations of βCD (0, 2, 4, 6, 8 and 10 mM) in a conical flask, an excessive quantity of OLZ (50 mg) was put added. The suspensions were agitated for 24 h on a rotary shaker (SISCO, India) at room temperature. Following 24 h of agitation, 3 mL of the clear top solution was taken and filtered. The filtered samples were appropriately diluted using 0.1 N HCl and the absorbances were determined at 259 nm using UV spectrophotometer (SL159, ELICO, India). Phase solubility studies of OLZ with HPβCD and βCD+HPβCD were conducted in the same manner as above. A graph was drawn with the cyclodextrin concentration on the x axis and olanzapine concentration on the y axis. The stability constant (K_s) of the complex formed between drug and cyclodextrin was calculated with the formula,

$$K_{1:1} = \frac{Slope}{S_0(1-Slope)} \quad (1)$$

where slope is acquired from the graph and S_0 = equilibrium solubility of OLZ.

Determining complexation efficiency (CE) is a more specific parameter for estimating the solubilizing property of cyclodextrins. Complexation efficiency is the

ratio of concentration of cyclodextrin complexed with the drug and concentration of uncomplexed cyclodextrin and is obtained using the Eq.2 [25]:

$$CE = S_0 K_{1:1} = \frac{Slope}{(1-Slope)} \quad (2)$$

Gibbs free energy of transfer (ΔG_{tr}^0), a thermodynamic parameter was obtained by:

$$\Delta G_{tr}^0 = -2.303RT\log\left(\frac{S_c}{S_0}\right) \quad (3)$$

where S_c is molar solubility of OLZ in a cyclodextrin solution, S_0 is molar solubility of OLZ in distilled water without cyclodextrin, R is universal gas constant (8.314 J K mol^{-1}) and T is temperature in Kelvin.

The change in Gibbs free energy (ΔG) was obtained by:

$$\Delta G = -RT\ln K \quad (4)$$

Preparation of OLZ - CD complexes

There are numerous techniques available for the preparation of drug-cyclodextrin complexes and the physicochemical characteristics of the prepared complexes are highly influenced by the method of preparation. Thereby, optimization of method of preparation is essential in cyclodextrin complexation. The methods used for preparation of cyclodextrin complexes include methods in solid state, methods in semisolid state and methods in solution [26]. Physical mixing and slugging methods belong to solid state methods; kneading, hydration and granulation methods belong to methods in the semisolid state. The cyclodextrin complexes of olanzapine with βCD, HPβCD and βCD + HPβCD were prepared in molar ratio of 1:1.

In physical mixing technique, the cyclodextrin and the drug were mixed thoroughly for 45 min. The contents were then sieved using sieve no. 100 to get a powder mixture with uniform size. Slugging method involves mixing of cyclodextrin and drug and compressing this homogenous mixture into tablets of 100 mg strength. Finally, the compressed tablets were again broken and triturated to get a fine powder and the triturate was sieved [27]. In kneading method, a little amount of purified water was put into the homogenous mixture of cylcodextrin and drug and the entire contents were triturated for 20 min. The resulting mass was dried using an oven at 65˚C; the solid was grounded and then passed through 100 #. Hydration method includes addition of about 5 mL of water to cyclodextrin and was triturated vigorously for 30 min. Later, the weighed quantity of drug was introduced to it and was kneaded for 20 min. The contents were kept in an oven at 65°C to dry the pulverized solid mass and was sieved through 100 sieves. In granulation method, a dough mass of cyclodextrin and the drug was prepared with the required amount of water; then the dough lump was allowed to pass through sieve no. 16 for granulation. The formed granules were dried in an oven, powdered, finally sieved, and stored. The nomenclature of the prepared cyclodextrin complexes is presented in Table 1.

Characterization of prepared complexes

A total of fifteen inclusion complexes of olanzapine were prepared. The drug : cyclodextrin complexes prepared by different methods were assessed for percentage yield, solubility, assay and dissolution studies. Solid state characterization of the optimized complexes was done using FT-IR, DSC, XRD and SEM.

Percentage Yield

Calculation of percentage yield (PY) gives the efficiency of a method and useful in the selection of an appropriate method. Percentage yield is calculated from the Eq. 5:

$$PY = \frac{\text{Weight of inclusion complex}}{\text{Weight of OLZ+CD}} \times 100 \quad (5)$$

Solubility

Excessive quantities of each cyclodextrin complex was added to 10 mL of distilled water. Then, the suspensions were allowed to rotate on a shaker for a period of 24 h. Aliquots were collected after attaining

Table 1. Formulation of complexes.

Method	βCD	HPβCD	βCD HPβCD
Physical mixing	C1	C6	C11
Slugging	C2	C7	C12
Kneading	C3	C8	C13
Hydration	C4	C9	C14
Wet granulation	C5	C10	C15

equilibrium; filtered diluted using 0.1 N HCl. The quantity of drug was analysed using a UV-visible spectrophotometer at a λ_{max} of 259 nm.

Assay

Calculated quantity of inclusion complex, equivalent to 10 mg of the drug was mixed with small quantity of 0.1 N HCl and was thoroughly shaken to dissolve the drug and made up to 100 mL volume. The resulting suspension was passed through filter and was diluted to estimate the drug content using a UV spectrophotometer [28]. The drug content is given by the Eq. 6:

$$\text{Drug content} = \frac{\text{Observed concentration}}{\text{Theoretical concentration}} \times 100 \quad (6)$$

Dissolution studies

The drug release study of OLZ and cyclodextrin complexes was conducted using distilled water (900 mL) as dissolution medium in dissolution apparatus (TDT-08L, ELECTROLAB, India) maintained at a temperature of 37 ± 0.5°C and an agitation speed of 50 ± 2 rpm. The weight of complexes equal to 10 mg of OLZ was taken into the dissolution medium. 5 mL sample was removed with the help of a syringe at every time point of 5 min, 10 min, 20 min, 30 min, 45 min and 60 min; and 5 mL of new dissolution medium was added to the dissolution vessel. The withdrawn samples were passed through filter, diluted using 0.1 N HCl and observed for absorbance at a λ_{max} of 259 nm in UV - visible spectrophotometer to calculate the amount of OLZ released.

Fourier transform infra-red spectroscopy (FT-IR)

The spectra of OLZ, βCD, HPβCD and binary complexes were obtained with an infrared spectrophotometer (Alpha-T, Bruker, Germany). The test specimens were dispersed in KBr (1:99 w/w) to form a homogenous mixture and were pressed into pellets. The pellets were scanned from 500 to 4000 cm^{-1} to obtain the spectra.

Differential scanning calorimetry (DSC)

OLZ and complexes were studied using STA-7300, Hitachi, Germany, a differential scanning calorimeter, for their thermal behaviour. The test sample to be tested was placed in a standard aluminium pan which was hermetically sealed and was heated. The calorimeter was operated in the temperature range from 50°C to 250°C and heating at a rate of 10°C min^{-1} heating rate in an atmosphere of nitrogen which is kept at 50 mL min^{-1} flow rate.

X-ray diffraction (XRD)

XRD studies were done to assess the extent of crystalline nature of OLZ in the complexes using x-ray diffraction unit, X'Pert Pro, PANalytical, Netherlands with Data Collector software. The patterns were recorded employing copper anode at K-Alpha1 of 1.54 Å and generator settings of voltage of 45 kV and current of 40 mA current. The diffraction unit was scanned in the range of $10 < {}^{o}2\theta < 90$ with a step size of 0.008 $^{o}2\theta$. The relative degree of crystallinity (RDC) was determined by:

$$RDC = \frac{I_{sam}}{I_{ref}} \quad (7)$$

where I_{sam} is sample's peak height and I_{ref} is reference's peak height.

Scanning electron microscopy (SEM)

Scanning electron microscope (JSM-6610LV, Jeol Asia PTE Ltd, Japan) was used to study the outer surface's morphologies of OLZ and complexes which was run at 20 kV voltage. The particles were kept in a brass stub using a tape and were coated with gold using vacuum.

RESULTS AND DISCUSSION

Phase solubility studies

The purpose of conducting solubility studies is to determine the complexation ability of various types of

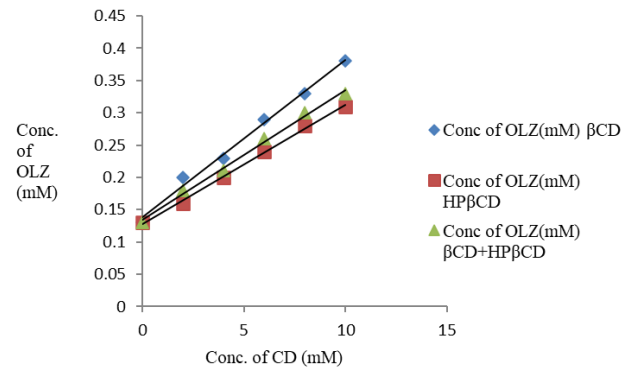

Fig. 1. Phase solubility curve.

Table 2. Phase solubility parameters.

Parameters	βCD	HPβCD	βCD+HPβCD
R^2	0.992	0.997	0.994
Slope	0.024	0.018	0.020
Intercept	0.138	0.127	0.134
Stability constant, M^{-1}	188.98	140.63	157.48
CE	0.025	0.018	0.020
Solubilising efficiency	2.990	2.452	2.614
ΔG, J mol^{-1}	-13081.134	-12342.481	-12624.467

Table 3. Phase solubility studies of OLZ in CD solutions.

Conc. of CD (mM)	ΔG_{tr}^0, J mol^{-1}		
	βCD	HPβCD	βCD+ HPβCD
0	---	---	---
2	-1074.692	-517.231	-810.329
4	-1425.26	-1074.692	-1195.379
6	-1999.961	-1528.706	-1729.851
8	-2327.541	-1913.756	-2086.166
10	-2678.109	-2166.625	-2327.541

cylcodextrins and from these diagrams' stoichiometry involved in complexation and stability constant can be estimated. The obtained phase solubility curves (Fig. 1) are A_L type which indicated that the solubility of OLZ in water was enhanced with a rise in cyclodextrin concentration in a linear manner. The value of slopes calculated from solubility graphs were below one, specifying the association of drug : CD complex in 1:1 stoichiometry, that is, one drug molecule inserted into the hollow space of one CD molecule. According to the literature reported [29], the calculated stability constant, $K_{1:1}$ value should be between 20 and 2000 M^{-1}. The $K_{1:1}$ values obtained were 188.98 M^{-1} and 140.63 M^{-1} and 157.48 M^{-1} with βCD, HPβCD and βCD+HPβCD (Table 2) respectively and indicated that the cyclodextrin complexes formed are stable. The order of the calculated stability constant of the complexes prepared with different types of cyclodextrins is, HPβCD < βCD + HPβCD < βCD. The higher the stability constant, greater is the binding affinity between the cyclodextrin and the drug molecule [30]. The characteristics of drug molecule and the characteristics of CD molecule influence binding affinity between them [31]. The binding affinity between HPβCD and drug is lower when compared to βCD because the propyl substituents near the cavity in HPβCD might obstruct the inclusion of drug [23]. CE which is obtained from the slope of solubility graphs, is not dependent of intrinsic solubility and exhibit smaller variation than K values. Lower CE values of 0.025 (βCD), 0.018 (HPβCD) and 0.02 (βCD+HPβCD) indicate that free cyclodextrin was more available in aqueous media [32].

The thermodynamics of solubilization of drug in CD solution is predicted by Gibbs free energy of transfer, G_{tr}^0 values. The values of G_{tr}^0 were negative at all concentrations of cyclodextrins, suggesting the spontaneous character of OLZ solubilization (Table 3) and lessened with a rise in cyclodextrin concentration. A similar result was observed in earlier reports [33]. The Gibbs free energy values calculated are -13081.134 J mol^{-1} for βCD, -12342.482 J mol^{-1} for HPβCD and -12624.467 J mol^{-1} for βCD+HPβCD. The values are

Table 4. Characterization of different complexes.

Cyclodextrin Complexes	Percentage yield	Aqueous solubility, mg mL^{-1}*	No of folds increase in solubility	Drug content, %*
Pure drug	---	0.0328 ± 0.001	---	---
C1	92.59	0.0823 ± 0.004	2.51	97.82 ± 0.179
C2	85.45	0.0882 ± 0.006	2.69	96.21 ± 0.528
C3	89.56	0.0901 ± 0.005	2.75	101.88 ± 0.642
C4	89.73	0.1204 ± 0.026	3.67	103.53 ± 0.928
C5	83.20	0.0926 ± 0.004	2.82	95.73 ± 0.741
C6	93.41	0.0743 ± 0.008	2.27	98.75 ± 0.586
C7	82.25	0.0760 ± 0.004	2.32	96.93 ± 0.272
C8	86.00	0.0821 ± 0.007	2.50	99.02 ± 0.245
C9	87.26	0.0871 ± 0.002	2.60	103.56 ± 0.598
C10	82.52	0.0837 ± 0.001	2.55	95.6 ± 0.829
C11	94.55	0.0804 ± 0.005	2.45	99.62 ± 0.133
C12	83.94	0.0830 ± 0.006	2.53	95.6 ± 0.615
C13	86.59	0.0912 ± 0.009	2.78	104.23 ± 0.810
C14	88.61	0.0984 ± 0.002	3.00	102.27 ± 0.456
C15	85.90	0.0963 ± 0.008	2.94	97.43 ± 0.728

**Values are expressed as mean ± SD, n = 3*

less than zero, suggesting a spontaneous interaction with between drug and cyclodextrins. The stability constants are inversely proportional to Gibb's free energy. More negative, energy values are, greater the stability constant [34].

Characterization of prepared complexes

The results of percentage yield, saturation solubility and drug content of complexes C1 - C15 are presented in Table 4. The percentage yields were high in physical mixing method, followed by kneading method and hydration method. Lower yields were observed in slugging method and granulation method. All the cyclodextrin complexes showed improved aqueous solubility when compared to OLZ and the reasons for enhanced solubility might be wetting property and hydrophilicity of CD. The solubility results of complexes prepared by different cyclodextrins were like those obtained in solubility studies. The order of increase in solubility of complexes prepared with different cyclodextrins was found to be: HPβCD < βCD + + HPβCD < βCD. There were 2.27 to 3.67 fold increments in the solubility with binary complexes. Physical mixing and slugging methods do not involve any addition of water in their preparation. Water was used in the preparation of complexes by kneading, hydration, and granulation methods. In physical mixing and slugging methods, the cyclodextrin is in solid form, thereby, only the surface molecules are available for complexation. In kneading, hydration, and granulation methods, the cyclodextrin is in solution form, so, more

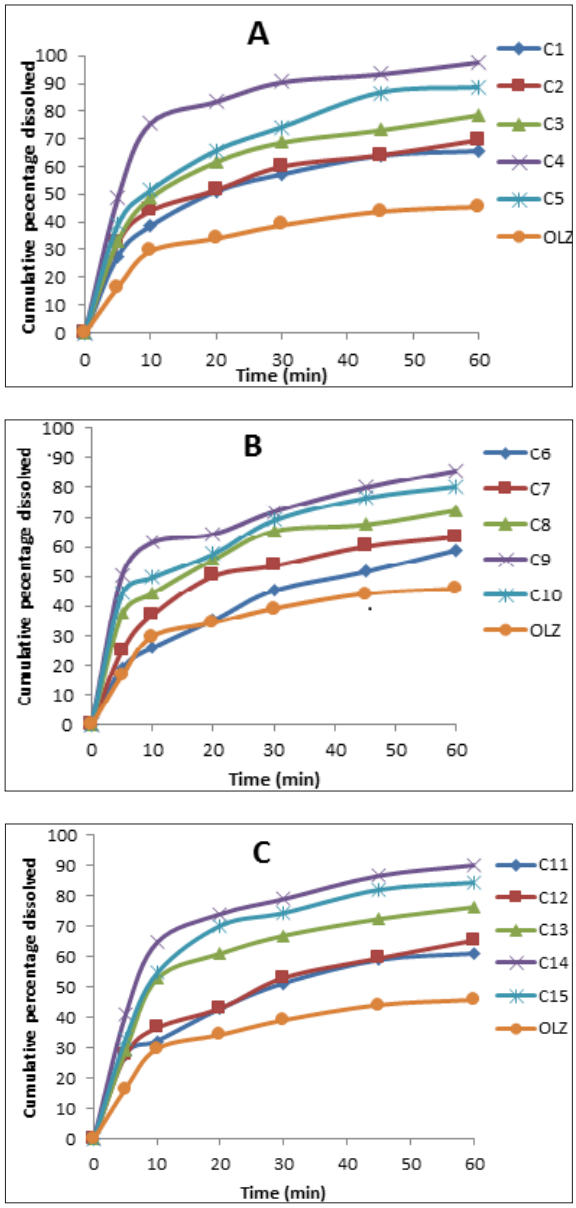

Fig. 2. Dissolution profiles of OLZ-cyclodextrin complexes and pure drug.

cyclodextrin molecules are accessible for complexation. The most used solvent for performing complexation reactions is water because of two reasons, one is, water is very easily displaced and the second is, water is easily removed to obtain solvent-free complexes [35]. The inclusion complexes produced by the hydration method exhibited the highest solubility among all the methods. The highest enhancement in aqueous solubility in hydration method might be due to a reduction in aggregate formation of CDs in water, caused by intensive trituration before the addition of the drug.

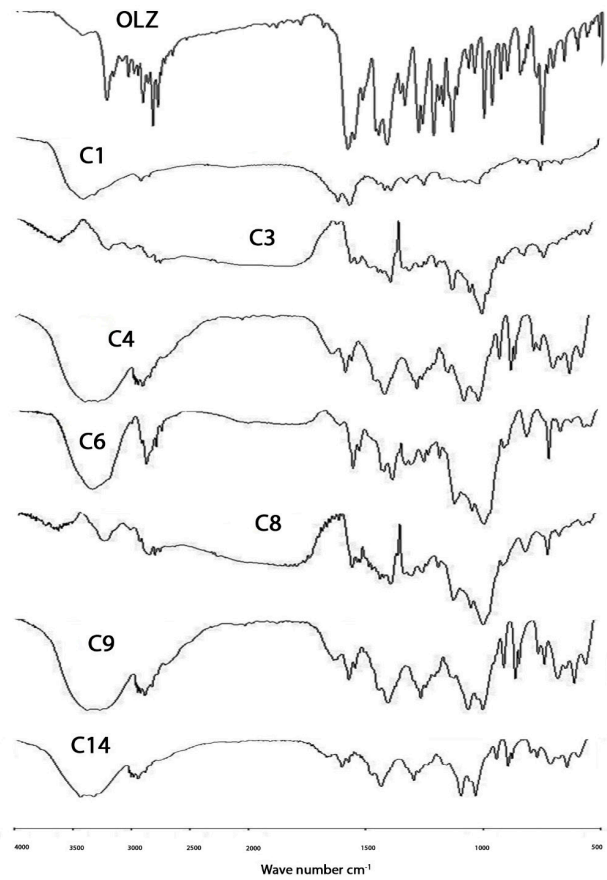

Fig. 3. FT-IR of OLZ, C1, C3, C4, C6, C8, C9 and C14.

Self-assembled cyclodextrin aggregates will disintegrate easily under unfavorable environments like sonication, intensive shaking, and temperature increase [36]. It was well known that more the solubility of the cyclodextrins in the solvent, more the availability of molecules for complexation. The content of OLZ in the complexes was found to be within 95.40 % to 101.71 % and the values were within the range of 90 % to 110 % according to IP. The dissolution graphs of pure drug and complexes are presented in Fig. 2. The drug released was only 45 % in 60 min for the pure drug because of the lower solubility of the drug in water. Cyclodextrin complexes of drug exhibited higher dissolution profiles when compared to OLZ. The enhancement of dissolution rate can be related to surfactant nature of cyclodextrins, which reduces the interfacial tension in between the dissolution medium and the drug; increased solubility of the complexes and decreased crystallinity of OLZ. The drug released

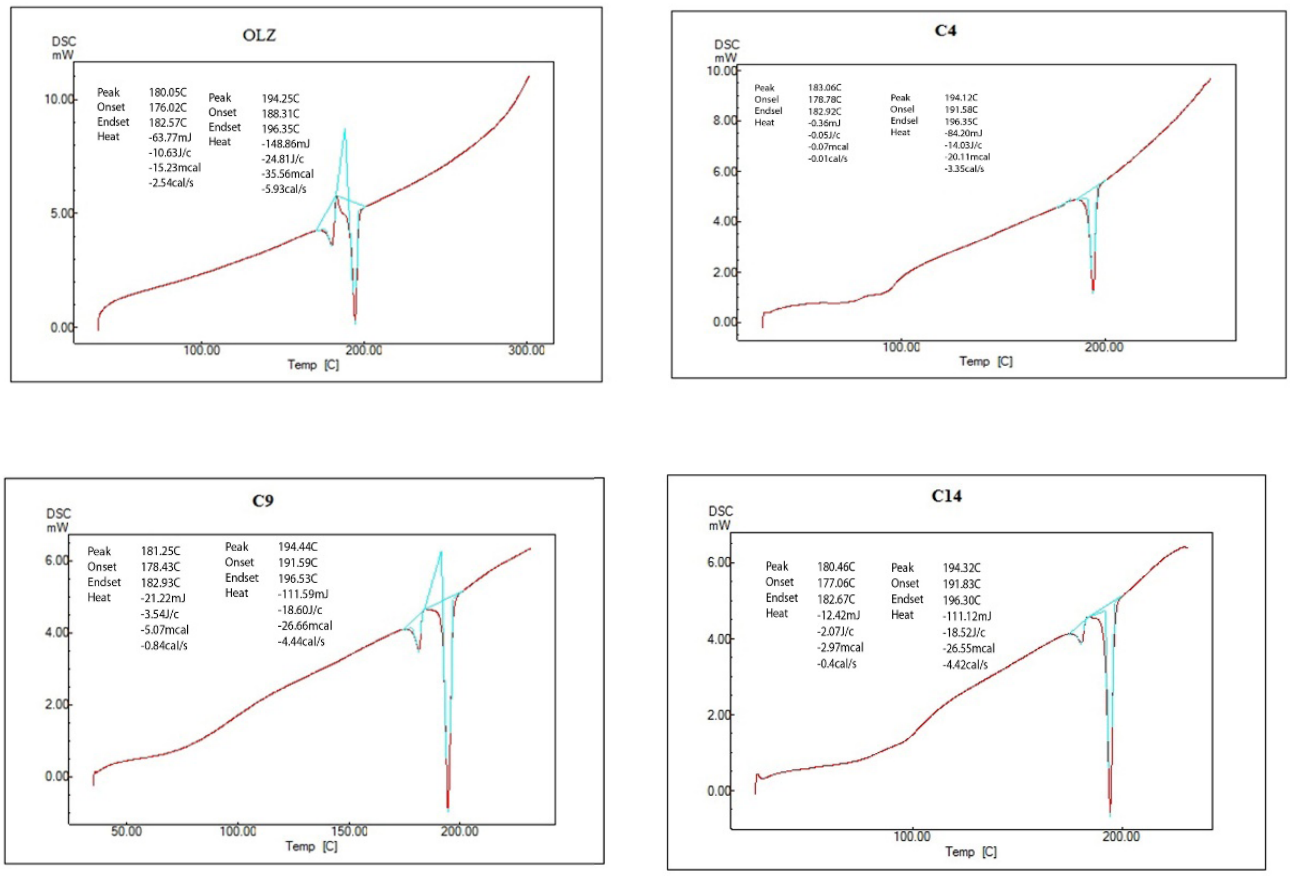

Fig. 4. DSC of OLZ, C4, C9 and C14.

is low in the complexes produced by physical mixing and slugging methods when compared to kneading, hydration and granulation methods.

The IR spectra of OLZ and complexes are given in Fig. 3. The spectrum of OLZ revealed characteristic peaks of 2933 cm^{-1} (CH stretching), 1600-1500 cm^{-1} (double bonds coupled partially to CH and NH bending deformation), 1500-1300 cm^{-1} (deformation of methyl, methylene and CH groups), 1300-1100 cm^{-1} (CC and CN stretching), 1009 cm^{-1} (deformation of piperazinyl group coupled to methyl group) and 745 cm^{-1} (out of plane deformation of CH bonds of the same group) [37]. The decrease in the intensity of 1450-1600 cm^{-1} band confirms that complexation occurs between the aromatic ring of the drug and hydrophobic cavity of βCD. In CD complexes, either the peaks shifted to higher or lower wave numbers, or their intensity was decreased as observed in earlier works [38]. A remarkable decrease in the intensity of specific peaks of OLZ was observed in complex prepared using βCD prepared by hydration technique. When drugs are incorporated into the cavities of cyclodextrins, their sublimation, boiling or melting points either increase or decrease or totally absent. The thermograms of OLZ and complexes are given in Fig. 4. Pure OLZ showed an endothermic peak at 194.25°C which represents its melting point. The endothermic peaks were noticed at the same temperature in cyclodextrin complexes but ΔH values were lower compared to pure drug [39]. The thermograms of cyclodextrin complexes contained endothermic peaks at the same temperature which suggests the presence of uncomplexed drug molecules in the complexes indicating partial complexation. But the differences in melting enthalpy values of complexes is suggestive

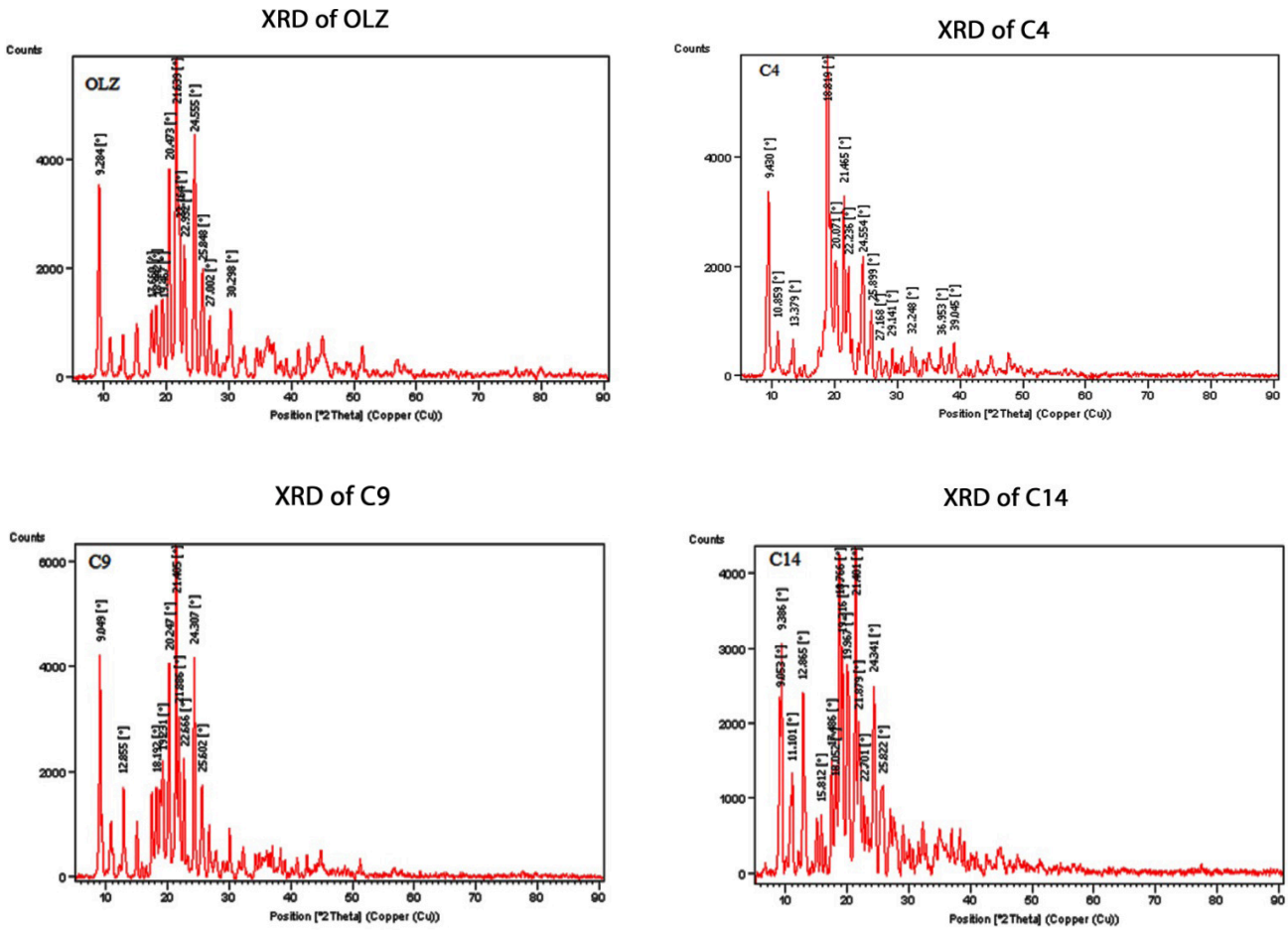

Fig. 5. XRD of OLZ, C4, C9 and C14.

Table 5. Relative degree of crystallinity (RDC).

^{0}2θ	OLZ	C4	C9	C14
21.64	1	0.54	0.86	0.75
24.56	1	0.46	0.97	0.58
20.47	1	0.50	0.81	0.70

of interactions between drug and cyclodextrins. XRD patterns of OLZ and complexes are used for identifying any transformation in crystallinity of OLZ. The diffraction pattern of OLZ and complexes are given in Fig. 5**.** In the XRD graph of OLZ, characteristic peaks were observed at 21.64, 24.56, 20.47 ^{0}2θ indicating that OLZ is having crystalline property. In the XRD graphs of cyclodextrin complexes, the height of the peak reduced, and the width of the peak increased which indicates a reduction in the crystallinity of OLZ. The results of this study correlate with the findings of Jessie et al. [40]. Relative degree in crystallinity (RDC) (Table 5) was calculated which decreased in the following order: OLZ > binary complexes. The βCD inclusion complexes showed lowest RDC when compared to HPβCD and βCD+HPβCD. Decrease in crystalline nature of drug

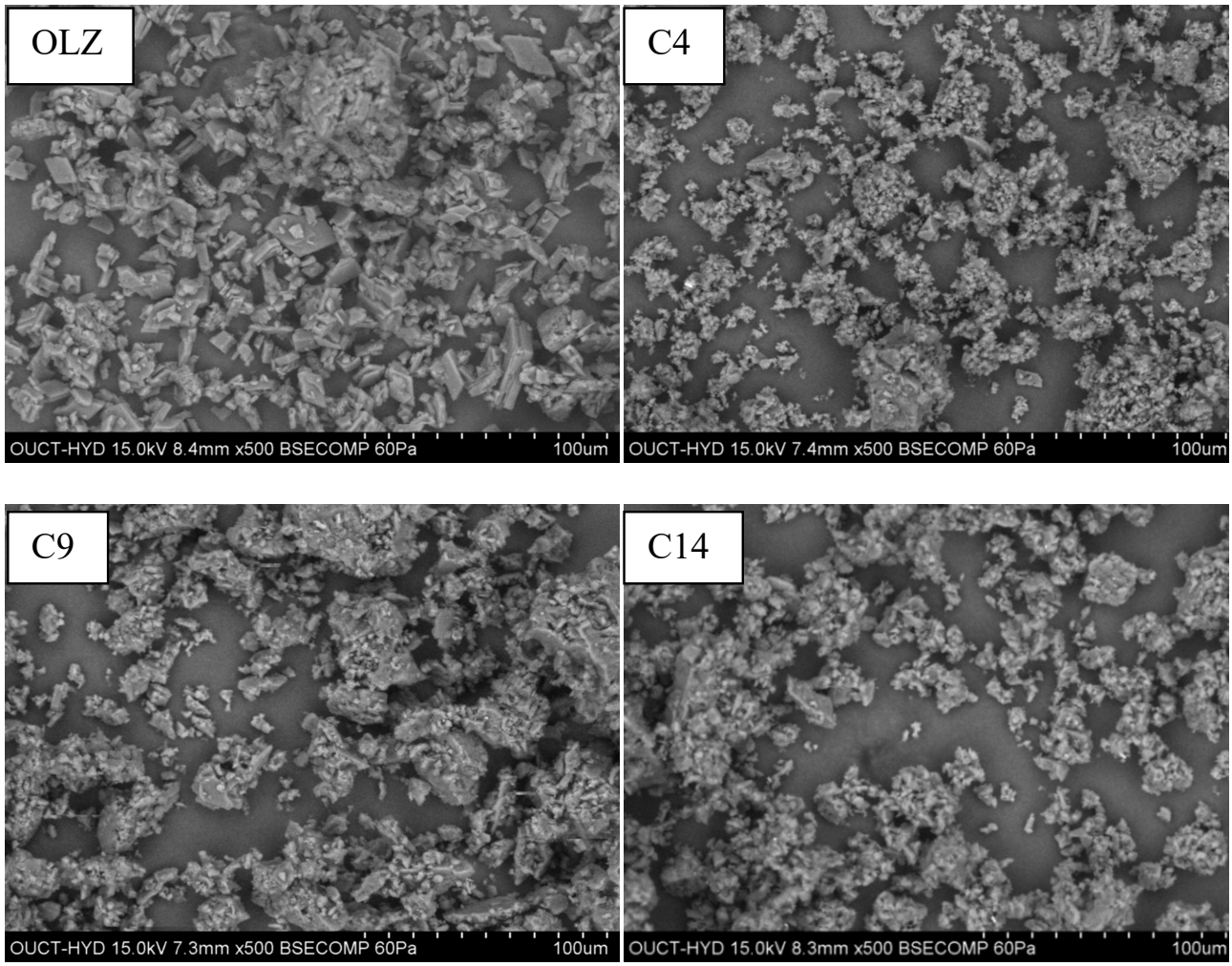

Fig. 6. SEM photographs of OLZ, C4, C9 and C14.

supports the formation of drug-cyclodextrin complexes. The results of XRD studies are like the findings of DSC studies. The photograph of OLZ showed drug particles as irregular-shaped crystals (Fig. 6). The photographs of cyclodextrin complexes clearly showed a change in particle morphology (Fig. 6). Amorphous aggregates were observed in cyclodextrin complexes. Earlier reports also contained similar findings and it indicates the formation of complexes [41].

CONCLUSIONS

The present work was designed to study the impact of combined cyclodextrin complexation on the aqueous solubility and dissolution enhancement of olanzapine. Cyclodextrin complexes of OLZ : CD (1:1 M) were produced by physical mixing, slugging, kneading, hydration, and granulation methods. All the inclusion complexes of OLZ exhibited higher dissolution rates when compared to the pure drug. Of all the prepared complexes, complex with βCD prepared by hydration method showed highest dissolution rate. The method of preparation of cyclodextrin inclusion complexes used only water as a solvent which does not cause any harm to the individual and the environment and thereby, the method is a potential eco-friendly method. The interaction between CD cavity and drug molecule was observed in FT-IR results. The reduction in the drug's crystalline nature was observed in the results of DSC, XRD and SEM studies. Though the solubility of unsubstituted natural βCD is less

than modified HPβCD, stable complexes were formed with OLZ. Due to lower molecular weight of βCD than HPβCD, the formulation bulk of tablets will be lower. The formulation containing drug-βCD will be economical due to low cost of natural cyclodextrin, βCD when compared to derived cyclodextrin, HPβCD.

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