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Solubility and Dissolution Rate Enhancement of Olmesartan Medoxomil by Complexation and Development of Mouth Dissolving Tablets

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Abstract: The main objective of the research work is to improve the solubility and dissolution rate of olmesartan medoxomil by complexation with β-Cyclodextrins. The inclusion complexes were prepared by kneading method. The prepared complexes were characterized by Fourier Transform Infrared Spectroscopy (FTIR), X-Ray Diffraction (XRD) and Differential Scanning Calorimetry (DSC). The FTIR and XRD spectra of olmesartan/ β-Cyclodextrins solid complexes showed that olmesartan medoxomil could form inclusion complex with β-Cyclodextrins in solid state. The XRD spectra of olmesartan/ β-Cyclodextrins solid complexes indicated olmesartanmedoxomilexisted in amorphous state, this could be explained the fact that the aqueous solubility of olmesartan medoxomil was increased. From the prepared inclusion complexes, fast dissolving tablets were formulated by using various superdisintegrants like sodium starch glycolate and croscarmellosesodium in various concentrations (5-15%).Prepared tablets were evaluated for physical parameters and drug release by *invitro* dissolution studies. Dissolution studies showed fast release of olmesartan medoxomil in tablets containing a high level of sodium starch glycolate. Complexation of olmesartan medoxomil with β-CD significantly improved the solubility of the drug and improved the mechanical properties of tablets produced by direct compression.

Key words: Olmesartan Medoxomil · B-Cyclodextrins · Sodium Starch Glycolate · Croscarmellose Sodium · Orodispersible Tablets

INTRODUCTION

Orally disintegrating tablets (ODT) are an emerging trend in formulation, gaining popularity due to ease of administration and better patient compliance especially for geriatric and pediatric patients [1]. Conventional tablets and capsules pose difficulty for swallowing in patient groups such as elderly, children and patients mentally retarded, uncooperative, or on reduced liquid intake diets [2, 3]. To fulfill the above needs, formulators have developed ODT. Orally disintegrating tabletsare the solid dosage forms containing medicinal substances which disintegrates rapidly, usually within a matter of seconds when placed upon the tongue. The performance of an ODT depends on the technology used in its manufacture. The disintegrating property of the tablet is attributable to a quick ingress of water into the tablet matrix, which creates porous structure and results in rapid disintegration. Hence, the basic approaches to develop ODT include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent and using highly water-soluble excipients in the formulation. Techniques, which have been used by various researchers to prepare ODT include freeze-drying, tablet moulding, spray drying, sublimation, direct compression, cotton candy process and mass-extrusion, however most of these techniques are patented. The direct compression process using superdisintegrants is promising approach in the preparation of ODT [4-6]. Superdisintegrants are newer substances which are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. On contact with water the superdisintegrants swell, hydrate, change volume or form and produce a disruptive change in the tablet. Sodium starch glycolate is the sodium salt of a carboxymethyl ether of starch. It is effective at a concentration of 2-8%. It can take up more than 20 times its weight in water and the resulting high

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swelling capacity combined with rapid uptake of water accounts for its high disintegration rate and efficiency [7, 8]. Croscarmellose Sodium is a white, free flowing powder with high absorption capacity. It has a high swelling capacity and thus provides rapid disintegration and drug dissolution at lower levels. It also has an outstanding water wicking capability and its cross-linked chemical structure creates an insoluble hydrophilic, highly absorbent material resulting in excellent swelling properties [9, 10].

The enhancement of solubility and dissolution rate of poorly water soluble drugs remains one of the most challenging aspects of drug development. Several approaches have been followed in improving solubility of such drugs, one being complexation using cyclodextrins. One of the most important characteristics of cyclodextrins is their ability to form inclusion complexes to improve pharmaceutical properties like solubility, dissolution rate, bioavailability, stability and even palatability without affecting their intrinsic lipophilicity or pharmacological properties [11-14]. Olmesartan medoxomil is the latest angiotensin II receptor blocker approved by FDA for the treatment of hypertension. It is white to light yellowish-white powder or crystalline powder. It is practically insoluble in water and sparingly soluble in methanol. Its oral bioavailability is 26% and having 99% plasma protein binding. It is metabolized in liver. Elimination half-life of olmesartan medoxomil is 13 hrs [15]. Based on the above physicochemical and biopharmaceutical properties, Olmesartan medoxomil was selected as a drug candidate.

The aim of the present investigation is to enhance the solubility, dissolution rate and mask the taste of the olmesartan by preparing inclusion complexes with β-cyclodextrins. The prepared complexes were characterized by x-ray diffractometry (XRD), differential scanningcolorimetry (DSC), fourier transform infrared spectroscopy (FTIR) and by dissolution studies. Further these complexes are used for the formulation of orodispersible tablets using sodium starch glycolate (SSG) and crosscaremellose sodium (CCS) as superdisintegrants.

MATERIALS AND METHODS

Olmesartan Medoxomi l (OLM) was a gift sample from M/S Apotexpharma Pvt Ltd, Bangalore, β-cyclodextrins (β-CD), Sodium starch glycolate (SSG) and Croscarmellose sodium (CCS) were gift samples obtained from M/s. NATCO Pharma Ltd, Hyderabad. Potassium dihydrogen phosphate, Sodium hydroxide, Microcrystalline cellulose (MCC), Magnesium stearate and ethanol were procured from S.D Fine Chem., Ltd., Mumbai. All other materials used were of pharmacopoeial grade.

Table 1: Phase Solubility Studies of Olmesartan medoxomil

Concentration of β-cyclodextrins (mM/L)	Amount drug dissolved (mg)	Concentration of OLM (mM/L)
0	34.6	6.2
2	41.3	7.4
4	49.1	8.8
6	59.2	10.6
8	70.3	12.6
10	80.4	14.4

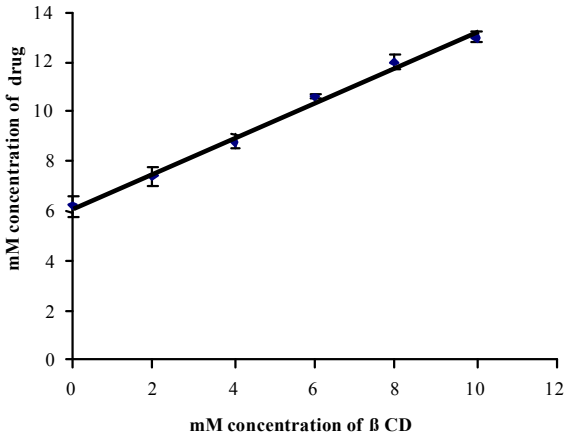

Fig. 1: Phase Solubility Curve of Olmesartan medoxomil

Phase-Solubility Studies: Phase-solubility studies were carried out according to the method reported by Higuchi and Connors [11]. It Permits the evaluation of the affinity between the carrier and drug in aqueous solution and to know the stable inclusion complex. An excess amount of olmesartan was added to an aqueous solution into a conical flasks with increase in concentration of β-cyclodextrins (2-10mm). These flasks were shaken at 25°C for 48 hours. Then the samples were filtered through a Whatman filter paperwith a pore size 0.45 µm. The filtrate was diluted and assayed for OLM content spectrophotometrically at 256 nm. The apparent stability constants were calculated from the phase solubility diagrams and according to equation, Kc = Slope / Intercept (1-slope). The results were shown in Table 1 and the phase solubility curve was shown in Figure 1.

Preparation of Cyclodextrin Inclusion Complexes: Inclusion complexes with 1:1 molar ratio of drug and β-CD were prepared on the results of phase solubility studies by kneading method. In kneading technique olmesartan

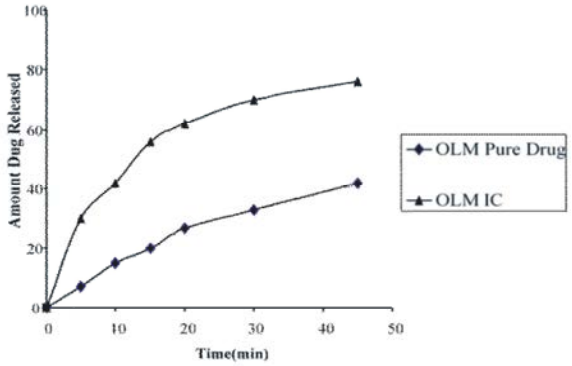

Fig. 2: Dissolution Profiles of Prepared OLM-βCD Complexes by Different Methods In Comparison With Pure Drug.

and β-CD were mixed in 1:1 molar ratio and kneaded for 45 minutes. During the kneading, 40% ethanol: water (27:75 v/v) mixture was added to the mixture to maintain a proper consistency. The product then was dried at 40°C for 24 hours and the resultant solids were pulverized and then sieved through 100 # and stored in desiccator overnight [16].

Estimation of Drug Content for Inclusion Complexes: Inclusion complexes of olmesartan equivalent to 40mg was weighed and transferred into a 100ml volumetric flask. To this small quantity of methanol was added to dissolve. It was shaken occasionally for about 15 minutes and the volume was made up to 100ml by adding 6.8 pH buffer. The solution was filtered by using a Whatman filter paper with a pore size 0.45 µm. The filtrate was subsequently diluted with 6.8 pH buffer and the absorbance was measured at 256nm using 6.8 pH buffer as blank. This test was repeated six times (N=6).

***In Vitro* Dissolution Studies for OLM-CD Complexes:** Dissolution studies on prepared inclusion complexes were performed in a calibrated 8 station dissolution test apparatus (LABINDIA) equipped with paddles (USP apparatus II method) employing 900 ml of 6.8 pHbuffer as dissolution medium. The paddles were operated at 50 rpm and temperature was maintained at 37.0±0.5°C throughout the experiment. The samples (10 ml) were withdrawn at 5, 10, 15, 20, 30 and 45 minutes.and replaced with equal volume of same dissolution medium to maintain the constant volume throughout the experiment. Samples withdrawn at various time intervals were suitably diluted with same dissolution medium and the amount of the drug dissolved was estimated by ELICO double beam U.V spectrophotometer at 256 nm. The dissolution profiles were show in Figure 2.

Characterization of Inclusion Complexes

Ftir Spectral Analysis: Infrared spectra of drug and its inclusion complexes were recorded by KBr pellet method using Fourier Transform Infrared Spectrophotometer (BRUKER 8400S). A base line correction was made using dried potassium bromide and then spectra of dried mixtures of drug and inclusion complexes with potassium bromide were recorded. The Samples were prepared by KBr pellet press method. The scanning range was 400 to 4000 cm^{-1}. The spectra were shown in Figures 3-5.

Differential Scanning Colorimetry (DSC): The DSC studies were performed for pure drug, pure cyclodextrins and inclusion complexes. These studies were carried out with PERKIN ELMER DSC model 7 using Al 40 µl crucible at 10° C/min heating range. The temperature range used was 0–300°C. The thermograms were shown in Figures 6-8.

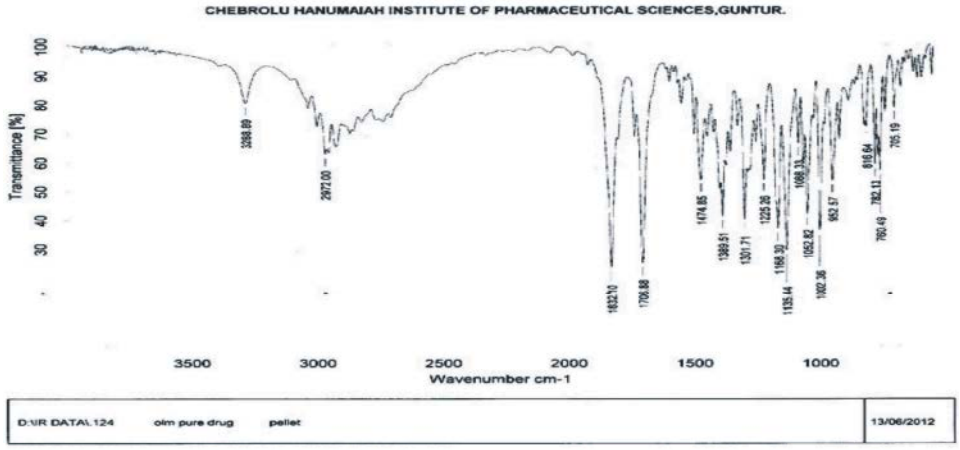

Fig. 3: FTIR Spectra of Pure Olmesartan medoxomil

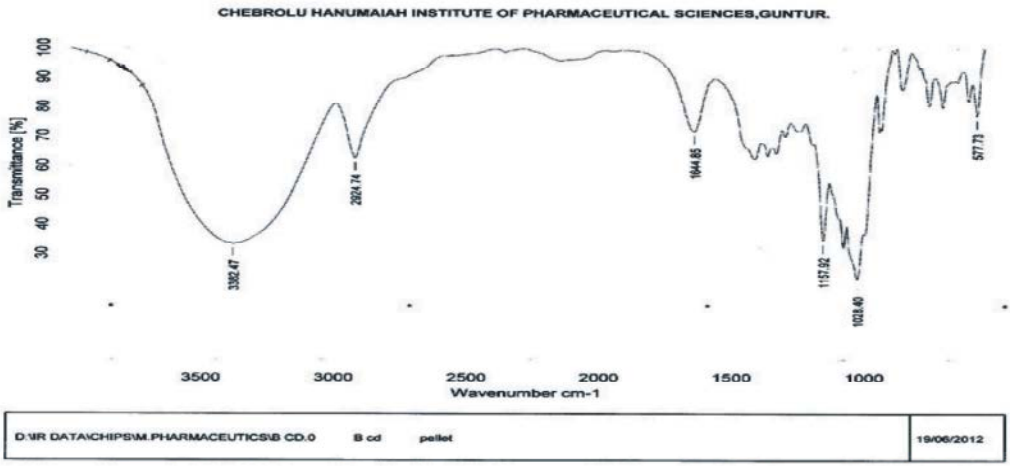

Fig. 4: FTIR Spectra of β-Cyclodextrin

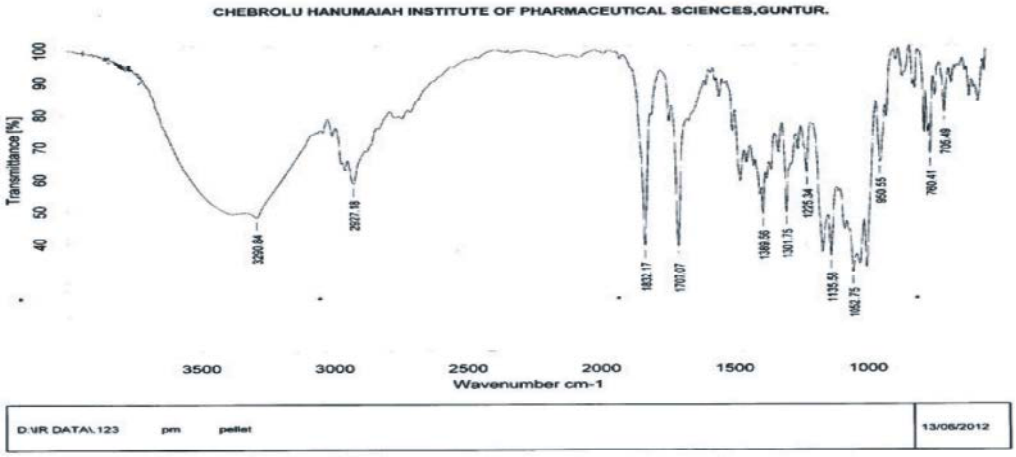

Fig. 5: FTIR Spectra of Inclusion Complex (Kneading Method)

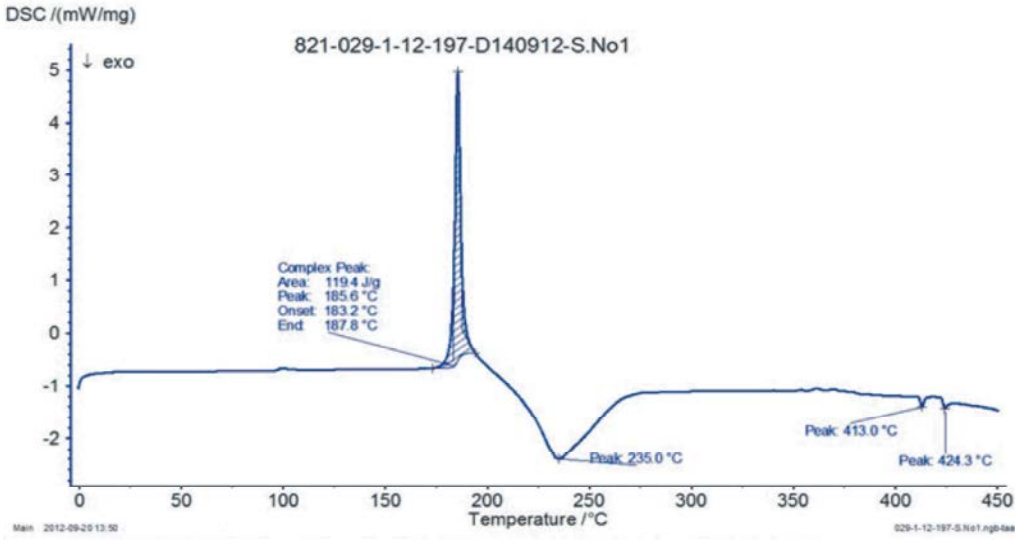

Fig. 6: DSC Thermogram of Olmesartan Medoxomil Drug

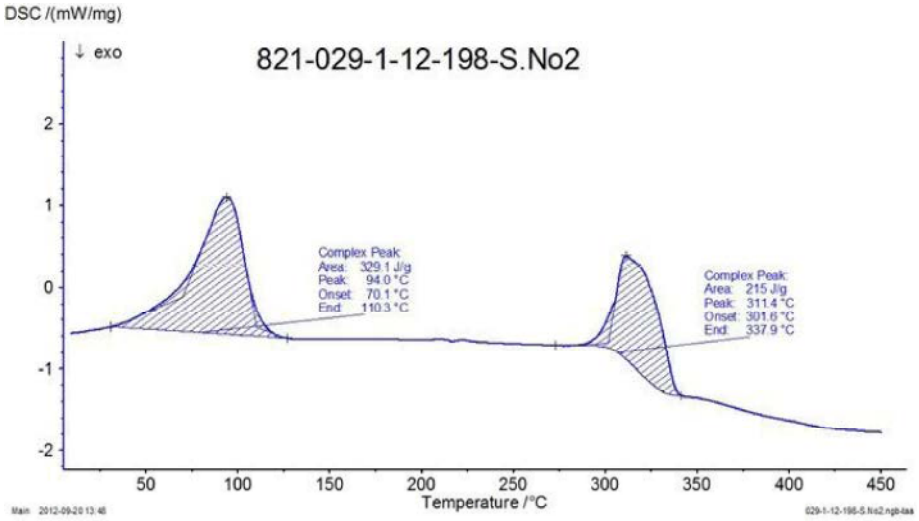

Fig. 7: DSC Thermogram of β-Cyclodextrin

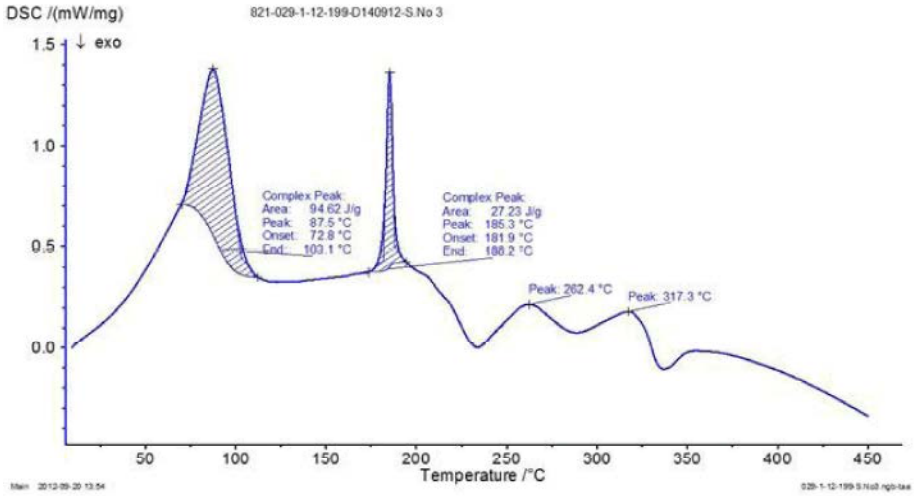

Fig. 8: DSC Thermogram of Olmesartan Inclusion Complex

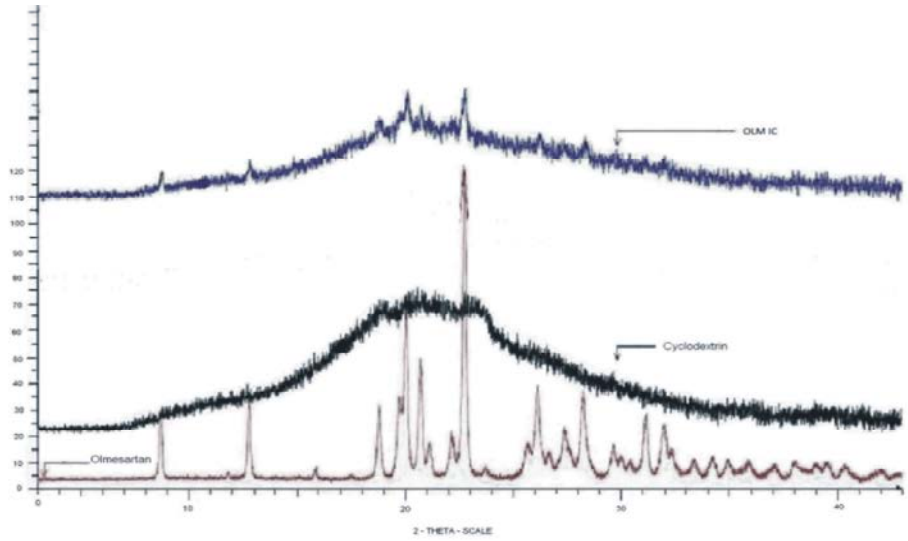

Fig. 9: PXRD data of Drug, Cyclodextrin, Inclusion Complex.

Table 2: Composition of Olmesartan medoxomil Fast dissolving Tablets

Ingredients (mg/Tablet)	F1	F2	F3	F4	F5	F6	F7
Drug+β CD complex (eq 40mg)	121.5	121.5	121.5	121.5	121.5	121.5	121.5
Sodium starch glycolate	-	10	20	30	-	-	-
Croscarmellose Sodium	-	-	-	-	10	20	30
Mannitol	20	20	20	20	20	20	20
Avicel pH 102	56.5	46.5	36.5	26.5	46.5	36.5	26.5
Magnesium stearate	2	2	2	2	2	2	2
Total wt	200	200	200	200	200	200	200

Table 3: Physical Parameters of OLM Orodispersible Tablets

S.NO	Tablet Formulation	Weight uniformity (mg/tablet)	Friability loss (%)	Hardness (kg/cm^2)	Drug content* (mg)
1	F1	199±2	0.40	3.0±0.3	39±0.3
2	F2	202±1	0.59	3.0±0.2	40±0.2
3	F3	198±2	0.66	3.0±0.2	38±0.1
4	F4	199±2	0.72	3.0±0.1	39±0.2
5	F5	199±3	0.58	3.0±0.2	39±0.1
6	F6	200±1	0.60	3.0±0.1	39±0.3
7	F7	198±2	0.64	3.0±0.3	39±0.4

Table 4: Evaluation Parameters of Olmesartan Tablets.

S.NO	Tablet Formulations	Wetting time (seconds)	Water absorption ratio	*In Vitro* Disintegration time (seconds)	Moisture Uptake (%)
1	F1	26.8±2.0	70.2	54±2.5	4.2±2.0
2	F2	28.0±4.0	78.8	41±1.6	5.0±1.8
3	F3	32.8±3.2	82.3	35±2.8	4.6±1.6
4	F4	24.8±2.3	89.2	28±4.5	5.2±2.0
5	F5	24.8±5.2	76.4	45±3.5	4.6±1.4
6	F6	29.2±3.6	80.2	38±3.5	4.7±1.8
7	F7	27.2±3.8	84.2	34±2.6	4.9±2.0

X-Ray Powder Diffraction (XRD): The powder crystallinity of the pioglitazone and the pioglitazone solid dispersions were determined using Bruker D8 Advance XRD with copper target instrument. The conditions were maintained at 40 Kv voltages, with 40 MA current at room temperature. The scanning rate employed was 0.1° /sec over a range of 2θ values from 3° to 45°. The difractograms were shown in Figures 9.

Preparation of Olmesartan Medoxomil Orodispersible Tablets: Olmesartan medoxomil containing orodispersible tablets were prepared by direct compression process. All the ingredients were properly mixed and the blends were passed through sieve (#40) and compressed on rotary compression machine (Clit Mini press). The Inclusion complexes equivalent to 40mg of olmesartan prepared by different methods were blended with super disintegrants like SSG and CCS in varying concentration (5-15%) along with MCC as a diluent, mannitol as sweetener and 1% magnesium stearate as lubricant and then directly compressed. The compositions of various tablet formulations were given in Table 2.

Evaluation of Tablets: Physical parameters such as weight variation, hardness, friability and disintegration were evaluated for prepared tablets. The prepared orodispersible tablets were further evaluated for physical parameters like drug content, wetting time, water absorption ratio, moisture uptake studies and *in-vitro* dissolution studies and their results were shown in Tables 3 & 4. The moisture uptake study is carried out by keeping ten tablets along with calcium chloride in a desiccator maintained at 37°C for 24 hrs to ensure complete drying of the tablets. The tablets are then weighed and exposed to 75% RH, at room temperature for 2 weeks. The required humidity can be achieved by keeping saturated sodium chloride solution in the desiccator for 24 hrs. The tablets are reweighed and the percentage increase in weight is recorded. If the moisture uptake tendency of a product is high, it requires special dehumidified area for manufacturing and packing [17]. Wetting Time is carried out by taking five circular tissue papers of 10 cm diameter were placed in a Petri dish with 10 cm diameter.10 ml of water containing Amaranth, water soluble dye was added to the Petri dish. One tablet was

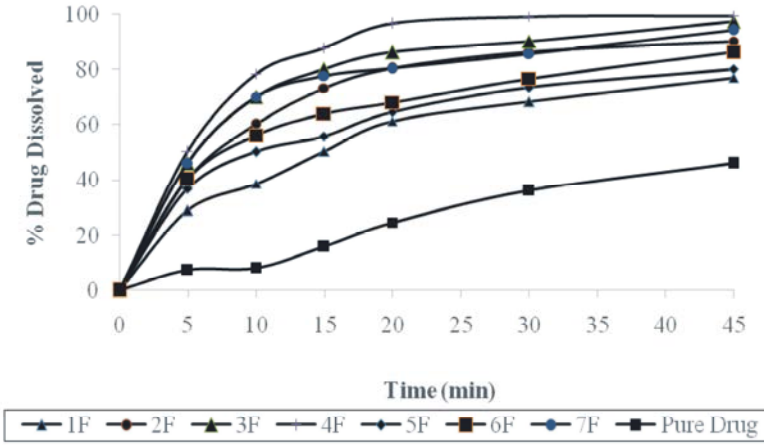

Fig. 10: Dissolution Profile of OLM Fast Dissolving Tablets

Table 5: *In Vitro*Dissolution Parameters of Olmesartan Fast Dissolving Tablets

					Zero order		First order		Hixson Crowell	
S.NO	Tablet Formulations	T_{50}%	T_{75}%	DE_{30}%	R^2	K (mg/min)	R^2	K (min^1)	R^2	K ($mg^{1/3}$)
1	F1	8	29	80.0	0.700	1.481	0.976	0.029	0.856	0.014
2	F2	10	20	86.2	0.494	1.619	0.919	0.100	0.554	0.009
3	F3	8	23	78.0	0.702	1.515	0.981	0.033	0.896	0.014
4	F4	6	12	80.4	0.559	1.519	0.978	0.044	0.861	0.010
5	F5	15	30	80.7	0.591	1.773	0.925	0.070	0.545	0.009
6	F6	12	30	86.2	0.494	1.619	0.919	0.100	0.554	0.009
7	F7	10	26	78.0	0.702	1.515	0.981	0.033	0.896	0.014

carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet was noted as a wetting time [18]. Water Absorption Ratio is carried out by taking a piece of tissue paper folded twice was placed in a small Petri dish (internal diameter = 6.5cm) containing 5 ml of distilled water. A tablet was placed on the tissue paper. The wetted tablet was weighed. The test was done in triplicate. The water absorption ratio (R) was determined according to the equation, Water absorption ratio (R) = Wa-Wb / Wa X 100. Where, Wa is the weight of the tablets before the test and Wb is the weight of the tablet after water absorption. Disintegration time of orodispersible tablets were carried out by the method given by Gohel *et al.* for this a Petri dish was filled with 10 ml of water and the tablet was carefully placed in the center of petridish and the time taken for the tablet to completely disintegrate in to fine particles was noted [19].

***In vitro* Dissolution Studies:** Dissolution studies on each tablet formulation were performed in a calibrated 8 station dissolution test apparatus (LABINDIA) equipped with paddles (USP apparatus II method) employing 900 ml of 6.8 pH buffer as a dissolution medium. The paddles were operated at 50 rpm and temperature was maintained at 37° C ± 1° C throughout the experiment. The samples (10 ml) were withdrawn at 5, 10, 15, 20, 30 and 45 minutesand replaced with equal volume of same dissolution medium to maintain the constant volume throughout the experiment. Samples withdrawn at various time intervals were suitably diluted with same dissolution medium and the amount of the drug dissolved was estimated by ELICO double beam U.V spectrophotometer at 256 nm. The dissolution studies on each formulation were conducted in triplicate. From the dissolution profiles various parameters like $T_{50,}$ T_{75} and $DE_{30\%}$ were calculated. The dissolution profiles for all formulations were shown in Figures 10 and the *In vitro* dissolution parameters were given in the Table 5.

RESULTS

Phase Solubility Studies: Phase solubility study is useful in determination of inclusion complexation of drug with cyclodextrins in aqueous media. From the phase solubility studies it was observed that a linear increase in solubility with increasing concentration of β-CDs which was shown in the Figure 1. The slope values obtained were

less than 1 (i.e.0.8), which indicated that the 1:1 molar ratio of drug-β CD complex is stable. The stability constant, Ks was found to be 615 M^{-1} indicating the formation of 1:1 stable complex. The *in vitro* dissolution studies were performed for prepared inclusion complexes in 6.8 pH phosphate buffer and compared with that of pure drug and from these studies it was observed that the inclusion complex prepared by kneading method released the drug rapidly than the pure drug alone. The profiles were shown in Figure 2.

Characterization of Drug-β Cyclodextrin Complexes: The possible interaction between the drug and the carrier was studied by FTIR spectroscopy. IR spectra of pure olmesartan medoxomil showed characteristic peaks at 3288 cm^{-1} (Broad intermolecular hydrogen bond, O-H stretch), 2972 cm^{-} (Aliphatic C-H stretch), 1706 cm^{-1} (C=O of carboxylic group), 1474 cm^{-1}(C-N stretch), 1389 cm^{-1} (in plane O-H bend), 1052 cm^{-1} (ring C-O-C stretch). The FTIR spectra of β-CD showed prominent peaks at 3382 cm^{-1} (O-H), 2924 cm^{-1} (C-H), 1644 cm^{-1} (H-O-H bending) and 1028 cm^{-1} (C-O-C). The IR spectra were given in the Figures 3-5.

DSC analysis was performed for the Pure drug, β-CD and for complexes prepared by kneading method. DSC thermogram for pure olmesartan shows onset of peak at 183.2°C, which represents the melting point of OLM. DSC thermogram of inclusion complex shows onset of peaks at 181.9°C. The DSC thermograms were shown in the Figures 6-8.

The XRD patterns of olmesartan and complexes prepared by kneading were shown in Figure 9. The powder diffraction patterns of pure olmesartan showed characteristic high diffraction peaks. On the other hand the diffraction patterns of complexes showed decrease in the peak intensity.

Evaluation of Orodispersible Tablets: Orodispersible tablets of olmesartan were prepared by using superdisintegrants SSG and CCS in different concentrations i.e., 5, 10 and 15%. Tablet formulations were further evaluated for physical parameters. Moisture uptake studies for orodispersible tablets were conducted to assess the stability of formulation. The results of physical parameters evaluation were given in Table 3.

***In vitro* Dissolution Studies:** The dissolution studies of orodispersible tablets were performed in pH 6.8 buffer by using USP-II paddle method. Based upon the data obtained from the dissolution studies, various parameters such as T_{50}, T_{75}, DE_{30}% and first order and zero order release rate constants were estimated. The dissolution parameters such as T_{50} and T_{75} were measured directly from the dissolution profile curves and DE_{30}% was estimated by employing trapezoidal rule to the dissolution profiles. The drug release from all the tablet formulations were found to release the drug at a faster rate than compared to pure drug. It was found that the tablet formulation F4 with 15% SSG showed the rapid drug release when compared to pure drug and other formulations. The drug release of tablet formulations in the presence of various superdisintegrants were in the order of SSG>CCS. The rate of drug release of tablet formulations was found to be linear with first order rate constant. The r^2 values of all tablet formulations were in the range of 0.92 to 0.99. Hence suitable as fast dissolving tablets.

DISCUSSION

From the phase solubility studies it was observed that a linear increase in solubility with increasing concentration of β-CDs. Hence the drug Inclusion complexes were prepared by kneading method using β-CD in 1:1 molar ratio and these combinations were found to be stable and suitable for masking the metallic taste of drug and enhances the dissolution rate of olmesartan. From the *in vitro* dissolution studies it was observed that the inclusion complex prepared by kneading method released the drug rapidly than the pure drug alone.

The possible interaction between the drug and the carrier was studied by FTIR spectroscopy. In the FTIR study, the breakdown of the intermolecular hydrogen bond between the crystalline drug molecule and formation of hydrogen bond between the drug and the polymers might be related to the slight shift of the absorption band. However FTIR spectra of complexes showed that no changes have occurred in chemical structure. Broadening of peak indicates the formation of inclusion complex between the drug and β-CD. DSC analysis was performed for the Pure drug, β-CD and for complexes prepared by kneading method. From the DSC thermogram, it was observed that the drug was incorporated in the polymer, so the graph was extended. It indicated that there was no drug and polymer interaction.

The XRD patterns of olmesartan and complexes prepared by kneading method were studied. The powder diffraction patterns of pure olmesartan showed characteristic high diffraction peaks. On the other hand

the diffraction patterns of complexes showed decrease in the peak intensity and finally absence of peaks was observed in complexes which indicated the amorphous nature of olmesartan in inclusion complexes and are considered to be the reason for the dissolution and solubility enhancement.

From the prepared inclusion complexes orodispersible tablets were prepared by using superdisintegrants such as SSG and CCS. The direct compression process was found to be suitable for compressing the tablet formulations as fast dissolving tablets. Tablet formulations were further evaluated for physical parameters. All the tablet formulations were found to be stable with in the I.P specified limits for weight uniformity, friability and drug content. Moisture uptake studies for orodispersible tablets were conducted to assess the stability of formulation. The results indicated that tablets containing high concentration of superdisintegrantsi.e F4 (SSG 15%) get softened and absorb more atmospheric moisture.

The dissolution studies of orodispersible tablets were performed in pH 6.8 hydrochloric acid buffer by using USP-II paddle method. The drug release from all the tablet formulations were found to release the drug at a faster rate than compared to pure drug. It was found that the tablet formulation F4 with 15% SSG showed the rapid drug release when compared to pure drug and other formulations containing CCS. This may be due to the remarkable rapid water penetration andextensive swelling capability of SSG. SSG was reported to possess capability to absorb water and swell about 300 times itsvolume and not affected by increase in compressionpressure. The dissolution profiles were shown in Figure 10. The drug release of tablet formulations in the presence of various superdisintegrants were in the order of SSG>CCS. The rate of drug release of tablet formulations was found to be linear with first order rate constant. The r^2 values of all tablet formulations were in the range of 0.92 to 0.99.

CONCLUSION

The present study has shown that it is possible to increase the solubility and dissolution rate of poorly soluble drug olmesartan medoxomil by preparing it as inclusion complexes with β-cyclodextrins. The inclusion complexes exhibited faster dissolution characteristics as compared to that of pure drug. This was due to solubilizing effect of the complexing agent. It was found that the inclusion complex prepared by the kneading method release the drug rapidly than the pure drug. The orodispersible tablets of olmesartan prepared with 15% Sodium starch glycolate (F4) as superdisintegrant showed rapid drug release when compared to pure drug and other tablet formulations.

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