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FORMULATION AND OPTIMIZATION OF ORODISPERSIBLE TABLETS OF OLMESARTAN MEDOXOMIL

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ABSTRACT: Olmesartan medoxomil (OLM) is an angiotensin II receptor blocker used for the treatment of hypertension. In this work an attempt was made to mask the metallic taste and enhance the solubility and dissolution rate of poorly soluble OLM by formulating it as inclusion complexes with β-cyclodextrins (β-CDs) as complexing agent in 1:1 molar ratio. The drug – CDs complexes were prepared by physical mixing and co-evaporation methods. The complex formation with in solid state was confirmed by Fourier transform infrared spectroscopy, x-ray diffractometry, differential scanning colorimetry and by scanning electron microscope analysis. From the prepared inclusion complexes, orodispersible tablets (ODTs) were formulated by using various superdisintegrants like sodium starch glycolate (SSG) and crospovidone in various concentrations (5-15%). Prepared tablets were evaluated for physical parameters and drug release by in vitro dissolution studies. ODTs containing SSG (15%) as super-disintegrant showed fastest disintegration and in vitro drug release. In conclusion, the present investigation demonstrates that the combination of inclusion complexation and using of superdisintegrants was a promising approach in the preparation of tastes masked ODTs of OLM.

INTRODUCTION: Despite of the tremendous advancements in drug delivery, oral administration remains to be the most preferred route for the administration of therapeutic agents. But the most evident drawback of the commonly used oral dosage forms like tablets and capsules is difficulty in swallowing (dysphasia) and delivery of unpalatable drugs [1]. Therefore, to improve the compliance and quality of life of mainly pediatric and geriatric patients, emphasis is laid on the development of novel drug delivery systems.

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One such approach is formulation of orodispersible tablets (ODTs). ODTs are the solid dosage forms containing a medicinal substance which disintegrates rapidly, usually within a matter of seconds when placed upon the tongue [2-3]. These tablets are expected to dissolve or disintegrate in oral cavity without drinking water. The disintegrated mass can slide down smoothly along the esophagus with the help of saliva, so, even people who have swallowing or chewing difficulties can take it with ease [4-5]. The convenient means in the formulation of ODTs is the use of super-disintegrants [6-8]. 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 (CDs).

One of the most important characteristics of CDs 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 [9-10].

Olmesartan medoxomil (OLM) is the angiotensin II receptor blocker approved by FDA for the treatment of hypertension. It is practically insoluble in water and sparingly soluble in methanol. Its oral bioavailability is 26 % and has 99 % plasma protein binding. It is metabolized in liver. Elimination half-life of OLM is 13 h. Potential advantages of this drug include once-daily dosing, an absence of significant adverse reactions, a well-tolerated side-effect profile, and cost-effectiveness. Based on the above physicochemical and biopharmaceutical properties, OLM was selected as a drug candidate for the preparation of orodispersible tablets [11].

The aim of the present investigation was to enhance the solubility as well as dissolution rate and also to mask the taste of the OLM by preparing inclusion complexes with β- cyclodextrins (β-CDs). The prepared complexes were characterized by x-ray diffractometry (XRD), differential scaning colorimetry (DSC), Fourier transform infrared spectroscopy (FTIR) and by dissolution studies. Further, these complexes were used for the formulation of ODTs using sodium starch glycolate (SSG) and crosspovidone (CP) as super-disintegrants.

MATERIALS AND METHODS:

Materials: Olmesartan medoxomil was a gift sample from M/S Apotex pharma Pvt. Ltd, Bangalore, SSG and CP were gift samples obtained from M/s. NATCO Pharma Ltd, Hyderabad. β Cyclodextrins (β-CDs) were commercially procured from Yarrow Chemicals, Mumbai. Potassium dihydrogen phosphate, sodium hydroxide, microcrystalline cellulose, magnesium stearate and ethanol were procured from S.D Fine Chem., Ltd., Mumbai. All other materials used were of pharmacopoeial grade.

Methods:

Saturated solubility studies: Saturated solubility studies (12) of OLM were performed in different dissolution media. 100 mg of OLM was weighed and transferred into different conical flasks containing 10 ml of different dissolution media i.e. distilled water, phosphate buffer (pH 6.8), 0.1 N HCl and were closed appropriately. All the conical flasks were placed in a REMI incubator shaker at 50 rpm, 37ºC±1ºC for 24 h. The conical flasks were then removed from the incubator shaker and samples were filtered using Whatman filter paper. The clear solution obtained by filtration was suitably diluted with appropriate dissolution media and the absorbance values were noted at 256 nm by using corresponding dissolution media as blank solutions on double beam UV-Visible spectrophotometer (Lab INDIA SL 218).

Phase solubility studies: Phase solubility studies were carried out according to the method reported by Higuchi and Connors [13]. It permits the evaluation of the affinity between the carrier and the drug in aqueous solution and to know the stable inclusion complex. An excess amount of OLM was added to an aqueous solution into conical flasks with increase in concentration of β-CDs (2-10 mM). These flasks were shaken at 25°C for 48 h. Then the samples were filtered through a Whatman filter paper. The filtrate was diluted and assayed for OLM content spectrophotometrically at 256 nm. The apparent stability constants (Kc) were calculated from the phase solubility diagrams and according to equation,

$$Kc = \text{slope} / \text{intercept} (1 - \text{slope}).$$

Preparation of Cyclodextrin inclusion Complexes: Inclusion complexes with 1:1 molar ratio of drug and β-CD were prepared based on the results of phase solubility studies by physical mixing and co-evaporation techniques. The physical mixture of OLM and β-CD were prepared by mixing OLM with β-CD in 1:1 molar ratio in a mortar for about 1 h with constant trituration, passed through sieve number 100 and stored in desiccator at a room temperature until further use. In co-evaporation technique, OLM and β-CD were mixed in 1:1 molar ratio and 10 ml of ethanolic solution of OLM was added slowly to 10 ml aqueous solution of CD followed by stirring at 500-600 rpm using magnetic stirrer at 37^{o}C for 24 h. The solvents were then evaporated at 40-50^{o}C. The resultant solids were pulverized and then sieved through sieve number 100 and stored in desiccator overnight [14].

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

***In vitro* dissolution studies for olmesartan modoxomil-cyclodextrin 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 buffer (pH 6.8) as dissolution medium. The paddles were operated at 50 rpm and temperature was maintained at 37ºC±0.5ºC throughout the experiment. The samples (10 ml) were withdrawn at 5, 10, 15, 20, 30 and 45 min 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 [15].

Characterization of Inclusion Complexes [16]:

1. **Fourier Transform Infrared 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}.

2. **Differential scanning Colorimetry (DSC):** The DSC studies were performed for pure drug, pure CDs, physical mixture and inclusion complexes. These studies were carried out with PERKIN ELMER DSC model 7 using Aluminium pan 40 µl crucible at 10^{o}C/min heating range. The temperature range used was 0 – 300^{o}C.

3. X- **Ray diffraction of powder (XRD):** The powder crystallinity of the OLM and the OLM inclusion complexes was determined using Bruker D8 Advance XRD with copper target instrument. The conditions were maintained at 40 Kv, with 40 MA current at room temperature. The scanning rate employed was 0.1 0 /sec over a range of 2θ values from 30 to 450.

4. **Scanning Electron Microscopy (SEM):** The samples (Pure drug and inclusion complexes) were coated with a thin gold layer by sputter coater unit (SPI, Sputter, USA). Then, the SEM photographs were taken by a scanning electron microscope (Scanning electron microscope JSM-6390, Japan) operated at an accelerated voltage of 15kV.

Preparation of Olmesartan Medoxomil Orodispersible Tablets: Olmesartan medoximil ODTs were prepared by direct compression process. All the ingredients were properly mixed and the blends were passed through sieve number 40 and compressed on rotary compression machine (Clit Mini press). The Inclusion complexes equivalent to 40 mg of OLM prepared by different methods were blended with super -disintegrants like SSG and CP in varying concentration (5-15%) along with microcrystalline cellulose as a diluent, mannitol as sweetener and 1% magnesium stearate as lubricant.

Evaluation of Tablets: Physical parameters such as weight variation, hardness, friability and disintegration were evaluated for prepared tablets. The prepared ODTs were further evaluated for parameters like drug content, wetting time, water absorption ratio, moisture uptake studies and in vitro dissolution studies. The moisture uptake study was carried out by keeping ten tablets along with calcium chloride in a desiccator maintained at 37°C for 24 h to ensure complete drying of the tablets.

The tablets were 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 h. The tablets were reweighed and the percentage increase in weight was recorded. If the moisture uptake tendency of a product is high, it requires special dehumidified area for manufacturing and packing of the tablets [16].

Wetting time was carried out by taking five circular tissue papers of 10 cm diameter which were placed in a petri dish with 10 cm diameter. 10 ml of water containing amaranth dye, water soluble dye was added to the petri dish. One tablet was 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 [17]. Water absorption ratio is carried out by taking a piece of tissue paper folded twice which 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 ODTs was carried out by the method given by Gohel (18). For this a petri dish was filled with 10 ml of water and the tablet was carefully placed in the center of petri dish and the time taken for the tablet to completely disintegrate to fine particles was noted.

***In vitro* dissolution studies:** Dissolution studies on each tablet formulation were performed in a calibrated 8 station dissolution test apparatus (LABINDIA Make, DISSO 2000) equipped with paddles (USP apparatus II method) employing 900 ml of buffer (pH 6.8) as a dissolution medium. The paddles were operated at 50 rpm and temperature was maintained at 37 º C ± 1 º 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 the same dissolution medium and the amount of the drug dissolved was estimated by ELICO Made SL 218 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 T50 (time taken for 50% dissolution), T75 (time taken for 75% dissolution) and DE30% (dissolution efficiency) were calculated.

Taste Masking Evaluation: Five human volunteers were asked to hold optimized drug solution (PF4, SF4) in their mouth for 30 seconds (for taste evaluation) and to spit out the solution. Then the oral cavity was rinsed thoroughly with drinking water. The volunteers were asked for mouth feel. The study protocol has been approved by the institutional ethical committee (Ethical committee approval number is 1529/PO/A/11/CPSea).

RESULTS: Saturated solubility studies were carried out for OLM in different media. From the solubility studies it was observed that OLM showed maximum solubility phosphate buffer (pH 6.8), among the different media used. The drug concentration was measured at 256 nm using UV spectrophotometer for all the dissolution media.

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 will happen with increasing concentration of β-CDs. 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 phase solubility curve and corresponding values were shown in **Fig. 1 and Table 1**.

TABLE 1: PHASE SOLUBILITY STUDIES OF OLMESARTAN MEDOXOMIL

Concentration of β-CDs (mM/L)	Amount of 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

β-CDs; β-cyclodextrins, OLM; Olmesartan medoxomil

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 phosphate buffer (pH 6.8) 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 more rapid than the complexes prepared by physical mixing and pure drug alone.

The profiles are shown in **Fig. 2**. The possible interaction between the drug and the carrier was studied by FTIR spectroscopy. The FTIR spectra of pure OLM showed characteristic peaks at 3288 cm-1(broad intermolecular hydrogen bond, O-H stretch), 2972 cm-1 (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 FTIR spectra were given in the **Figures 3-6**.

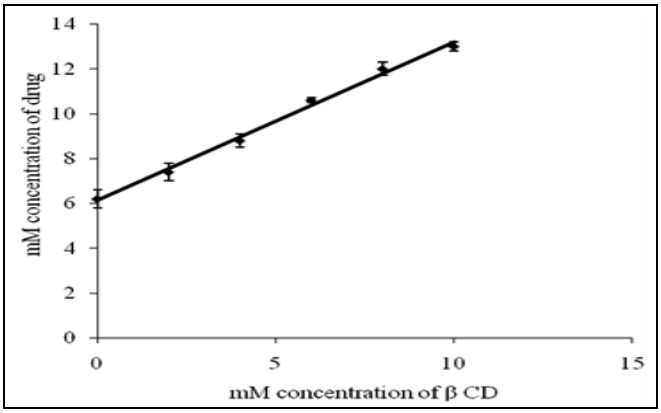


FIG. 1: PHASE SOLUBILITY CURVE OF OLMESARTAN MEDOXOMIL

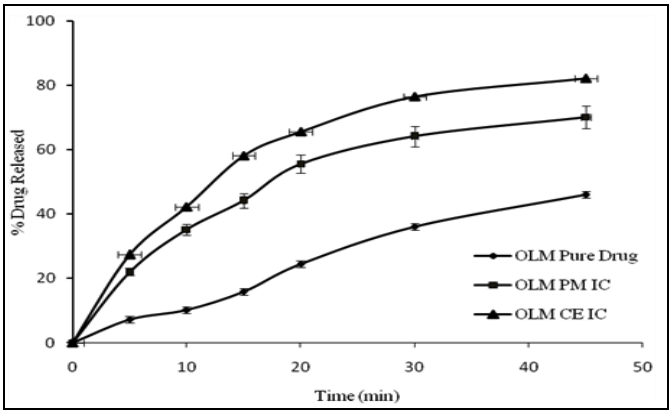


FIG. 2: DISSOLUTION PROFILES OF PREPARED OLMESARTAN MEDOXOMIL β- CYCLODEXTRIN COMPLEXES BY DIFFERENT METHODS IN COMPARISON WITH PURE DRUG

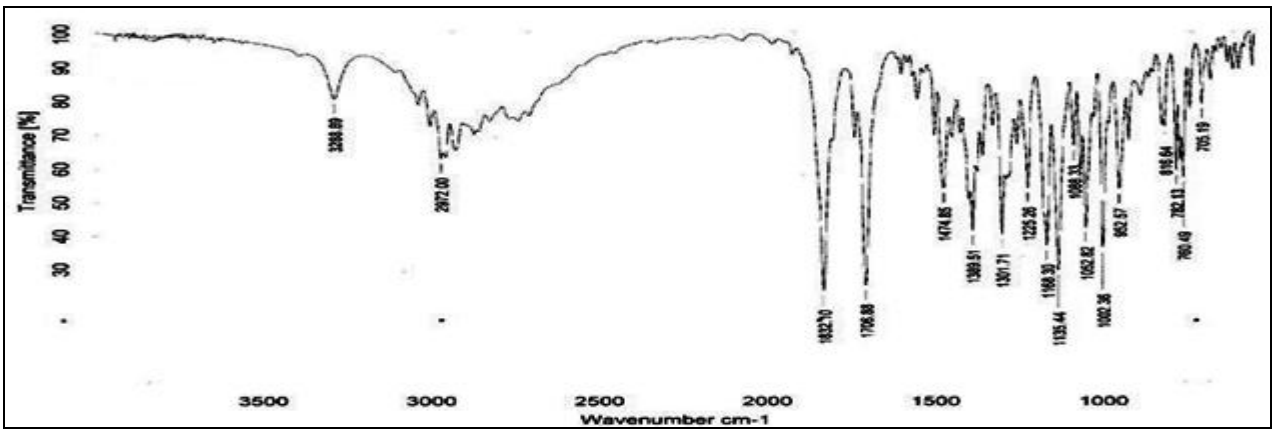


FIG. 3: FTIR SPECTRA OF PURE OLMESARTAN MEDOXOMIL

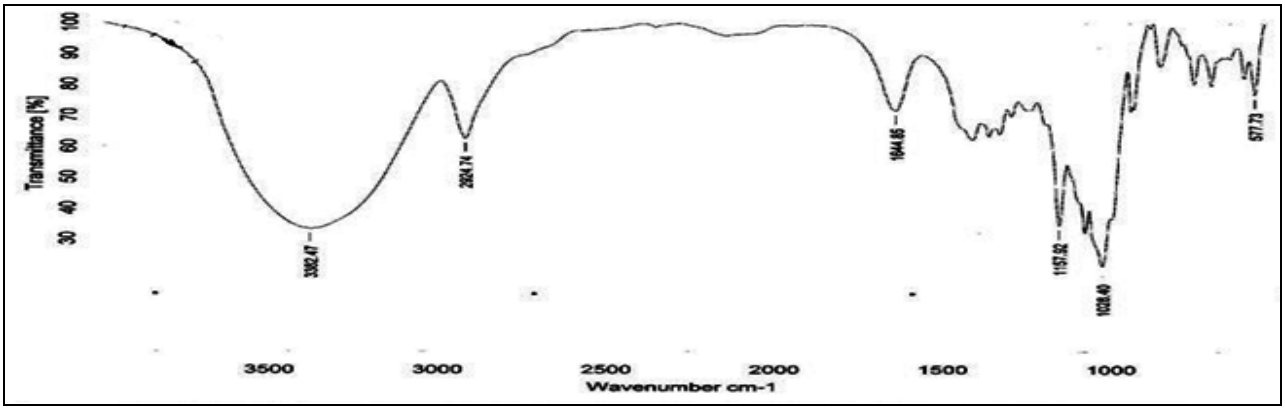


FIG. 4: FTIR SPECTRA OF β-CYCLODEXTRINS

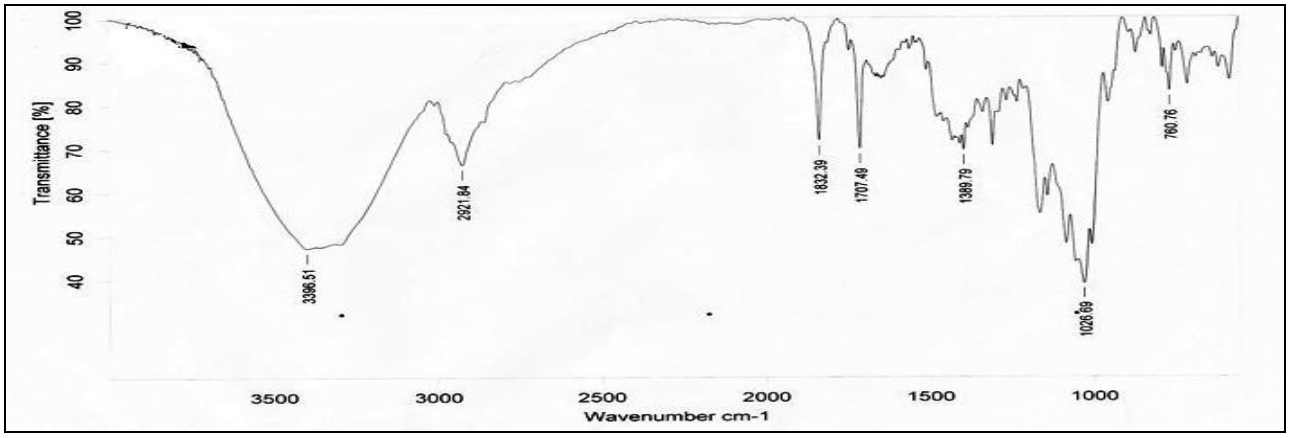


FIG. 5: FTIR SPECTRA OF INCLUSION COMPLEX (PHYSICAL MIXING)

Differential scanning colorimetry analysis was performed for the Pure drug, β-CD and for complexes prepared by physical mixing and kneading method. DSC thermogram for pure OLM shows onset of peak at 183.20C, which represents the melting point of OLM. DSC thermograms of optimized formulations SF4 and SF7 showed onset of peaks at 181.90C and 181.30C. The DSC thermograms were shown in the **Fig. 7**.

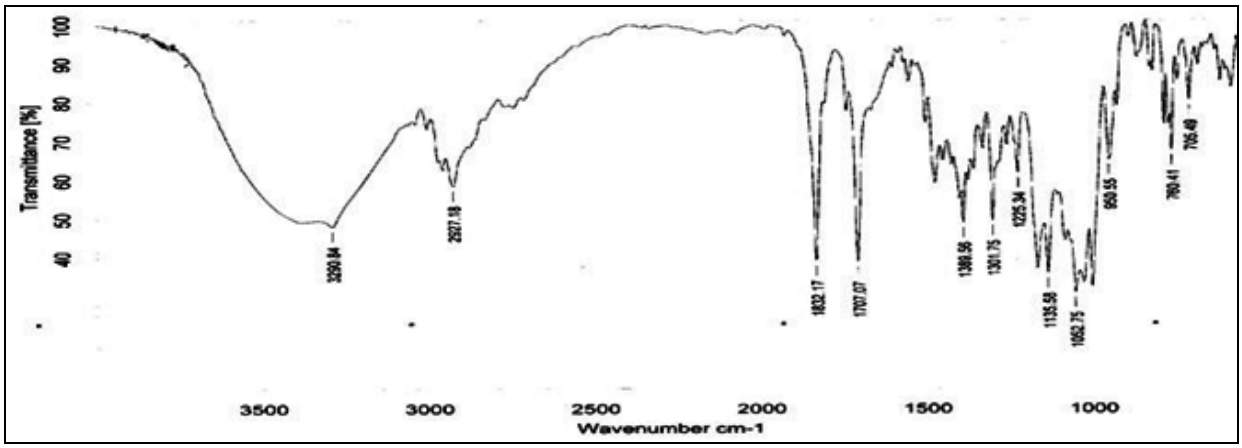
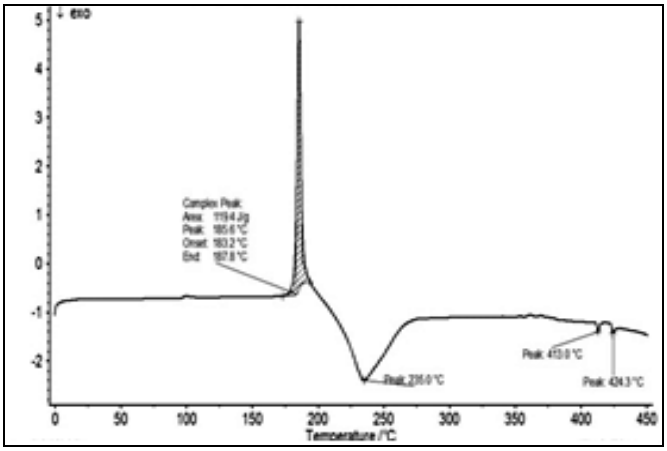
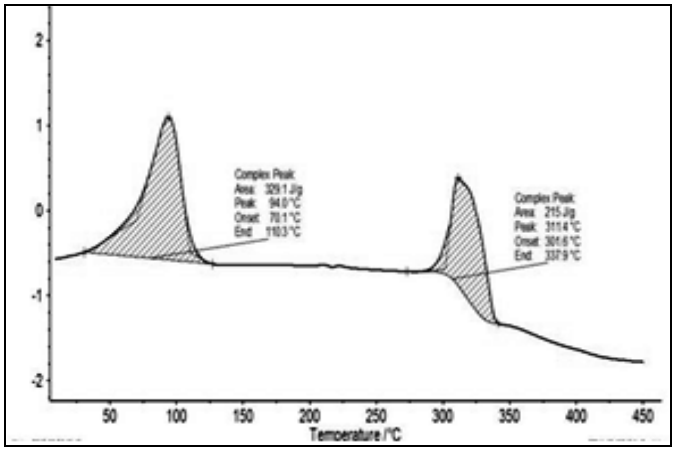


FIG. 6: FTIR SPECTRA OF INCLUSION COMPLEX (SOLVENT EVAPORATION)

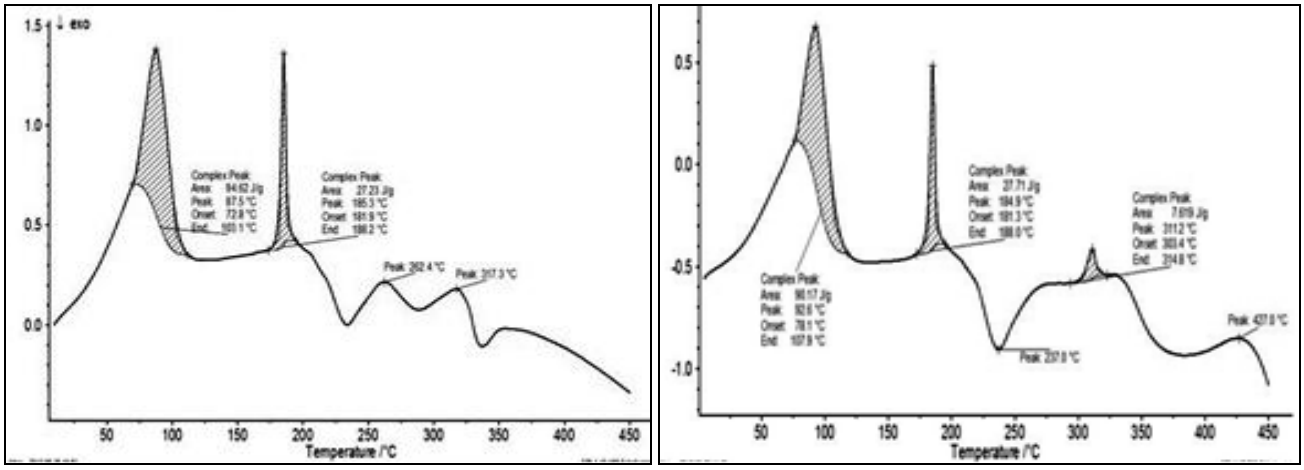
The XRD patterns of OLM, and complexes prepared by physical mixing and kneading are shown in **Fig. 8**. The powder diffraction patterns of pure OLM showed characteristic high diffraction peaks. On the other hand the diffraction patterns of complexes showed decrease in the peak intensity.



A



B



C **D**

FIG. 7: DSC THERMOGRAMS A) PURE DRUG B) B-CYCLODEXTRIN C) PF4 D) SF4

Scanning electron microscopy photographs were taken for OLM pure drug and inclusion complex prepared by physical mixing and co evaporation. The SEM images are shown in the **Figures 9a, 9b**. The SEM image of pure olmesartan powder was appeared in the form of irregular shaped crystals while the SEM images of the prepared inclusion complexes were regular in shape with smooth and regular surface.

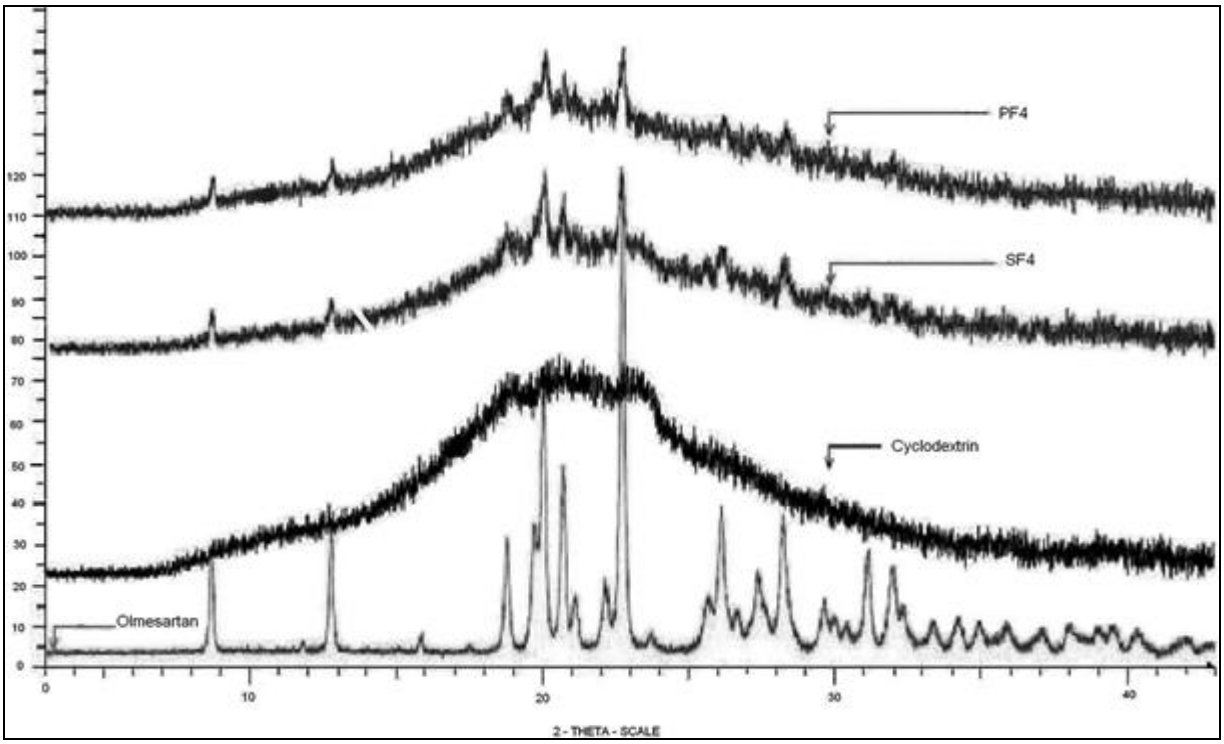


FIG. 8: POWDER XRAY DIFRACTOGRAMS DATA OF OLM, CYCLODEXTRIN, SPF4, PF4

Orodispersible tablets of OLM were prepared by using superdisintegrants SSG and CP in different concentrations i.e., 5, 10 and 15%. The compositions of various tablet formulations are given in **Table 2**. The flow properties such as angle of repose and Carr's index were evaluated for various tablet powder formulations and were found to exhibit good flow characteristics. The angle of repose values obtained for various formulations were in the range of 20.18 ± 0.5 - 25.62 ± 0.2 .and Carr's index were in the range of 11.24 ± 0.6 -19.27 ± 0.5 %. Hausner's ratio for various formulations was in the range of 1.11-1.25. Tablet formulations were further evaluated for physical parameters. Moisture uptake studies for ODTs were conducted to assess the stability of formulation. The results of physical parameters evaluation are given in **Table 3**.

TABLE 2: COMPOSITION OF ORODISPERSIBLE TABLETS OF OLMESARTAN MEDOXOMIL

Ingredients (mg/tablet)	PF1	PF2	PF3	PF4	SF1	SF2	SF3	SF4
Drug + β-CD complex physical mixing (equivalent to 40 mg of OLM)	121.5	121.5	121.5	121.5	-	-	-	-
Drug + β-CD complex co-evaporation (eq-40 mg)	-	-	-	-	121.5	121.5	121.5	121.5
Sodium starch glycolate	20	30	-	-	20	30	-	-
Crospovidone	-	-	20	30	-	-	20	30
Mannitol	20	20	20	20	20	20	20	20
Avicel pH 102	36.5	26.5	36.5	26.5	36.5	26.5	36.5	26.5
Magnesium stearate	2	2	2	2	2	2	2	2
Total weight	200	200	200	200	200	200	200	200

β-CD; β-cyclodextrin

TABLE 3: PHYSICAL PARAMETERS OF OLMESARTAN MEDOXOMIL ORODISPERSIBLE TABLETS

S. NO.	Tablet formulation	Weight uniformity (mg/tablet)	Friability loss (%)	Hardness (kg/cm^2)	Drug content (mg)
1	PF1	201 ± 1	0.68	3.0 ± 0.3	40 ± 0.1
2	PF2	199 ± 2	0.78	3.0 ± 0.2	39 ± 0.2
3	PF3	202 ± 1	0.58	3.0 ± 0.2	40 ± 0.4
4	PF4	198 ± 2	0.62	3.0 ± 0.1	38 ± 0.2
5	SF1	199 ± 1	0.78	3.0 ± 0.2	39 ± 0.2
6	SF2	200 ± 2	0.80	3.0 ± 0.1	39 ± 0.1
7	SF3	199 ± 2	0.70	3.0 ± 0.3	39 ± 0.3
8	SF4	200 ± 3	0.74	3.0 ± 0.1	39 ± 0.2

The dissolution studies of ODTs were performed in buffer (pH 6.8) by using USP-II apparatus (paddle method). Based on the data obtained from the dissolution studies, various parameters such as T50, T75, DE30 %, first order and zero order release rate constants were estimated. The dissolution parameters such as T50 and T75 were measured directly from the dissolution profile curves and DE30 % was estimated by employing trapezoidal rule to the dissolution profiles. The drug release rate from all the tablet formulations was found faster as compared to pure drug. It was found that the tablet formulation SF4 with 15 % SSG showed the rapid drug release when compared to pure drug and inclusion complex prepared by physical mixing.

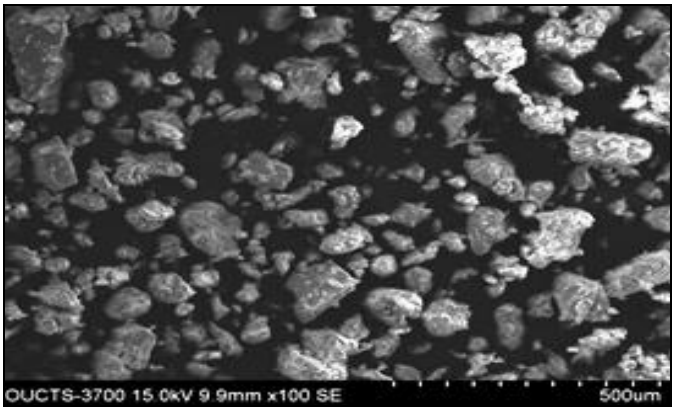


FIG. 9(A): SEM PHOTOGRAPH OF OLMESARTAN MEDOXOMIL

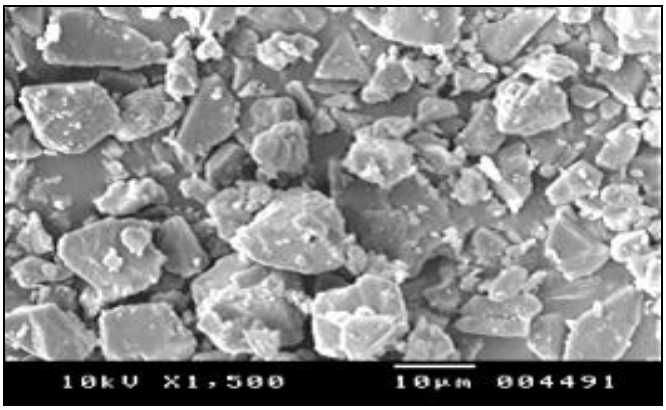
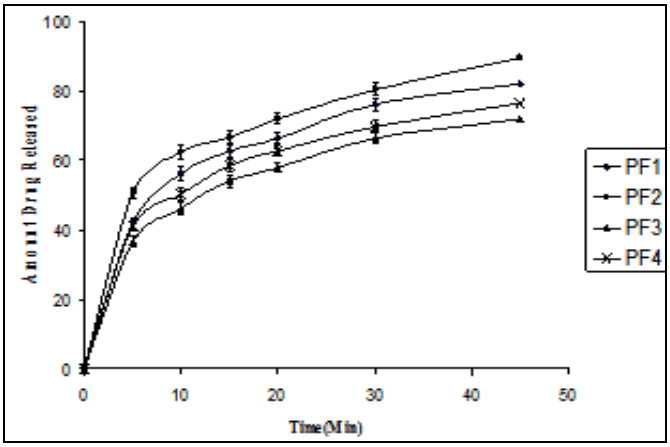


FIG. 9(B): SEM PHOTOGRAPH OF INCLUSION COMPLEX

Dissolution profiles are shown in **Figures 10a, 10b**. The drug release of tablet formulations in the presence of superdisintegrants were in the order of SSG>CP. 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 orodispersible tablets.

The taste evaluation for the optimized formulations was carried out. The volunteers were asked for the mouth feel of the selected formulations. It was observed that the metallic taste of OLM was masked effectively for the formulation SF4 prepared by kneading method.



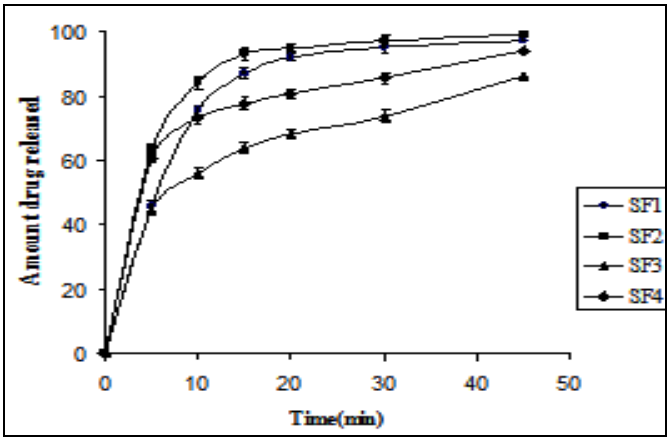


FIG. 10: DISSOLUTION PROFILE OF ORODISPERSIBLE TABLETS OF OLMESARTAN MEDOXOMIL. A; PF1 TO PF4, B; SF1 TO SF4

DISCUSSION: Olmesartan medoxomil showed maximum solubility in phosphate buffer (pH 6.8), among the different media used. From the phase solubility studies it was observed that a linear increase in solubility exist with increasing concentration of β-CDs. Hence the drug Inclusion complexes were prepared in 1:1 molar ratio and these combinations were found to be stable and suitable for masking the metallic taste of drug and enhancing the dissolution rate of OLM.

From the *in vitro* dissolution studies it was observed that the inclusion complex prepared by kneading method released the drug more rapid than the complexes prepared by physical mixing and pure drug alone. This was due to inclusion complex formed in kneading method which was shown PXRD patterns of OLM in formulations shown by kneading method which showed decrease in the peak intensity and finally absence of peaks was observed in complexes. This indicated the amorphous nature of OLM in inclusion complexes and is considered to be the reason for the dissolution and solubility enhancement.

From the SEM images it was observed that the pure OLM powder was appeared in the form of irregular shaped crystals whereas the SEM images for the prepared inclusion complexes were regular in shape with smooth surface.

From the prepared inclusion complexes ODTs were prepared by using superdisintegrants at a concentration of 10-15% after checking the possible interaction between the drug and the carrier by FTIR spectroscopy and by DSC analysis. However FTIR spectra of complexes and DSC thermograms showed no interaction between the drug and excipients.

All the tablet formulations prepared were found to be stable with in the I.P specified limits [19] for weight uniformity, friability, and drug content. Moisture uptake studies for ODTs were conducted to assess the stability of formulation. The results indicated that tablets containing high concentration of superdisintegrants i.e. SF4 became soft and absorbed much more of atmospheric moisture.

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 SF4 with 15 % SSG showed the rapid drug release when compared to pure drug and inclusion complex prepared by physical mixing. The faster drug release is due to rapid disintegration of the tablets containing SSG. Disintegration occurred by rapid uptake of water followed by rapid and enormous swelling. The mechanism by which this action takes place involves rapid absorption of water leading to an enormous increase in volume and result in rapid and uniform disintegration.

The taste evaluation for the optimized formulations was carried out. The volunteers were asked for the mouth feel of the selected formulations and it was observed that the metallic taste of OLM was masked effectively for the formulation SF4 prepared by kneading method.

CONCLUSION: From the present study, it is concluded that the solubility and dissolution rate of poorly soluble drug OLM may be increased by preparing it as inclusion complexes with β-CDs. 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 released the drug more rapid than the pure drug and complexes prepared by physical mixture and the metallic taste of the OLM was effectively masked by inclusion complexation with CDs. The orodispersible tablets of OLM prepared with SSG as superdisintegrant showed rapid drug release when compared to pure drug and other tablet formulations.

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