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Pharmaceutical Sciences **Research Article……!!!**

FORMULATION AND EVALUATION OF TERNARY SOLID DISPERSION OF OLMESARTAN MEDOXOMIL

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KEYWORDS:

Hydroxy propyl beta cyclodextrin, Olmesartan Medoximil, Kneading method.

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ABSTRACT

The present study was carried out to improve solubility and dissolution of Olmesartan Medoximil in order to increase its bioavailability. Solid dispersions were prepared with Poloxamer 407 and Hydroxy propyl beta cyclodextrin using kneading method. The prepared solid dispersions were subjected to various evaluations like solubility and *in vitro* drug release studies.The compatibility study between drug and carriers was performed by FTIR, DSC. The crystallinity was determined by XRD. The surface morphology was determined by SEM. The FTIR and DSC studies confirmed that no chemical interaction had taken place between Olmesartan medoximil and excipients. The XRD results indicated that the crystalline drug was converted into amorphous form. The SEM studies indicated that particles were almost uniform sized with rough surface.

INTRODUCTION:

Oral drug delivery is the most convenient route of drug administration due to ease of administration, patient perspective, flexibility in formulation, easily available etc. However in case of the oral route there are limitations such as limited drug absorption causing poor bioavailability and low pharmacological response resulting into inadequate and low oral absorption.[1]

Oral bioavailability of a drug depends on its solubility and or dissolution rate. The dissolution is be the rate determining step for the onset of therapeutic activity. Most of the new compounds which are undergoing development, about 40 % are subject to dissolution problems. To overcome this pharmaceutical challenge, various solubilization technologies have been developed including solid dispersions, nanocrystals, use of surfactants, cyclodextrin complexes and lipid formulations with the increase in the number of FDA-approved products, solid dispersions are now widely used technology for the formulation and development of poorly water -soluble drugs. [2]

The concept of solid dispersions (SD) is a technology utilized to improve bioavailability of poorly soluble compounds. The properties of solid dispersion, in which the drug is dispersed mainly in nanocrystals or in amorphous state are enhanced resulting in increased dissolution.[3]

Olmesartan medoximil is an antihypertensive agent, which belongs to the class of medications called angiotensin II receptor blockers. It is indicated for the treatment of high blood pressure. It is a specific angiotensin II type 1 (AT1) receptor antagonist, which blocks the blood pressure increasing effects of angiotensin II via the renin-angiotensin-aldosterone system (RAAS). The solubility of Olmesartan in water is 0.0105 mg/mL and poor bioavailability after oral administration (26%)[4]. Thus there is a need to increase aqueous solubility and dissolution. Therefore solid dispersions were prepared to enhance solubility and dissolution of olmesartan medoximil with poloxamer 407 and hydroxy propyl beta cyclodextrin. The solid dispersions were prepared by kneading method.

MATERIALS AND METHODS

The Olmesartan medoximil was obtained from Apotex Pharma India. Poloxamer 407 was obtained as a gift sample from BASF, Germany India and Hydroxy propyl beta cyclodextrin was obtained from Roquette, France. All other chemicals and solvents were of analytical grade.

Table 1 :- COMPOSITION OF SOLID DISPERSION

Formulation Code	Ratios	Carriers (in mg)	
		Poloxamer 407	Hydroxy propyl Beta Cyclodextrin
F1	1:1	20	80
F2		60	40
F3		50	50
F4		40	60
F5		80	20
F6	1:1.5	120	30
F7		60	90
F8		75	75
F9		90	60
F10		30	120
F11	1:2	120	80
F12		160	40
F13		100	100
F14		40	160
F15		80	120

PHASE SOLUBILITY STUDIES:[5]

Phase solubility study was performed by a method described by Higuchi and Connors. A known excess amount of olmesartan medoximil and carriers in different (w/w) ratios were placed in separate glass-vials containing 10 ml of distilled water. The samples were placed in an orbital shaker at 37.5ºC and 100 rpm until equilibrium was reached (48 hr.) The aliquots were filtered through Whatman filter paper. The aliquots were diluted appropriately in respective media and analyzed spectrophotometrically at 257 nm for olmesartan medoximil using suitable blank.

CHARATERIZIATION OF SOLID DISPERSION

Fourier Transform Infrared spectroscopy (FTIR):

The samples of Olmesartan medoximil, poloxamer 407, Hydroxy propyl beta cyclodextrin and solid dispersions were prepared in the form of KBr pellets and subjected for scanning from 4000 cm^{-1} to 400cm^{-1}. Using (FTIR 8400s Shimadzu, Japan).

Differential Scanning Calorimetry:

The thermal behavior of Olmesartan, Poloxamer 407, andHydroxy propyl beta cyclodextrin solid dispersions was examined by a differential scanning calorimeter (DSC 60 Shimadzu, Japan) at a heating rate of 10 ºC/min from 30 ºC to 300º C in nitrogen atmosphere.

X ray Diffraction Studies:

XRD patterns of pure Olmesartan and selected formulation were recorded using XRD (X pert 3 powder diffractometer, Netherlands) with a copper target, voltage 30 kV and current 30 mA at an angle of (2θ).

Scanning Electron Microscopy:

The surface morphology and homogeneity of the particles of solid dispersion was examined by scanning electron microscopy (TESCAN-VEGA 3 LMU, Czech Republic) The samples of formulation were super- coated with gold at room temperature before examination to render the surface of particles electro –conductive. The scanning range was 450 cm^{-1} to 4000 cm^{-1} and resolution was 1 cm^{-1}.

***IN VITRO* DISSOLUTION STUDIES**

In vitro dissolution study was performed by using USP dissolution testing apparatus II (Paddle method). An accurately weighed quantity of solid dispersion equivalent to 20 mg of Olmesartan medoximil different formulation were kept in vessels of the dissolution apparatus containing 900 ml of distilled water maintained at 37±0.5ºC. At a pre-determined time intervals an aliquots was withdrawn and replenished with fresh medium. Amount of drug in each aliquot was assayed on a UV – Spectrophotometer (UV-1601, Japan) at 257 nm using distilled water as a blank.

MODEL INDEPENDENT PARAMETERS:[6]

Dissolution efficiency:

Dissolution efficiency is used to translate the profile difference into a single value. Dissolution efficiency was calculated by using following equation.

$$DE\ \% = \frac{\int_0^t y\ dt}{y_{100}} t \times 100$$

Where, y is the drug percent dissolved at time t.

Mean dissolution time:

Mean dissolution time represents the mean time for drug molecules to completely dissolve. It is used to characterize the drug release rate from a dosage form and indicates the drug release retarding efficiency of the polymer. MDT was calculated by using the following equation.

$$MDT = \frac{\sum_{i=1}^{i=n} t_{mid} \times \Delta M}{\sum_{i=1}^{i=n} \Delta M}$$

Where *'i'* is the dissolution sample number, *'n'* is the number of dissolution sample time, *'tmid'* is the time at the midpoint between '*i'* and *'i-1'*, and *'ΔM'* is the amount of drug dissolved between *'i'* and *'i-1'*.

RESULTS AND DISCUSSION

Olmesartan medoximil was found to be slightly soluble to practically insoluble, hence it is considered as low soluble as per Biopharmaceutical Classification System. Olmesartan medoximil showed pH dependent solubility profile. Solubility enhancement of drug was performed using hydrophilic carrier Hydroxy propyl beta cyclodextrin by preparation of solid dispersion.

The Phase solubility study of all the formulations was carried out in distilled water. Solubility of drug was successfully enhanced by preparing solid dispersion using different methods. Solid dispersions were prepared by Solvent evaporation method. Among the solid dispersions prepared by solvent evaporation method formulations F1 to F 15.The formulation containing F 12 showed highest drug release rate of 100.31%. The solubility of Olmesartan medoximil was enhanced with increasing concentration of carrier upto 1:2 drug to carrier ratios. In the phase solubility study the solubility of drug carrier mixture was found in the range between 12.198 to 23.250 mg/ml. The plot of concentration of drug verses concentration of carrier showed linearity with the regression coefficient value less than 1, indicating AN type of curve.

Table 2 :- Effect of solubility of surfactant with olmesartan medoximil

Concentration	Surfactant (%)	Solubility (mg/ml)
0.5	0.5	19.805±0.93
1		19.306±0.18
1.5		20.041±0.95
2		20.213±0.87
2.5		20.286±0.35
0.5	1	12.198±0.01
1		12.394±0.32
1.5		12.419±0.22
2		12.468±0.59
2.5		12.664±0.84
0.5		19.807±0.18
1		20.188±0.40

1.5	1.5	20.507±0.44
2		20.678±0.32
2.5		20.85±0.41
0.5	2	21.291±.66
1		23.585±0.74
1.5		22.272±0.19
2		23.250±0.39
2.5		23.114±0.87

Characterization of solid dispersion

Fourier Transform Infrared spectroscopy.

FTIR study was carried out for pure drug, excipient and selected formulations. The FTIR peaks of pure drug were found at 1234.48cm^{-1}, 1290.42 cm^{-1}, 1830.51 cm^{-1} and 3290.67cm^{-1}. It was found that there was no change in position of peaks related to different functional groups in spectra for pure drug. Thus no interaction had taken place between drug and excipients.

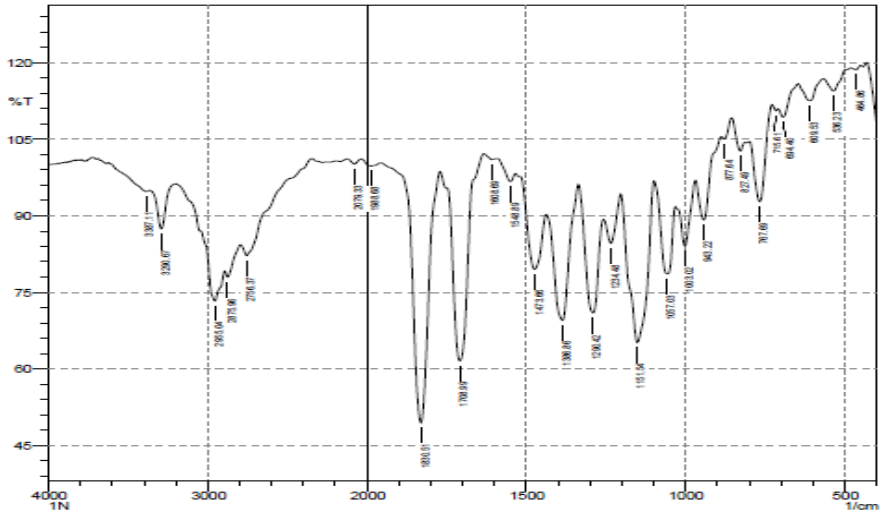

Figure 1 : FTIR spectra of pure olmesartan medoximil

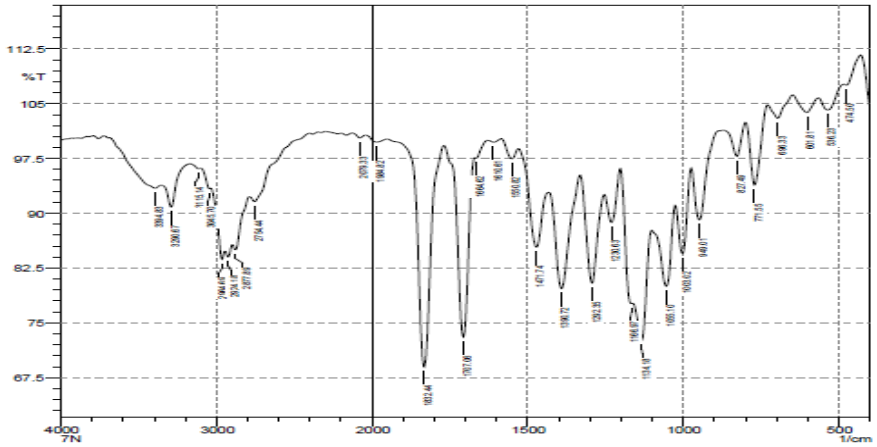

Figure 2: FTIR Spectra of selected formulation

Differential Scanning Calorimeter

DSC thermograms were obtained for the pure drug and selected solid dispersions prepared by solvent evaporation method. The DSC thermogram data is shown in figure indicated that there was no interaction between drug and the excipients.

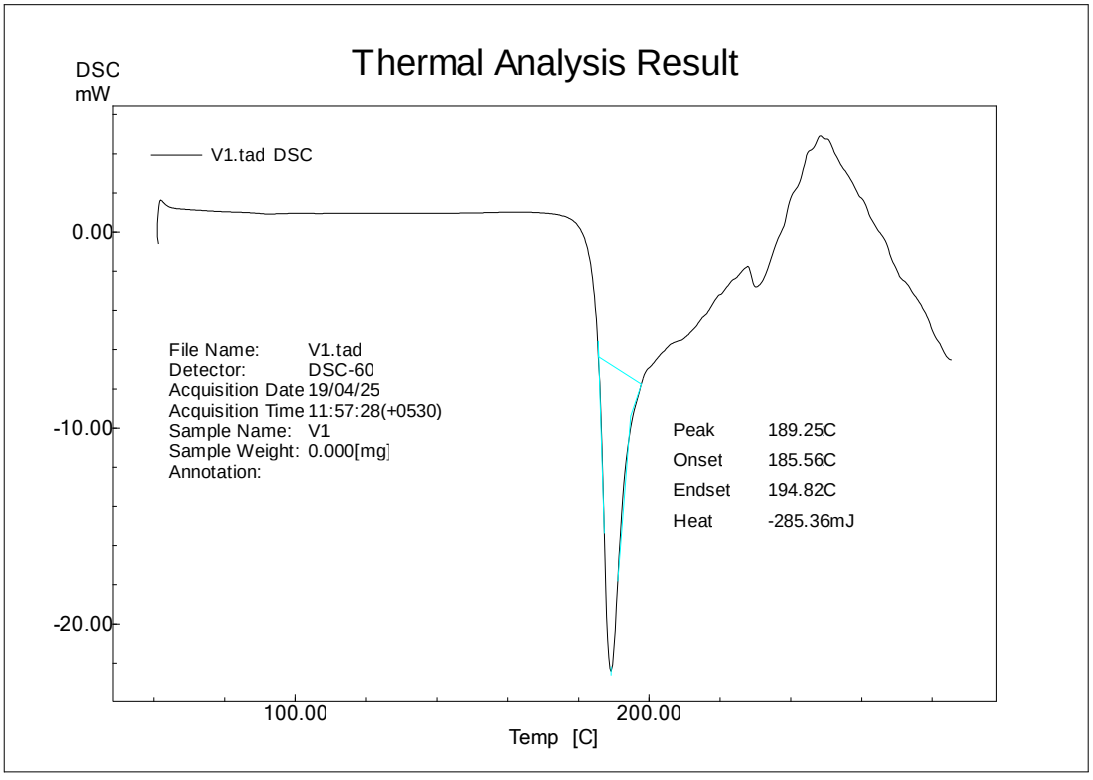

Figure 3 :- DSC Thermogram of pure olmesartan medoximil

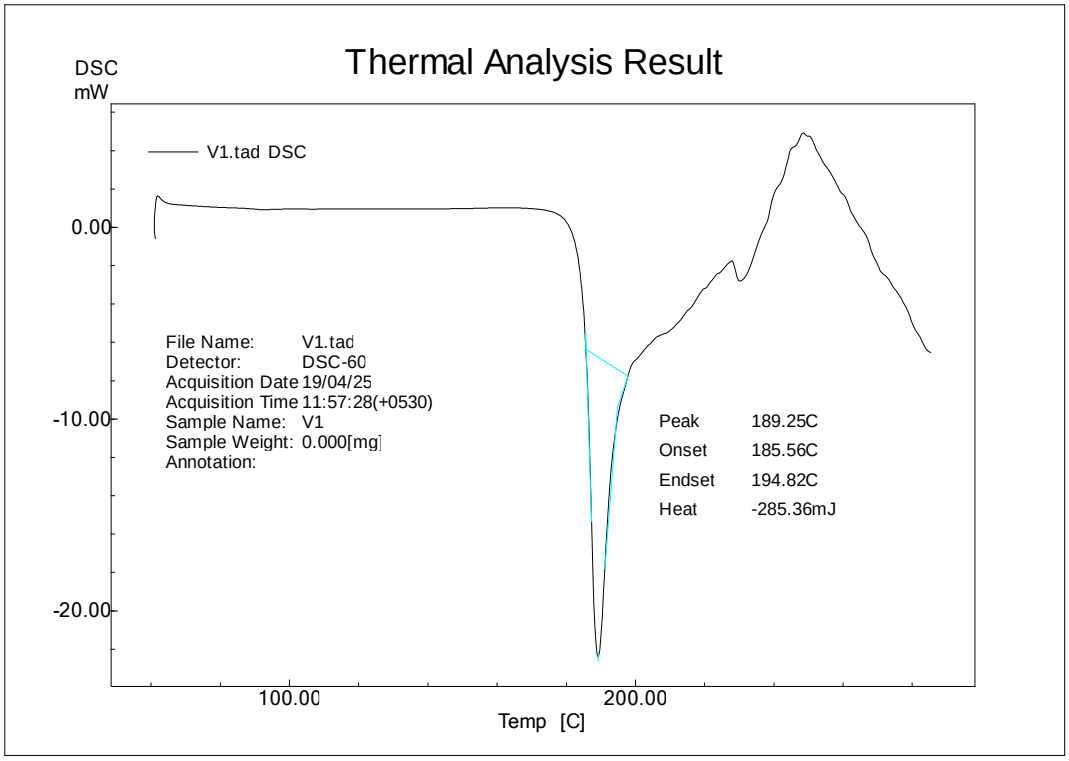

Figure 4 :- DSC Thermogram of selected formulation F 12

X ray Diffraction studies:

The XRD studies were carried out for the pure drug and selected solid dispersions prepared by solvent evaporation method. It was found that the crystalline drug was converted into amorphous form due to presence of diffuse peaks. Thus the drug was uniformly dispersed into carrier and crystanility of drug was reduced.

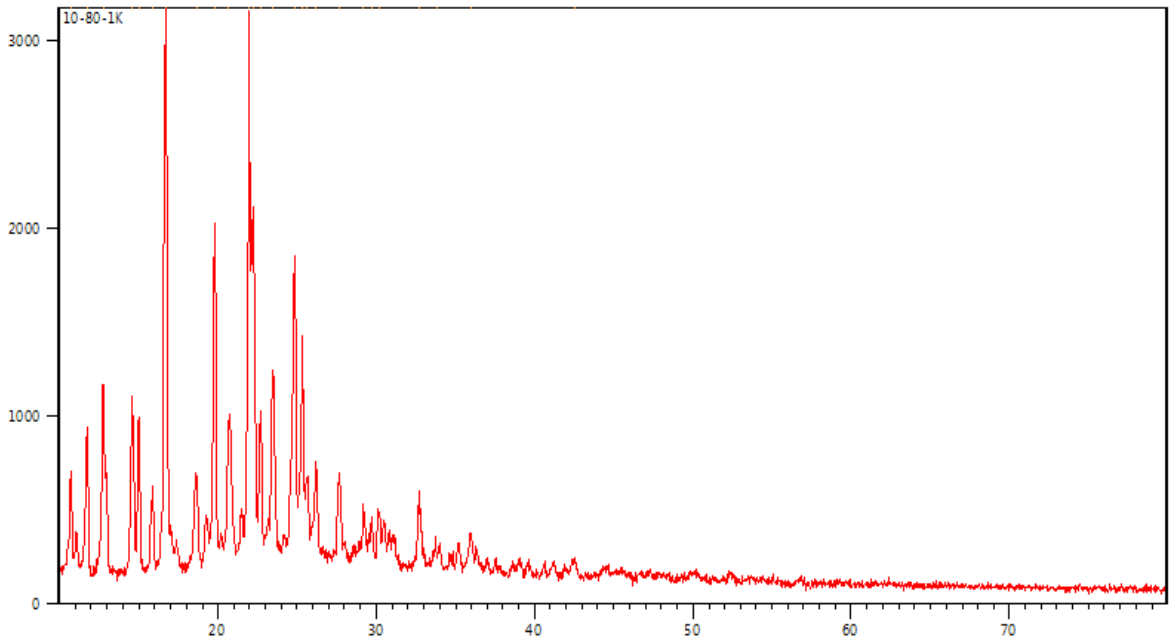

Figure 5 : XRD pattern of pure olmesartan medoximil

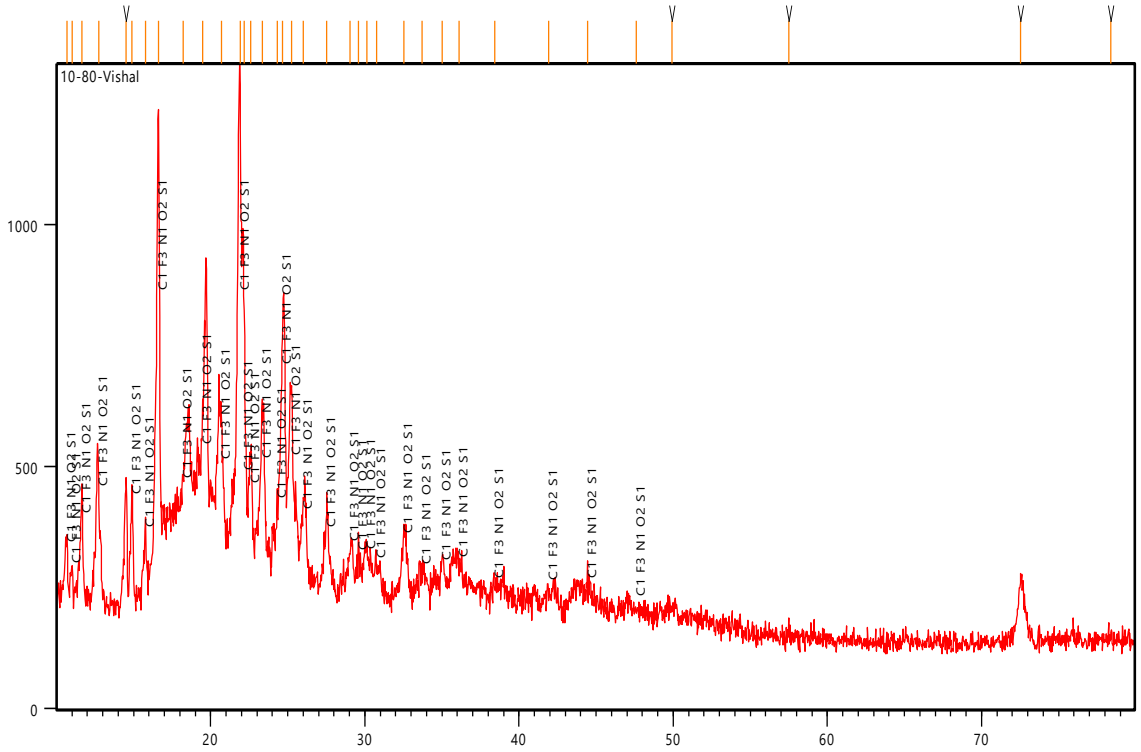

Figure 6 : XRD Pattern of selcted formulation

Scanning electron microscopy

The SEM was carried out for the pure drug and selected solid dispersions prepared by solvent evaporation method. The results showed almost uniform sized particles with rough surface.

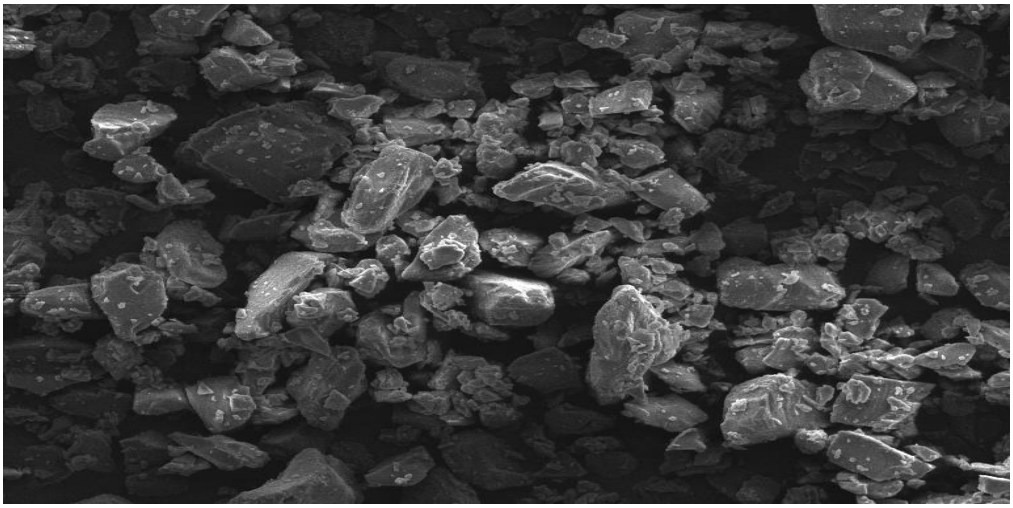

Figure 7: SEM of pure Olmesartan medoximil

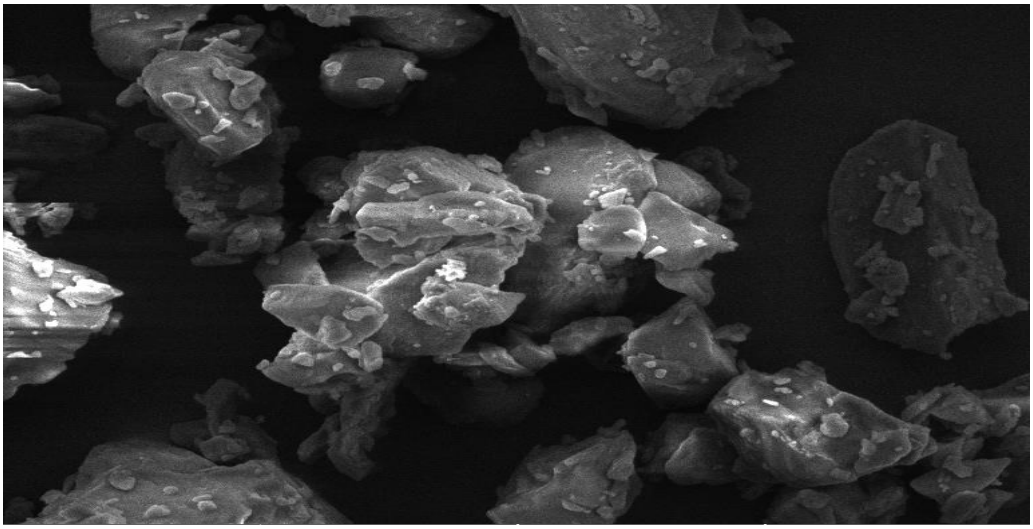

Figure 8: Scanning electron microscopy of selected formulation

***IN VIRO* DISSOLUTION STUDIES**

The solubility of all formulations was progressively improved when compared to pure Olmesartan medoximil with increasing the polymer proportion. Formulation containing ratio 1:2 showed highest solubility of 23.585mg/ml and showed the regression coefficient value less than 1, indicated AN type of curve. Among the various solid dispersions prepared, the formulation F 12 i.e., the solid dispersion of Olmesartan medoximil with Hydroxy propyl beta cyclodextrin (1:2 drug to carrier ratio) prepared by kneading method showed maximum drug release 100.31%. So, it was decided to use the formulation F 12to use for further study.

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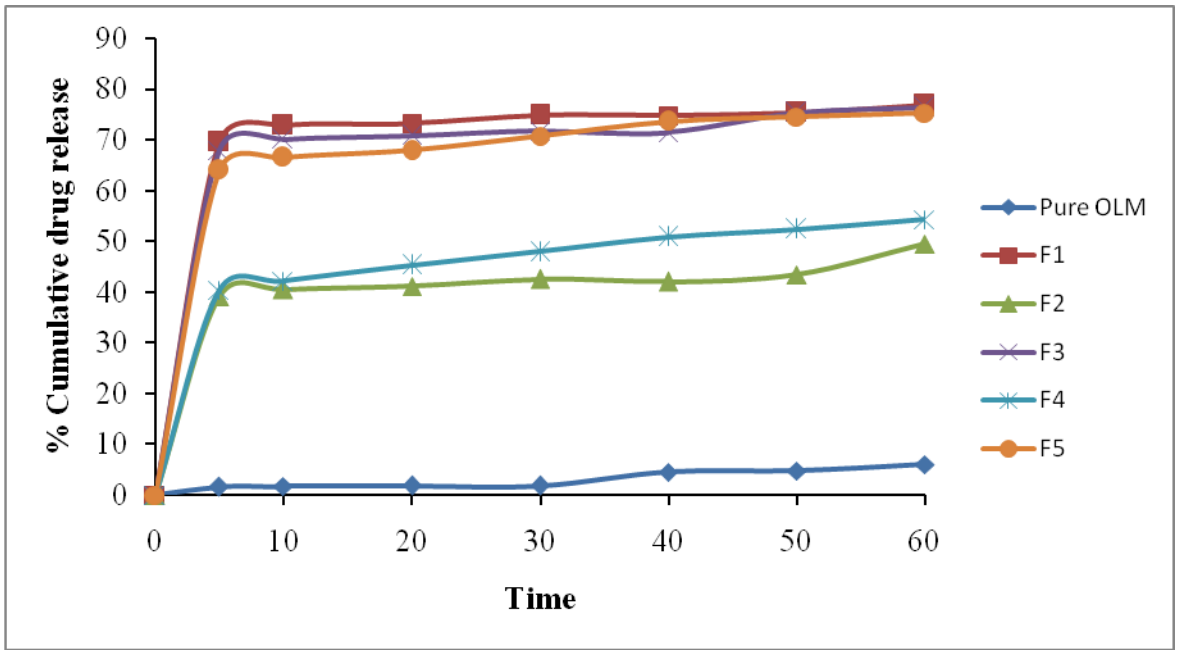

Figure 9: Comparison of *in vitro* dissolution profile of Olmesartan medoximil in pure form and F1, F2, F3, F4 and F5

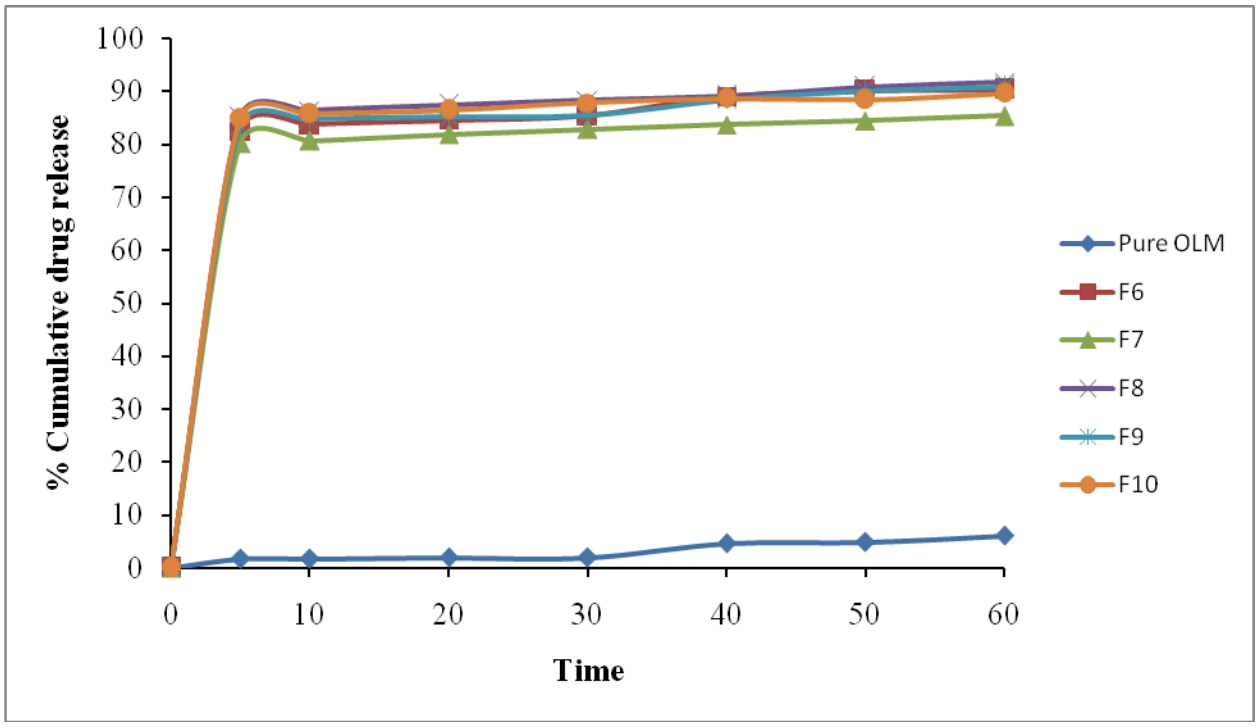

Figure 10: Comparison of *in vitro* dissolution profile of Olmesartan medoximil in pure form and F6, F7, F8, F9 and F10

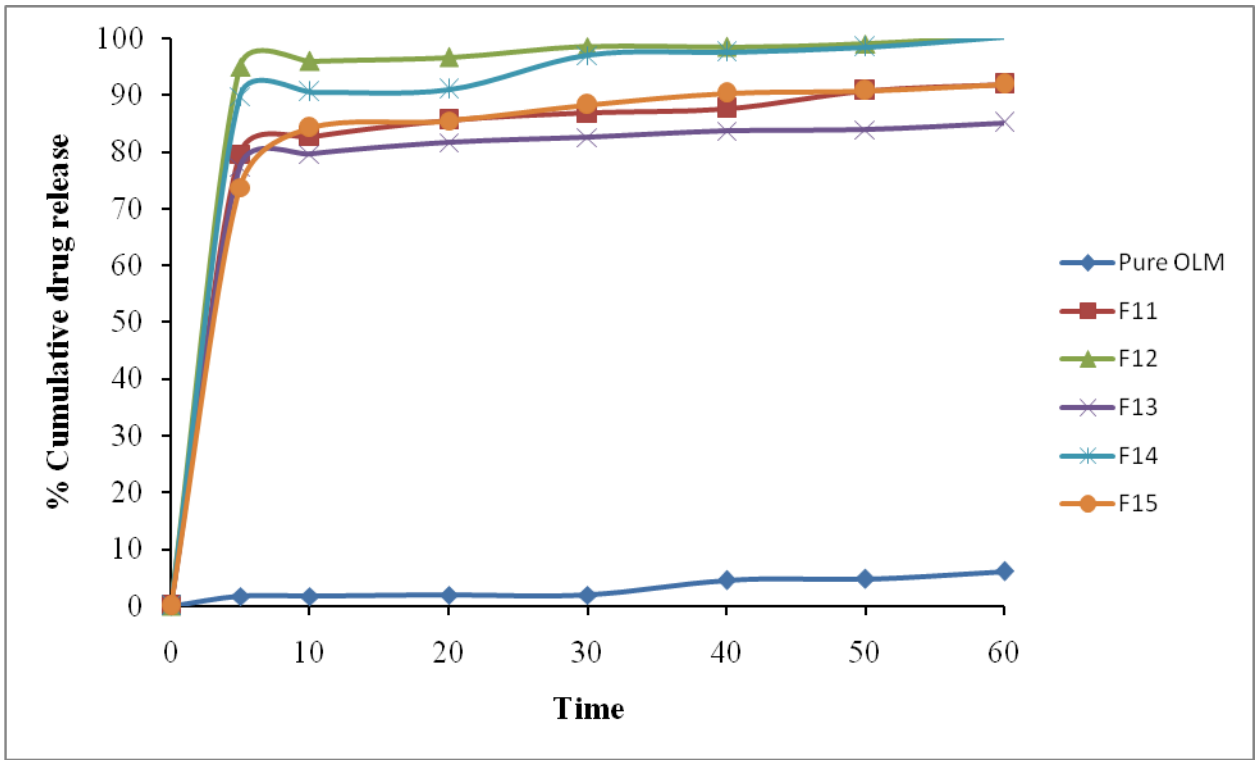

Figure 11 : Comparison of *in vitro* dissolution profile of Olmesartan medoximil in pure form and F11, F12, F13, F14 and F15.

Model independent parameters:

The model independent kinetic parameters were estimated for solid dispersion prepared by kneading method. The model independent parameters like mean dissolution time and % dissolution efficiency for the prepared solid dispersions. The MDT values of formulation ranged between 4.00 min to 10.96 min. The % DE of formulations F 1 to F 15 was between 81.72 % to 93.31%. The formulation F12 had shown % DE value of 93.31 % and MDT of 4.00 min. Hence it was selected for further study.

CONCLUSION:

Based upon the experimental results, it can be concluded that the solid dispersion prepared by technique is successful in improving the solubility, dissolution rate and subsequently bioavailability of Olmesartan medoximil.

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