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Solubility enhancement of antihypertensive agent by solid Dispersion technique

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Abstract: The present study was aimed to increase the solubility of the water insoluble drug Olmesartan Medoxomil (BCSII) by using polymers like Poloxmer 407, poloxmer188 and PEG 6000. Solid dispersions were prepared by solvent evaporation method. Prepared solid dispersions and pure drug were evaluated for Compatibility study, Phase solubility, Saturation solubility, XRD analysis and *in-vitro* dissolution study. All the polymers were found to be effective in increasing the dissolution rate of Olmesartan medoxomil in solid dispersions when compared to pure drug. FTIR used to study the compatibility and XRD Analysis revealed the Amorphization of drug solid dispersion with all polymers. In-vitro Dissolution was enhanced significantly after preparation of solid dispersion with all polymers but Poloxmer 188 showed maximum release.

Keywords: Solid dispersion, Olmesartan Medoxomil, solvent evaporation method.

Introduction: Oral bioavailability of a drug depends on its solubility and/or dissolution rate, and dissolution may be rate determining step for appearance of medicinal effect, therefore efforts to increase dissolution of drug with limited water solubility is often needed. Many methods are available to improve these characteristics, including salt formation, micronization and addition of solvent or

surface active agents. Solid dispersion (SD) is one of these methods and involved a dispersion of one or more active ingredients in an inner carrier or matrix in solid state prepared by melting, dissolution in solvent or melting solvent method.[1] Olmesartan Medoxomil chemically is (5-methyl-2-oxo-2H-1,3-dioxol-4-yl)methyl,4-(2-hydroxypropan-2-yl)-2-propyl -1-({4-[2-(2H-1,2,3,4- tetrazol5yl)phenyl] phenyl} methyl) -1H- imidazole-5-carboxylate. Olmesartan medoxomil is a selective AT1 subtype angiotensin-II receptor antagonist that is approved for the treatment of hypertension. OLM dose dependently reduces blood pressure through arterial vasodilatation and reduced sodium retention, as do other angiotensin receptor blockers. It is a prodrug that is rapidly de - esterified during absorption from the gastrointestinal tract to produce an active metabolite Olmesartan. Half-life of Olmesartan Medoxomil is 13 hours. Aqueous solubility of OLM is <7.75 µg/ml. Oral bioavailability of this tablet formulation is only 26% in healthy humans due to low aqueous solubility. The unabsorbed drug leads to gastrointestinal side effects such as abdominal pain, dyspepsia, gastroenteritis and nausea. Thus, improving oral bioavailability of olmesartan medoxomil can increase clinical efficacy, reduce the oral dose required to achieve the same effect and hence reduce the side effects. Enhancement can be achieved via solid dispersion formation by using hydrophilic polymers.[2, 3 ,4]

Material and Methods

A gift sample of olmesartan medoxomil was received from Emcure pharma pune, and all other polymers Poloxmer407 (PXM 407), Poloxmer188 (PXM188), PEG6000, PEG4000 were obtained from S.D. fine chemical (India). All polymers used are of an analytical grade.

Estimation of Olmesartan medoxomil

An U.V. spectrophotometrically method based on the measurement of absorbance at 257 nm in a methanol. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beers law in the concentration range of 2-10µg/ml (r^2=0.9996). When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variation were found to be 0.90% and 1.1% respectively. No interference by the excipients used in the studies was found.[5]

Solid dispersion of Olmesartan Medoximil

Solid dispersion of Olmesartan medoxomil at three different mass ratios (1:1, 1:3, 1:5) was prepared. The mixtures were passed through a sieve no. 60. The prepared mixtures were then filled in glass bottles, sealed and stored in a desiccator until further use.

Phase Solubility Studies

The phase solubility studies were carried out according the method reported by Higuchi and Connors. Excess amount of Olmesartan medoxomil was added to the screw capped vials containing 10 ml of aqueous carrier solution at various concentrations and placed on a rotatory shaker and agitated at room temperature for 48hours. After equilibrium, the solutions were carefully filtered through What man No.41 filter paper and after appropriate dilution; solutions were analyzed at 257 nm by using UV- visible spectrophotometry.[7,8]

Solid dispersion of Olmesartan medoxomil solvent evaporation method

The required amounts of olmesartan medoxomil and carriers were dissolved in methanol and allowed to stand overnight. The solvent was removed at 45°C in oven until the solid dispersion was dry. The dried mass was pulverized, passed through sieve #44 and stored in a desiccators until used for further studies. [9]

Characterization of solid dispersions:

Saturation Solubility Studies

The saturation solubility studies were carried out to determine the solubility of pure drug and solid dispersions. Weighed amount of solid dispersions were added to 250 ml conical flasks containing 25 ml of distilled water. The sealed flasks were shaken for 24hrs at 37±0.5ºC.Then aliquots were filtered through Whatman filter paper. The concentration of Olmesartan medoxomil was determined by UV spectrophotometer at 257 nm. [10]

Drug content

20 mg of solid dispersions were weighed accurately and dissolved in 10 ml of methanol. The solution was filtered, diluted suitably and drug content was analyzed at 257nm by UV spectrophotometer. Each sample analyzed in triplicate[11]. Actual drug content was calculated for all batches using the equation as follows:

$$\text{Drug Content} = \frac{O_{act}}{Oss} \times 100$$

O_{act} : Actual Olmesartan Medoxomil content in weight quantity of solid dispersion

Oss : Theoretical amount of olmesartan medoxomil solid dispersion

FT-IR Studies

Structural changes and lack of a crystal structure can lead to changes in bonding between functional groups which can be detected by infrared spectroscopy. The FT-IR spectra was obtained by using an FT-IRspectrometer-430(JASCO, Japan).The samples (Pure drug, and SDs) were previously ground and mixed thoroughly with potassium bromide at 1:100(sample: KBr) ratio, respectively. The scanning range was 4000-400 cm-1.[12]

XRD Studies

The X-ray diffraction patterns were obtained at room temperature using Breker model advance 008 Analytical X-ray BV (PW1710) with Cobalt as anode material and graph it monochromatic operated at a voltage of 40 Kv. The samples were analyzed in the 2θ angle range and process parameters were set as: scan size of 0.025º (2θ), scan step time of 1.25 s and time of acquisition of 1hr. [13]

***In vitro* Dissolution studies**

The release profile of an entrapped drug predicts how a delivery system might function and gives valuable Insight into its in vivo behavior. In vitro release profile for each solid dispersion as well as pure drug was performed using USP XXII Type II dissolution apparatus. Sample equivalent to 20 mg of Olmesartan medoxomil was added to 900ml of phosphate buffer pH 6.8 at 37^0 c stirred at 50rpm.[5.14]

Aliquot of 5 ml w a s withdrawn at time intervals of 2, 4, 6.8, 10, 15, 20,30, 45, 60, min. The withdrawn volume was replenished with the same volume of dissolution medium in order to keep the total volume constant. The absorbance of the samples was measured at λ-max 257nm after suitable dilution if necessary, using appropriate blank. Results of in vitro drug release studies obtained from absorbance data were s as cumulative percentage drug released versus time.

Stability studies

The stability of solid dispersions was checked by storing the tightly sealed vials at 40ºC and75%RH.Periodically samples were removed and analyzed for their stability.[15]

Results and Conclusion

The phase solubility studies were performed to determine stoichimetric proportions of Olmesartan Medoxomil and carriers- PXM 407, PXM 188, PEG 6000, The effects of polymers concentration at room temperature on solubility are shown in Fig. 1.

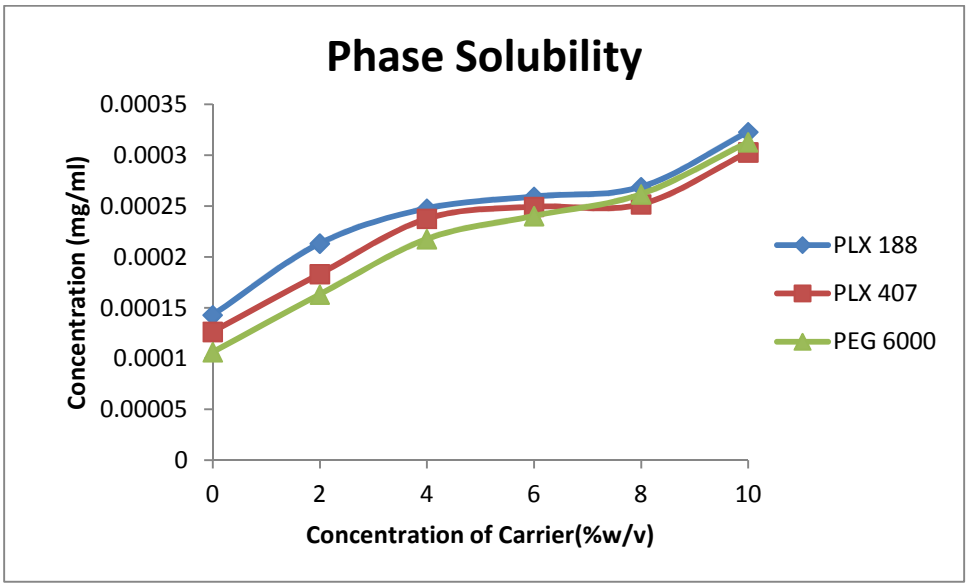

Fig. 1: Phase solubility diagram for Olmesartan medoxomil and carriers

The plot of drug solubility against polymer concentrations at room temperature indicated a linear relationship between drug and polymer solution i.e. the solubility of Olmesartan medoxomil increased with increasing carrier concentration.

Solid dispersions of Olmesartan medoxomil were prepared by solvent evaporation method using three different polymers: Poloxomer 407, PEG 6000, poloxomer 118, All solubility values are in µg/ml, SD: Solid Dispersion, DW: Distilled water,

It was found that solubility of Olmesartan medoxomil was increased in the solid dispersions of the carriers. The solubility was found to be increased in water .

The practical yield was found to be in the range of 93-97 %. As the amount of carrier increased (1:1, 1:3, 1:5) the practical yield also increased, but the practical yield was found to be decreased as the drug/carrier ratio was increased to 1:5.The content of Olmesartan medoxomil in each preparation was assayed by UV spectroscopy. The assay values were between 97% and 99% of the theoretical values.

FT-IR spectroscopic studies conducted for possible drug: carrier interactions. FT-IR

spectra of pure drug Olmesartan Medoxomil, and solid dispersions which are as shown in Fig. 2, indicating no significant evidence of chemical interaction between drug and carrier, which confirms the stability of drug with its solid dispersion.SD: Solid dispersion

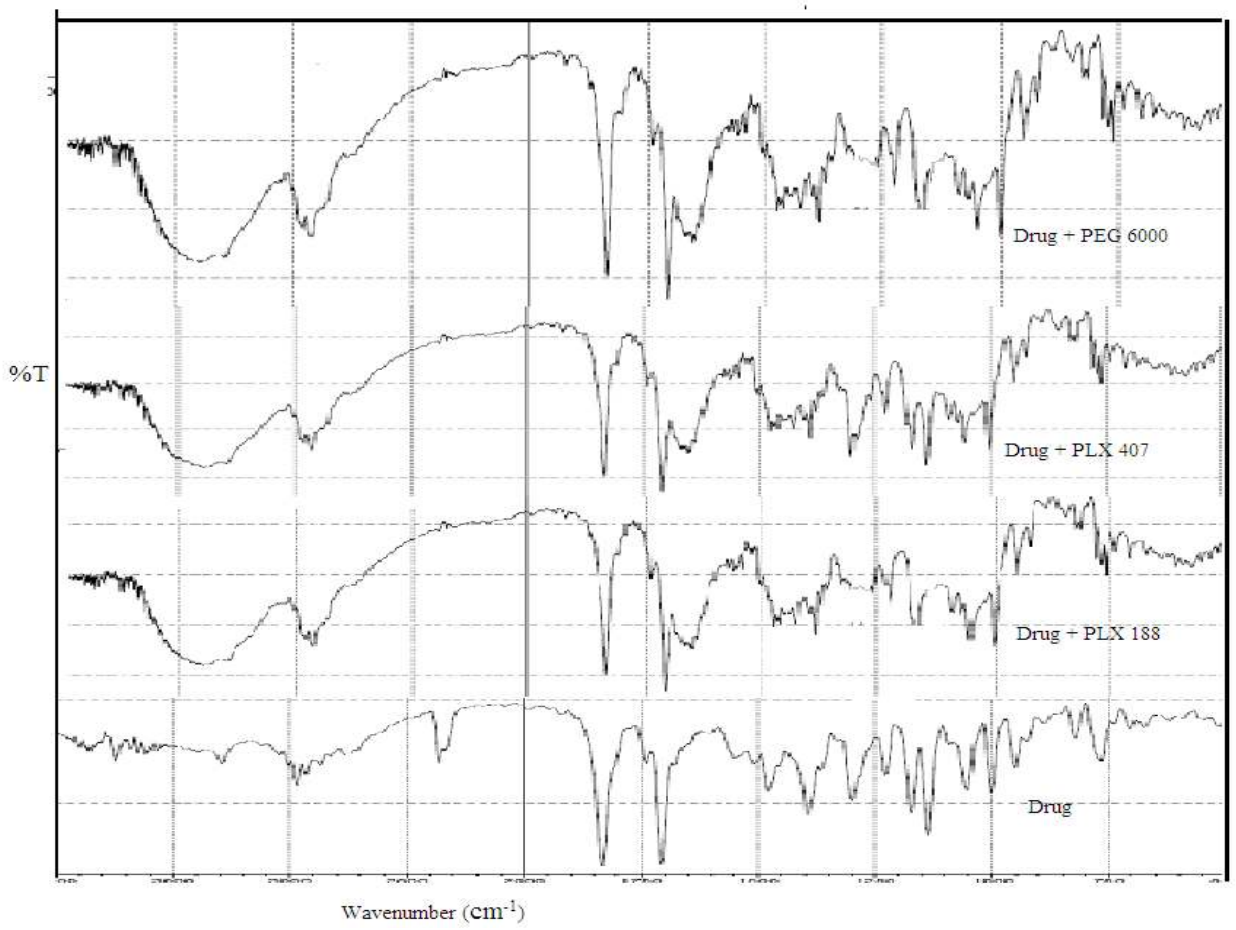

Fig. 2: FT-IR Spectra of Olmesartan medoxomil and solid Dispersions

It was found that there is no considerable change in the peak of the solid dispersion when compare to pure olmesartan .In FTIR study ,the breakdown of the intermolecular hydrogen bond between the crystalline drug and formation of hydrogen bond between the drug &the polymer there will be slight shift of absorption band .FTIR spectra of solid dispersion of shows that no change have occurred in chemical structure .result of IR shows an absence of any well defined interaction between olmesartan medoxomil & solid dispersion.

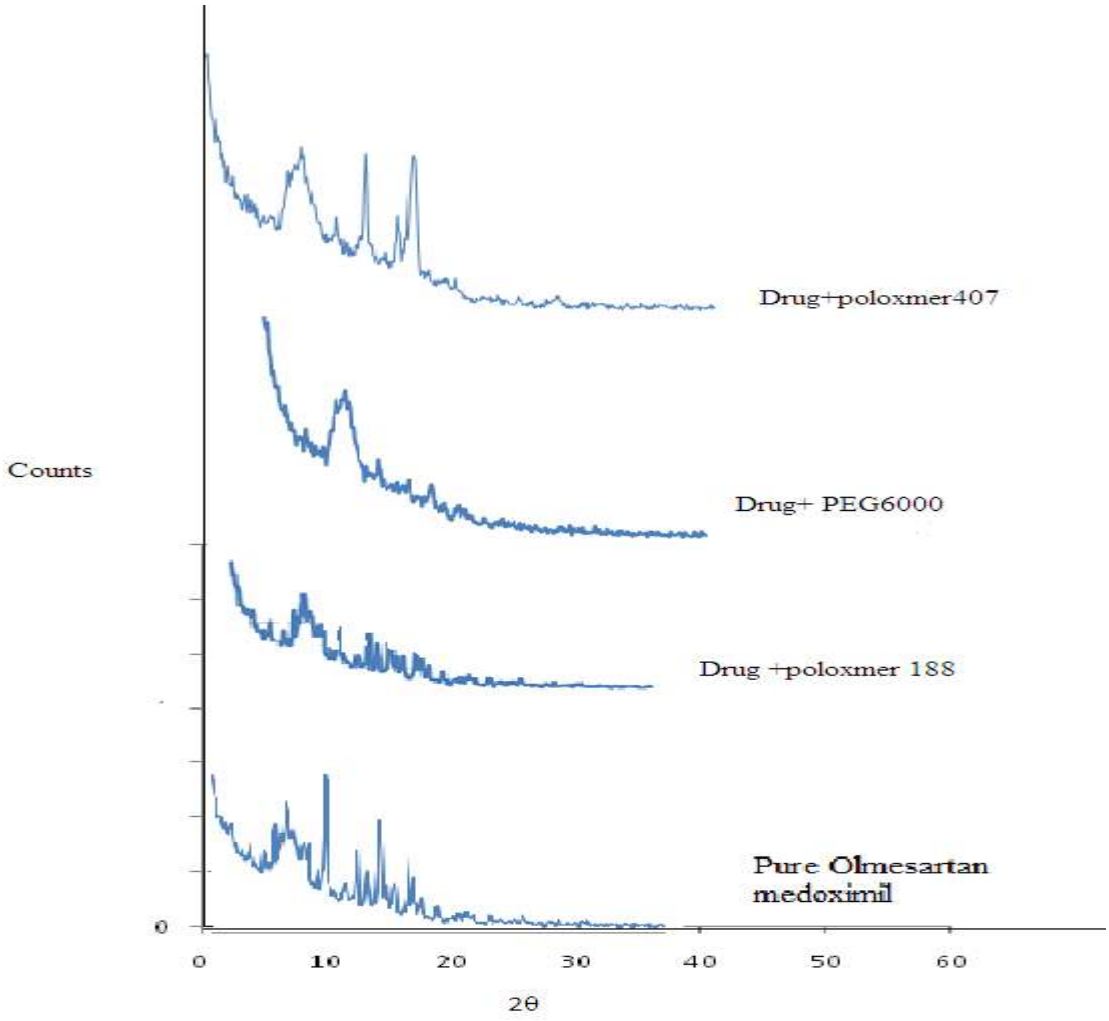

Fig. 3: XRD Spectra of Olmesartan medoxomil and solid Dispersion

XRD spectra of pure drug and solid dispersions are as shown in Fig. 3. It revealed complex formation between drug and carriers as all the peaks of drug are disappeared.

***In-Vitro* Drug Dissolution Profile:**

Time(min)	OLM	A1	A2	A3	B1	B2	B3	C1	C2	C3
0	0	0	0	0	0	0	0	0	0	0
2	12.18	20	33.12	44.92	2.21	7.88	32.02	4.36	7.49	18.93
4	13.49	23.45	35.16	49.53	4.78	10.31	39.61	7.54	23.11	21.09
6	14.71	27.62	38.34	52.61	7.18	15.41	43.66	9.77	17.99	22.69
8	15.95	30.65	45.65	60.42	11.26	18.22	49.52	12.22	22.49	25.97
10	17.59	32.06	50.56	64.69	13.54	21.16	54.25	14.51	27.91	28.4
15	19.05	36.31	60.34	70.76	22.48	24.12	58.65	17.21	29	30.85
20	21.89	39.54	69.12	73.86	28.39	27.7	64.36	22.96	32.24	33.43
25	23.88	45.13	74	76.69	30.85	31.13	68.26	27.31	33.66	37.2
30	25.69	51.96	78	81.79	35.09	36.83	74.06	29.27	37.63	46.1
40	29.48	54.95	84	85.4	35.96	41.72	77.18	36.62	40.08	53.04
50	31.84	58.75	85.43	87.84	36.83	49.69	80.33	42.38	42.25	56.04
60	33.25	63.31	86.3	90.12	39.69	63.31	81.64	45.28	42.3	63.95

Drug: Olmesartan medoxomil A: Poloxmer 188(1:1(A1),1:3(A2),1:5(A3)

B: Poloxmer 407(1:1(B1),1:3(B2),1:5(B3)

C: PEG6000(1:1(C1),1:3(C2),1:5(C3)

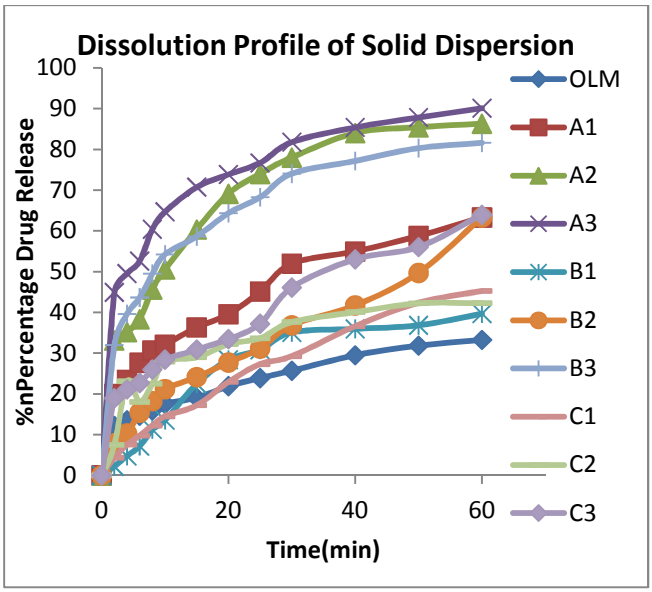

Fig. 4: Dissolution profile for of Olmesartan medoxomil and

solid dispersions

The *in-vitro* dissolution rate of Olmesartan medoxomil was studied using phosphate buffer pH 6.8 as dissolution media. The *in-vitro* dissolution rate of pure drug and its solid dispersion was found to be 33.89% for pure drug, 90.98% for Poloxmer 118, 81.23% for Poloxmer 407, 84% for PEG 6000.

The solid dispersions prepared using1:5 and 1:3 ratio showed marked drug release between80.435-91.467% in 60 min. In vitro release studies reveal that there is marked increase in the dissolution rate of Olmesartan Medoxomil **in** all the solid dispersions when compared to pure olmesartan Medoxomil itself. The increase in dissolution rate is in the order of:

PXM 118>peg 6000> poloxmer407 >

The dissolution rate of Olmesartan Medoxomil in solid dispersion was strongly dependent on the relative concentrations of the carrier. As the concentration of the carrier in the solid dispersion increased, the dissolution rate also increased. This may be attributed to the increase in the wettability, conversion to amorphous form and solubilisation of the drug due to hydrophilic carrier and solubilizing effect of surfactants.

For stability studies, drug content of solid dispersions were performed and the drug was found to be stable in the solid dispersion forms.

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