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Research Article

Formulation and Comparative Evaluation of Olmesartan Medoxomil Tablets by Solid Dispersion and Complexation Techniques

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Abstract

Olmesartan Medoxomil (OLM) is a selective AT1 subtype angiotensin-II receptor antagonist that is approved for the treatment of hypertension. It is having low aqueous solubility, so the present attempt is made to enhance the solubility of OLM by solid dispersion and complexation methods further formulating them into tablets by direct compression method. Solid dispersion and inclusion complex were prepared following solvent evaporation method using poloxamer 188 and β-cyclodextrin as a carrier.The prepared formulations were characterized for compatibility, drug content, saturation solubility and, dissolution studies. FT-IR study revealed no interaction between drug and excipients. Among all methods, solid dispersion (SD3) containing drug: poloxamer188 in the ratio of 1:3 showed rapid and higher drug release (85.36% within 45 min).The tablets prepared using SD3 solid dispersion and C3 inclusion complex were evaluated for both precompression and postcompression parameters. All the data obtained from the precompression and postcompression parameters fulfill the official requirements of tablets. The % drug release from the F1 batch tablet is higher (84.28%) than the F2 batch tablets (77.78%) within 45 minutes.Stability studies of F1 batch tablets showed no significant change in formulation during study period. Thus, it can be concluded that the formulation was stable.

Keywords: Solubility, olmesartan medoxomil, solid dispersion, complexation

Introduction

Solubility and dissolution rate are the two important parameters to be considered for achieving the therapeutic effectiveness of the drug through the oral administration. Poor aqueous solubility and dissolution profile of insoluble drugs remain the major problem in the formulation design and development of these dosage forms. Several techniques including micronization, nanonization, chemical modification, pH adjustment, solid dispersion, self emulsification, salt formation, co-solvency, complexation, etc have been defined to overcome the problems related to drug solubilization. Among these techniques complexation and solid dispersion are the most commonly used from the aspects of their simplicity as well as less time consuming and less expensive [1,2].

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug where matrix can be either crystalline or amorphous is dispersed molecularly, in amorphous particles (clusters) or in crystalline particles [3]. One of the underlying principles of formulation of solid dispersion is achievement of the amorphous state which is considered to be more soluble than the crystalline state because in the amorphous state, no energy is required to break the crystal lattice found in the crystalline phase [4].Various preparation methods for solid dispersion have been reported in literature including solvent evaporation, kneading, melting or fusion method, melt extrusion method, co-precipitation method (co-evaporates), spray drying method, gel entrapment technique, supercritical fluid technology, lyophilization technique [5].

Another method to increase drug solubility is by complexation with cyclodextrin which is advantageous because of low hygroscopicity, less toxicity, high fluidity, excellent compatibility and compressibility of cyclodextrin complexation improves the stability of drugs in a formulation, resulting in longer shelf life [6]. Lipophilic drug-cyclodextrin complexes, commonly known as inclusion complexes, can be prepared simply by adding the drug and excipients together, resulting in enhanced drug solubilization. Inclusion complexes are formed by the insertion of the nonpolar molecule (known as guest) into the cavity of another molecule (as host). The most commonly used host molecules are cyclodextrin [7].

Olmesartan Medoxomil (OLM) 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. Half-life of OLM is 13 hours and aqueous solubility is <7.75 µg/ml. Oral bioavailability of this tablet formulation is only 26% in healthy humans due to low aqueous solubility [8].

In present study, attempt is made for comparative study for enhancing the solubility of OLM by using solid dispersion and inclusion complexation methods and development of conventional tablet thereby to know which of these formulations shows the better aqueous solubility and dissolution profile as compared to the marketed product.

Materials and Methods

Materials: Olmesartan medoxomil was purchased from Yarrow Chem Products, Mumbai. Poloxamer188, □-cyclodextrin, lactose, magnessium sterate and talc were obtained from SD Fine Chem Ltd, Mumbai. All other materials used were of analytical grade.

Compatibility study using FT-IR:

Infrared spectroscopy was conducted using a Thermo Nicolet FTIR and the spectrum was recorded in the region of 4000 to 400 cm^{-1}. The procedure consisted of dispersing a sample (drug and drug-excipient mixture) in KBr (200-400 mg) and compressing into discs by applying a pressure of 5 tons for 5 min in a hydraulic press. All spectra were collected as an average of three scans at a resolution of 2 cm^{-1}. The interaction between drug-excipients was observed from IR□spectral studies by observing any shift in peaks of drug in the spectrum of physical mixture of drug [9].

Preparation of solid dispersion and inclusion complex of Olmesartan medoxomil:

Solvent evaporation method:

OLM solid dispersion was prepared by dissolving the OLM and poloxamer188 in sufficient quantity of methanol in the ratios 1:1, 1:2 and 1:3w/w in a separate china dish. The solvent was evaporated at 45 ºC in a hot air oven until dried solid mass remains in the china dish. The solid mass was then pulverized and passed through sieve no.60 and kept in a desiccator for further use [10]. Whereas inclusion complex was prepared by triturating OLM and β-cyclodextrin in ratios 1:1, 1:2 and 1:3 w/w with addition of few drops of 40% of ethanol to form a paste in a separate china dish. Then solvent was allowed to evaporate at 40 ^{0}C to form a dry solid mass which was further crushed to fine particles and passed through sieve no.60 and kept in a desiccator for further use [11]. The formulation design of solid dispersion and inclusion complex of OLM is shown in Table 1.

Table 1: Formulation design of solid dispersion and inclusion complex of OLM

Methods	Formulation Code	Drug : Carrier
Solid dispersion	SD1	1:1
	SD2	1:2
	SD3	1:3
Complexation	C1	1:1
	C2	1:2
	C3	1:3

Characterization of prepared solid dispersion and inclusion complexes:

Solubility studies: Solubility of pure drug, prepared solid dispersion and inclusion complexes were studied by adding excess amount in various solvents like water, phosphate buffer pH 6.8 and methanol separately. The mixtures were subjected to the mechanical agitation for 48 h in isothermal shaker at 25 ±1 ^{0}C followed by the filtration through Watmann's filter paper and determined by UV spectrometer at λ max 257 nm [3].

Drug content: All the prepared solid dispersion and inclusion complexes formulations equivalent to 20 mg of OLM were weighed accurately and dissolved in 100 ml of phosphate buffer pH 6.8 in a separate volumetric flask. The solution was filtered, diluted suitably with same solvent and drug content is analyzed at 257 nm by UV-spectrophotometer [12].

***In vitro* dissolution studies:** *In vitro* dissolution study of OLM and all prepared formulations were carried out by using USP rotating basket apparatus (Type I) for 45 min with rotation speed of 50 rpm. Phosphate buffer pH 6.8 was used as dissolution medium (900 ml) and temperature was maintained at 37 ± 0.5 ^{0}C. Samples equivalent to 20 mg of Olmesartan was filled in hard gelatin capsules and used for dissolution studies. Samples were collected at regular interval of time 5, 10, 15, 20, 30 and 45 min. The absorbances of the samples were measured at λ max 257 nm after suitable dilution using appropriate blank [13].

Preparation of OLM tablets using solid dispersion and inclusion complex:

Solid dispersion and inclusion complex prepared from the drug carrier ratio of 1:3 (SD3 and C3) were formulated into tablets. The tablet containing 20 mg of OLM were prepared by direct compression method as per the formula given in Table 2.

Evaluation of tablets

Precompression and postcompression parameters: Precompression parameters such as bulk density, tapped density, Hausner's ratio, Carr's compressibility index and angle of repose were evaluated for blended powders. Further post compression parameters like weight variation, hardness, friability, disintegration and *in vitro* dissolution studies were evaluated for prepared tablets [14].

Table 2: Formulation design of OLM tablet with solid dispersion and inclusion complexes

Ingredients	Formulation Code	
	F1	F2
Solid dispersion (drug eq.20mg)	80	-
Inclusion complex (eq.20mg)	-	80
Lactose	16	16
Magnessium sterate	2	2
Talc	1	1
Mint	1	1
Total weight	100 mg	100 mg

***In vitro* drug release:**

Dissolution study of marketed tablet as well as the tablet prepared from both formulations was carried in USP II apparatus by keeping 900 ml of 6.8 pH phosphate buffers as a dissolution medium. The paddles were operated at 100 rpm with 37 ± 1 ^{0}C of maintained temperature. The sample of 5 ml were withdrawn at 5, 10, 15, 20, 30, and 45 min and replaced with equal volume of dissolution medium. The withdrawn samples were suitably diluted with same dissolution medium and the amount of drug dissolved was estimated by UV spectrophotometer at 257 nm [14].

Further the release data were fitted into various mathematical models like zero order, first order, Higuchi and Korsmeyer-Peppas. Regressional analysis was performed by using axel software on the *in vitro* release data to best fit into various kinetic models according to the regression coefficient 'r' [15].

Stability study:

The optimized formulation was subjected for three month study according to standard guidelines. The selected formulation was packed in aluminum foil and kept tightly closed in a wide mouth bottle. Later stored at 40 ^{0}C / 75% RH for 3 months and evaluated periodically [9].

Results and Discussion:

Infra-red spectrum of drug and mixture of drug-polymers were determined by KBr disks method. Samples were prepared in KBr disks by means of a hydrostatic press at 5 tons pressure for 5 min and obtained spectra are shown in the Figure 1-3.

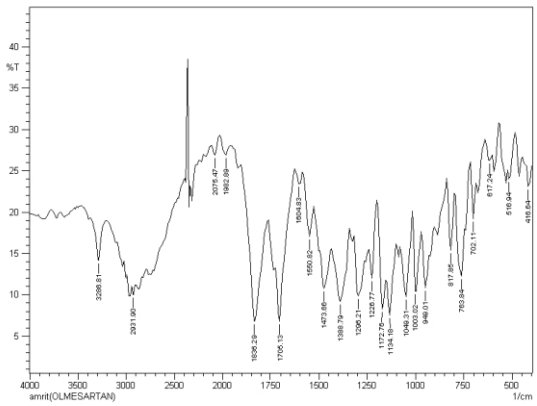

Figure 1: FT-IR spectrum of pure drug, olmesartan medoxomil

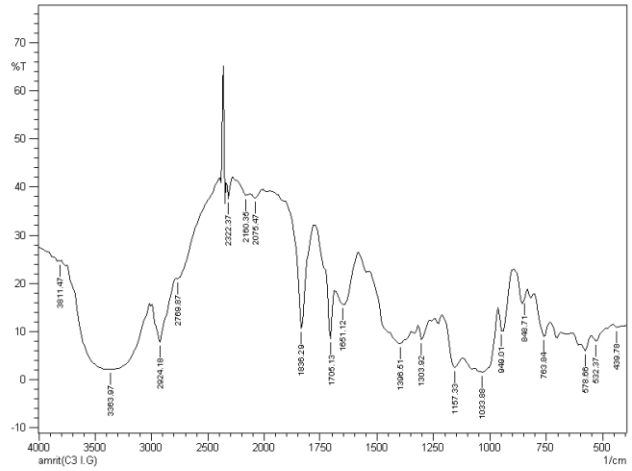

Figure 2: FT-IR spectrum of OLM+β-CD (C3)

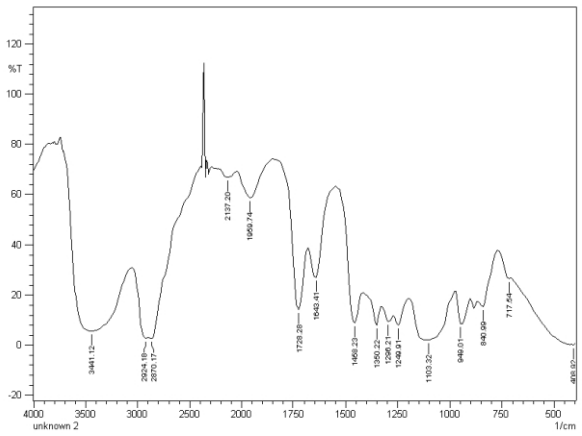

Figure 3: FT-IR Spectrum of OLM+Poloxamer188 (Sd3)

All the characteristic peaks of Olmesartan medoxomil were present in the spectrum of drug and polymer mixture, indicating compatibility between drug and polymer. The spectrum confirmed that there was no significant change in the chemical integrity of the drug. There was no change in functional group peaks of Olmesartan medoxomil in all the IR-spectra and are tabulated in Table 3.

The solubility data of pure drug and prepared formulations in different solvents are shown in the Table 4. All the formulations showed an increase in drug solubility compared to pure drug in all solvents among which solid dispersion having drug-carrier ratio 1:3 (SD3) showed maximum solubility (0.086 mg/ml) in methanol. Furthermore, enhancement in solubility of OLM was influenced by the concentration of polymers in solid dispersion as well as in inclusion complexes. With increase in polymers concentration, a predominant increase effect on solubility was observed.

Percentage drug content estimation of all formulations was done by UV spectrophotometer. The absorbances were measured and percentage drug content was calculated. Percentage drug content of all formulations were found in the range of 96.27% - 98.48% which was within the pharmacopoeial limits and shown in Table 5. *In vitro* drug release of solid dispersion and complexation formulations were compared with pure drug and data were tabulated in Table 6 and graphically represented in Figure 4. Dissolution studies were performed in 6.8 pH phosphate buffer.

Table 3: Interpretation of FT-IR spectrum

Ingredients	Functional groups with wave number (cm^{-1})			
	C-H (aromatic)	CooH (aromatic)	C=C (aromatic)	C=O
Olmesartan Pure drug	2931.90	1604.83	1550.82	1550.82
Complexation(C3)	2924.18	1643.41	1543.99	1543.99
Solid dispersion (SD3)	2924.18	1643.41	1552.08	1552.08

As compare to drug release of pure drug (26.38%), drug release of all prepared formulations were in the range of 54.78%-85.36% within 45 min of dissolution studies. Among all, the formulations prepared by using solid dispersion with poloxamer188 in the ratio of 1:3 (SD3) showed maximum drug release (85.36%) within 45 min. This showed that with increase in concentration of carrier (poloxamer188) the dissolution rate of OLM also increased significantly.

Table 4: Saturation solubility data of OLM and prepared formulations

Formulation	Drug: polymer	Distilled water (μg/ml)	Phosphate buffer pH 6.8 (μg/ml)	Methanol (μg/ml)
Pure drug	1:0	0.037	0.071	0.073
Solid dispersion (drug:poloxamer188)	1:1	0.041	0.079	0.081
	1:2	0.043	0.081	0.083
	1:3	0.048	0.084	0.086
Complexation (drug:β-CD)	1:1	0.038	0.076	0.078
	1:2	0.040	0.079	0.080
	1:3	0.044	0.083	0.084

Percentage drug content estimation of all formulations was done by UV spectrophotometer. The absorbances were measured and percentage drug content was calculated. Percentage drug content of all formulations were found in the range of 96.27% - 98.48% which was within the pharmacopoeial limits and shown in Table 5. *In vitro* drug release of solid dispersion and complexation formulations were compared with pure drug and data were tabulated in Table 6 and graphically represented in Figure 4. Dissolution studies were performed in 6.8 pH phosphate buffer. As compare to drug release of pure drug (26.38%), drug release of all prepared formulations were in the range of 54.78%-85.36% within 45 min of dissolution studies. Among all, the formulations prepared by using solid dispersion with poloxamer188 in the ratio of 1:3 (SD3) showed maximum drug release (85.36%) within 45 min. This showed that with increase in concentration of carrier (poloxamer188) the dissolution rate of OLM also increased significantly.

Table 5: % Drug content of prepared formulations

Sl.No	Formulation Code	% Drug Content
1	SD1	96.43
2	SD2	96.98
3	SD3	98.48
4	C1	96.27
5	C2	96.28
6	C3	96.91

Table 6: *In vitro* drug release profile

Time (min)	% Cumulative Drug Release						
	OLM	SD1	SD2	SD3	C1	C2	C3
0	0	0	0	0	0	0	0
5	11.44	13.56	19.56	22.12	14.23	17.25	18.59
10	13.56	16.44	27.82	34.76	18.56	20.21	22.53
15	15.33	23.20	43.43	48.51	22.74	24.89	31.21
20	18.21	27.43	55.31	62.37	25.36	37.91	42.78
30	22.89	35.98	67.65	75.26	32.25	54.68	59.34
45	26.38	54.78	77.23	85.36	52.57	64.83	75.32

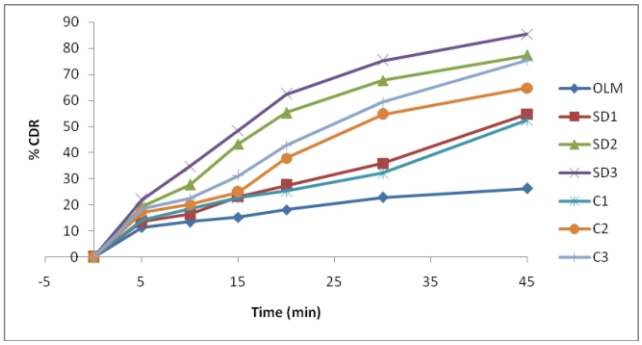

Figure 4: *In vitro* release of prepared solid dispersions and inclusion complexes

The increase in dissolution rate of OLM from solid dispersion of poloxamer188 might be due to the reduction of crystal size of the drug, conversion of drug to amorphous or microcrystalline state and decrease in wettability leading to formation of film surrounding the drug particle and hence decreasing the hydrophobicity of the drug.

On the other hand complexation of OLM with β-cyclodextrin also showed an increase in drug release from the inclusion complex formed compared to pure drug. With increase in concentration of β-cyclodextrin, the amount of drug release was also significantly increased. This might be due to the fact that β-cyclodextrin exhibited high solubility in water which resulted in better wettability and solubility of drug particles, which in turn enhanced its dissolution.

The pre-compression like bulk density, tapped density, Hausner's ratio, Carr's compressibility index, angle of repose and post-compression parameters for the prepared tablets were evaluated and tabulated in Table 7. All the results obtained are within the pharmacopoeial range. From the preformulation studies, it is clear that the OLM solid dispersion and inclusion complex (SD3 and C3) fulfilled the official requirements for compression of tablets through direct compression method.And from the physiomechanical parameters it is clear that all the tablets fulfilled official requirements of compressed tablets.

The *in vitro* drug release of the tablets prepared using SD3 formulation of solid dispersion (F1) and C3 formulation of inclusion complex (F2) was studied in USP II (paddle type) using 6.8 pH phosphate buffer and the percentage drug release was compared with pure drug. The % cumulative drug release data were shown in Table 8 and graphically represented in Figure 5. The results showed, drug release of all prepared formulations were in the range of 16.46%-84.28% within 45 min of dissolution studies which is comparatively higher than that of pure drug (26.38%). Among all, F1 formulations prepared by using solid dispersion with poloxamer188 in the ratio of 1:3 (SD3) showed maximum drug release (84.28%) within 45 min. This showed that with increase in concentration of carrier the dissolution rate of OLM also increased significantly.

Table 7: Evaluation of OLM tablets

Evaluation parameters	Formulation Code	
	F1	F2
Bulk density (gm/cc)	0.556	0.557
Tapped density (gm/cc)	0.655	0.637
Hausner's ratio	1.174	1.145
Carr's compressibility index (%)	15.084	12.610
Angle of repose (□)	18.360	16.596
Weight variation (%)	99.136	99.345
Hardness (kg/cm^2)	4.18	4.35
Drug content (%)	98.25	97.65
Friability (%)	0.74	0.69
Disintegration time (sec)	464	534

Table 8: *In vitro* drug release profile of OLM tablets

Sl.No.	Time (min)	% Cumulative drug release		
		OLM	F1	F2
1	0	0	0	0
2	5	11.44	18.46	16.46
3	10	13.56	23.21	21.24
4	15	15.33	35.45	32.58
5	20	18.21	44.89	42.26
6	30	22.89	67.33	63.77
7	45	26.38	84.28	77.78

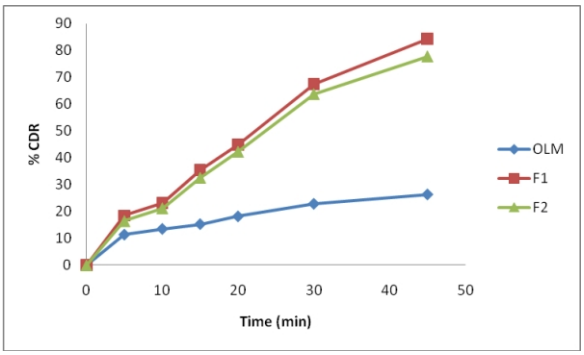

Figure 5: *In vitro* drug release profile of pure drug, formulations F1 and F2

The cumulative release data were subjected to various kinetics models and results obtained from release kinetics studies were depicted in Table 9. Both the formulations showed high linearity with slope (n) ranging from 1.1074 to 1.168, indicating that the drug was released from all formulations followed Super case II mechanism, as their 'n' values are higher than 0.89. So it was seen that all the formulations showed first order kinetics model following Super case II drug release mechanism.

Table 9: Release exponent and rate constant values for all formulations

Formulation Code	Kinetic Models				
	Zero Order	First Order	Higuchi	Korsmeyer-Peppas	
	R^2	R^2	R^2	R^2	N
F1	0.9151	0.9883	0.9831	0.9181	1.1618
F2	0.9797	0.9891	0.9524	0.9461	1.1074

The optimized formulation F1 was selected for stability study on the basis of their high cumulative % drug release. The selected formulation was subjected to accelerated stability studies at 40 ºC / 75% RH and observed up to till date. The formulation showed no significant change in the physical parameters during the period of study.

Conclusion

In this present study an attempt has been made to increase the solubility and dissolution rate of poorly water soluble drug OLM by two approaches; solid dispersion and complexation, thereby compressing the prepared formulations into tablets by direct compression method, since both formulations procedures were simple, inexpensive and less time consuming. FT-IR studies confirmed no possible interactions between drug and excipients. Drug content estimation for all formulations complies within the standard range. Solubility of formulations prepared from both methods showed higher solubility in methanol, water and 6.8 pH phosphate buffers than that of pure drug. iin vitro release study of all formulations showed increase in percentage drug release than that of pure drug and among the formulations, SD3 showed higher % drug release. Both the precompression and postcompression parameters of the prepared tablets were evaluated and the results were obtained within the standard range. The tablet prepared from F1 formulation showed 84.28 % of drug release than the tablet prepared from F2 formulation i.e. 77.78% within 45 min. The drug release pattern showed first order kinetics model following Super case II drug release mechanism. Stability study of F1 formulation showed no significant changes in physical properties of tablets within the study period.

Declaration of Interest

The authors do not have any conflict of interest.

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