



Enhancement of dissolution rate of Olmesartan medoxomil using urea as carrier by different solid dispersion techniques

B. Sangameswaran and M. Gomathi*

Department of Pharmaceutics, SSM college of Pharmacy, Bhavani, Erode, India

ABSTRACT

The poor solubility of drug substances in water and their low dissolution rate in aqueous G.I.T fluid often leads to insufficient bioavailability. As per Biopharmaceutical Classification System (BCS), Olmesartan belongs to the class-II category having poor solubility and high permeability. Since only dissolved drug can pass the gastrointestinal membrane, the proper solubility of the drug is ultimately desired. Its oral bioavailability is 26%. Hence, an attempt was made to enhance its solubility by formulating solid dispersions using different techniques viz., Melting, Kneading, Co-precipitation, Solvent evaporation and Physical mixing etc., Drug and carrier (Urea) in different ratios like 1: 1, 1: 2, 1: 3 and 1:4 were used for formulating solid dispersions. The compatibility of the drug with the carrier was checked by FTIR studies, these results revealed that there was no interaction between them. The angle of repose, bulk density, tapped density; Carr's index and Hausner ratio were calculated for the micrometric characterization of all the solid dispersions. The drug content was found to be high and uniform in all formulations. The prepared Solid dispersion SEM4 (1:4) showed minimal wetting time of 13 seconds compared with the other formulations. In vitro dissolution, release studies in Phosphate buffer pH of 6.8 revealed that the prepared solid dispersions showed faster drug release compared with the pure drug. The in vitro dissolution profile showed ascendancy on increasing the carrier concentration.

Keywords: *Olmesartan medoxomil; urea; Solid dispersion; dissolution rate.*

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Corresponding Author

Name: Ms. M. Gomathi
Email: gomathidurga24@gmail.com
Contact: + 91-7799140396

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INTRODUCTION

Oral bioavailability of drugs depend on its solubility and or dissolution rate, therefore major problems associated with these drugs was its very low solubility

in biological fluids, which results into poor bioavailability after oral administration. Poor aqueous solubility is one of the major hurdles in the development of new drugs into oral dosage forms since dissolution is the first step in the absorption of drugs. The solubility and dissolution behavior of a drug are key determinants to its oral bioavailability. An improvement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of drug development^[1]. There are several methods available for which drug dissolution rate or solubility can be enhanced, includes micronization, nanonization, salt formation, eutectic mixture, precipitation, inclusion complexes, solid dispersions etc.,

The solid dispersion was introduced in the early 1970's, refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug^[2]. In solid dispersion systems, a drug may exist as in amorphous form in polymeric carriers and this may result in improved solubility and dissolution rates as compared with crystalline material. The mechanisms for the enhancement of dissolution rate of solid dispersions have been proposed by several investigators. Drugs molecularly dispersed in polymeric carriers may achieve the highest levels of particle size reduction

and surface area enhancement, which result in improved dissolution [3].

Drugs belonging to class II category under Biopharmaceutical Classification System (BCS) are generally known for the characteristic features of inherently high permeability through biomembranes and low aqueous solubility. Solid dispersion technique has been used for a wide variety of poorly aqueous soluble drugs such as nimesulide, ketoprofen, tenoxicam, nifedipine, nimodipine, ursodeoxycholic acid and al-bendazole. Various hydrophilic carriers, such as polyethylene glycols, polyvinylpyrrolidone, hydroxypropylmethylcellulose, gums, sugar, mannitol, and urea have been investigated for improvement of dissolution characteristics and bioavailability of poorly aqueous soluble drugs [4].

Olmesartan is a specific angiotensin II type (AT1) receptor antagonist used in the treatment of hypertension. It effectively inhibits the AT1 mediated vasoconstrictive and aldosterone-secreting effects of angiotensin II and results in a decrease in vascular resistance and blood pressure. Its oral bioavailability is 26%. The half-life is approximately 13 hours. But the problem with this potentially useful antihypertensive agent is that it is practically insoluble in water [5].

The main objective of this work is to develop solid dispersions of Olmesartan medoxomil by incorporating urea as a carrier by different solid dispersion techniques to enhance its dissolution rate and solubility.

MATERIALS AND METHODS

Olmesartan medoxomil was a gift sample from Madras Pharmaceuticals, Chennai. Urea & Methanol were obtained from Loba Chemie, Mumbai. All other chemicals used were of analytical grade.

Calibration of Olmesartan medoxomil

A standard curve was prepared with different concentration (1 to 10 µg/ml) using pH 6.8 phosphate buffer solution. The absorbance of these solutions was measured at λ_{max} by UV- spectrophotometer. The calibration graph was drawn by taking the concentration on the X axis and respective absorbance in the Y axis, to get a straight line as per Beer's law. This standard curve was used to estimate the concentration of the drug release from the formulation during the *in vitro* dissolution studies [6].

Fourier Transform Infrared spectroscopic studies (FTIR)

FTIR Spectroscopic study was carried out to check the compatibility between drug and polymer. The spectrum of Olmesartan medoxomil (pure drug), Urea and its physical mixture were recorded using Fourier transform infrared spectrometer (Spectrum RX-1 Perkin-Elmer, German). Samples were prepared using KBr (Spectroscopic grade) discs by means of

hydraulic pellet press at a pressure of five tons for 30 seconds at a resolution of 4cm⁻¹ [7].

Preparation of Solid dispersion

Solid dispersions were prepared by using urea as a carrier in different ratios by various techniques namely Melting, Kneading, Co-precipitation, Solvent evaporation and Physical mixing etc. The various compositions of drug and hydrophilic carriers were shown in Table 1.

Melting method

In melting method the drug and carrier (urea) were mixed in 1:1, 1:2, 1:3 & 1:4 ratios in a china dish and heated on a water bath until it is completely melted. Then the molten mass is poured on a tile and cooled. The solidified mass is dried pulverized and passed through sieve No, 40 and stored in a desiccator [8].

Kneading method

A mixture of drug (Olmesartan) and carrier (urea) in different ratios (1: 1, 1: 2, 1: 3 & 1:4) are wetted with solvent (methanol) and water (1:1 ratio) and kneaded thoroughly for 30 minutes in a glass mortar. The paste formed is dried at room temperature for 24 hours. Dried powder is scrapped, crushed, pulverized and passed through sieve No. 40 and stored in a desiccator [9, 10].

Co-precipitation method

Olmesartan medoxomil solid dispersion is prepared by Co-precipitation method using carrier urea, in proportions viz., (1: 1, 1:2, 1: 3&1:4). Accurately weighed carrier (urea) is dissolved in water and the drug is dissolved in required quantity of methanol. After complete dissolution, the aqueous solution of the carrier is then poured into the organic solution of the drug with continuous stirring and kept in a water bath. The solvents are then evaporated. The dispersion is pulverized with pestle and mortar, sieved, dried and stored in desiccators [11].

Solvent evaporation method

Olmesartan medoxomil solid dispersion is prepared by solvent evaporation method using carrier urea, in proportions viz., (1: 1, 1:2, 1: 3&1:4). Dissolve the drug and carrier using methanol in a china dish and then it is heated until the solvent gets evaporated and a clear film of drug & carrier are obtained. Scrap the resultant solid dispersion with a spatula. Solid dispersions are pulverized in a mortar and pestle and passed through sieve No.40 before packing in an airtight container [12].

Physical mixing method

Using this method, it can be prepared by mixing the drug and carrier in various ratios (1:1, 1: 2, 1:3& 1:4) in a glass mortar. The solid mass is pulverized and

passed through sieve No. 40 to get uniformly sized particles and stored in desiccators until further use [13].

Micromeritic studies [14-16]

All the formulations were evaluated for bulk density, tapped density, the angle of repose, Compressibility index & Hausner ratio.

Determination of percentage practical yield [17]

The % practical yield of all the prepared formulations was found out using

$$\text{Practical yield} = \frac{\text{Practical mass}}{\text{theoretical mass}} \times 100$$

Determination of drug content

Solid dispersions equivalent to 10 mg of Olmesartan medoxomil were weighed accurately and dissolved in 10 ml of methanol, diluted with phosphate buffer pH 6.8 at λ_{max} by UV-spectrophotometer [18].

$$\% \text{ drug content} = \frac{\text{Sample absorbance}}{\text{Standard absorbance}} \times 100$$

Determination of wettability

Olmesartan medoxomil solid dispersions were placed in a sintered glass funnel plunging into a beaker containing water such that the surface of the water in the beaker remains at the same level of formulation in the funnel. Methylene blue and Amaranth powder layered uniformly on the surface of various formulations in the funnel separately and the time required for wetting dye powders were measured [19].

In vitro dissolution studies

A dissolution study was carried out by using USP rotating basket apparatus (Type I) for 1 hour, with a stirring rate of 100 rpm. Phosphate buffer pH 6.8, used as dissolution medium (900 ml) and the temperature was maintained at 37 ± 0.5 °C. Solid dispersions equivalent to 40 mg of Olmesartan medoxomil was filled in hard gelatin capsules used for dissolution studies. Samples (5ml) were collected at regular interval of time (10, 20, 30, 40, 50 & 60 min). The same volume of fresh buffer solution was replaced into the dissolution jar after each sample withdrawal. Similarly, the dissolution test was conducted for the pure drug. The absorbances of the samples were measured using Ultraviolet (UV) spectrophotometer at λ_{max} after suitable dilution using appropriate blank. [20, 21]

RESULTS AND DISCUSSION

The λ_{max} of Olmesartan medoxomil was determined by scanning the 10 $\mu\text{g}/\text{ml}$ of the drug solution in phosphate buffer solution pH 6.8 by UV-spectrophotometer. It showed the λ_{max} of 257 nm and obeys the Beer's law within the concentration range of 1- 10 $\mu\text{g}/\text{ml}$

was shown in Figure 1. Linear correlation coefficient obtained was $r^2 = 0.9999$ for its calibration.

FTIR spectrum of Pure Olmesartan medoxomil showed sharp characteristic peaks at 3005.20, 1832.44, 1707.06, 1602.9, 1502.60, 1390.72, 1136.11, 1089.92 cm^{-1} . All the above characteristic peaks appear in the spectra of all binary systems were within the same wave number. FTIR studies revealed that there was no interaction between the drug and polymeric carriers and shown in Figure 2(a-c).

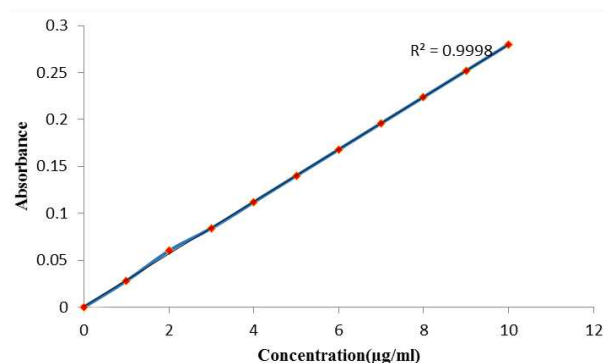
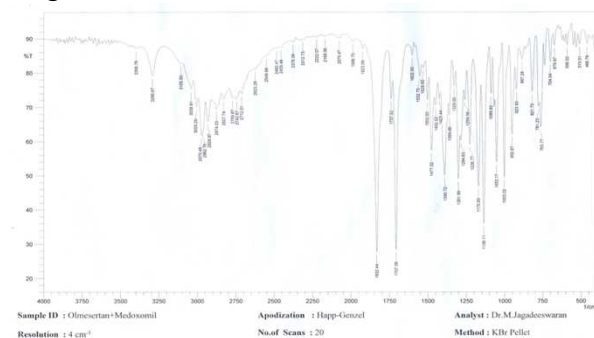
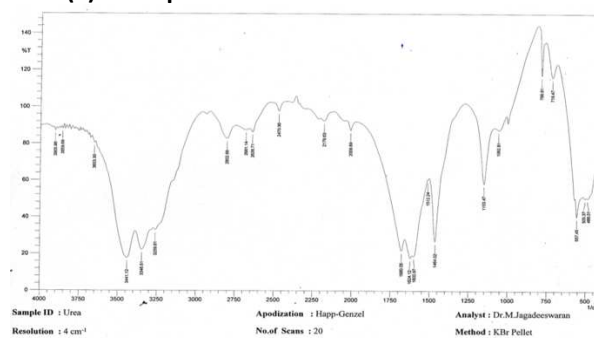


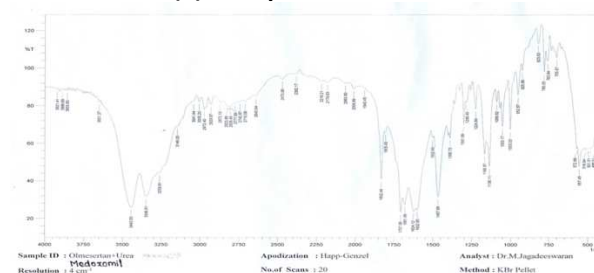
Figure 1: Standard curve of Olmesartan medoxomil



(a) FTIR spectrum of Olmesartan medoxomil



(b) FTIR spectrum of Urea



(c) FTIR spectrum of Olmesartan medoxomil + Urea

Figure 2: FTIR spectrum of Olmesartan medoxomil, Urea and Olmesartan medoxomil+urea

Table 1: Composition of Olmesartan medoxomil solid dispersion

S. No	Formulation Code	Drug: Carrier	Drug (Olmesartan)	Carrier (Urea)	Techniques Used
1	MM1	1:1	1gm	1gm	Melting Method
2	MM2	1:2	1gm	2gm	Melting Method
3	MM3	1:3	1gm	3gm	Melting Method
4	MM4	1:4	1gm	4gm	Melting Method
5	KM1	1:1	1gm	1gm	Kneading Method
6	KM2	1:2	1gm	2gm	Kneading Method
7	KM3	1:3	1gm	3gm	Kneading Method
8	KM4	1:4	1gm	4gm	Kneading Method
9	CPM1	1:1	1gm	1gm	Co Precipitation Method
10	CPM2	1:2	1gm	2gm	Co Precipitation Method
11	CPM3	1:3	1gm	3gm	Co Precipitation Method
12	CPM4	1:4	1gm	4gm	Co Precipitation Method
13	SEM1	1:1	1gm	1gm	Solvent Evaporation Method
14	SEM2	1:2	1gm	2gm	Solvent Evaporation Method
15	SEM3	1:3	1gm	3gm	Solvent Evaporation Method
16	SEM4	1:4	1gm	4gm	Solvent Evaporation Method
17	PM1	1:1	1gm	1gm	Physical Mixing Method
18	PM2	1:2	1gm	2gm	Physical Mixing Method
19	PM3	1:3	1gm	3gm	Physical Mixing Method
20	PM4	1:4	1gm	4gm	Physical Mixing Method

Table 2: Micromeritic evaluation of Olmesartan medoxomil solid dispersion

S.No	Formula Code	Bulk Density(gm/ml)	Tapped Density(gm/ml)	Carr's Index	Hausner Ratio	Angle Of Repose
1.	MM1	0.43	0.66	34.848%	1.534	21°81 ¹
2.	MM2	0.54	0.64	15.625%	1.185	23°49 ¹
3.	MM3	0.52	0.69	24.637%	1.326	23°72 ¹
4.	MM4	0.43	0.63	31.746%	1.465	22°05 ¹
5.	KM1	0.47	0.54	12.962%	1.148	23°44 ¹
6.	KM2	0.43	0.49	12.244%	1.139	26°28 ¹
7.	KM3	0.46	0.49	6.122%	1.065	21°47 ¹
8.	KM4	0.45	0.53	15.094%	1.177	22°68 ¹
9.	CPM1	0.43	0.52	17.307%	1.2093	23°62 ¹
10.	CPM2	0.34	0.39	12.820%	1.147	19°70 ¹
11.	CPM3	0.36	0.40	10.00%	1.111	24°88 ¹
12.	CPM4	0.36	0.44	18.181%	1.222	29°42 ¹
13	SEM1	0.41	0.55	25.454%	1.341	18°70 ¹
14	SEM2	0.43	0.52	17.307%	1.209	18°80 ¹
15	SEM3	0.46	0.53	13.207%	1.152	20°70 ¹
16	SEM4	0.40	0.49	18.367%	1.225	21°70 ¹
17	PM1	0.41	0.52	21.153%	1.268	21°44 ¹
18	PM2	0.42	0.50	16.00%	1.190	23°64 ¹
19	PM3	0.44	0.54	18.518%	1.227	24°18 ¹
20	PM4	0.42	0.52	19.230%	1.238	23°28 ¹

Twenty formulations were prepared using a carrier (Urea) in different ratios by different (Melting, Kneading, Co-precipitation, Solvent evaporation and Physical mixing) methods were shown in Table 1.

The results of % practical yield indicated that there was no considerable loss in the yield during the process & the drug content in the range of 94.8% to 98.5% indicating the uniform distribution of the drug in the formulations were depicted in Table 3. Among all the formulations minimum mean wetting time (13 seconds) was observed for the dispersion containing

urea (SEM4) prepared by Solvent evaporation method. The results obtained for the wettability study was shown in Table 3.

The *in vitro* dissolution testing was performed for 60 minutes to ascertain the effect of formulations on immediate drug release enhancement. The enhancement of carrier on drug release from solid dispersions was evaluated by comparing the solubility of drug present in the mixtures as well as the pure drug. Pure Olmesartan medoxomil exhibited a release of 34.9% at 60 minutes. There was a very low release of

Table 3: % Practical yield, drug content &wetting time of Olmesartan medoxomil solid dispersion

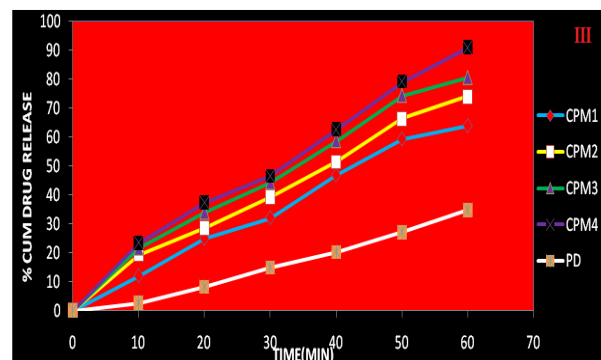
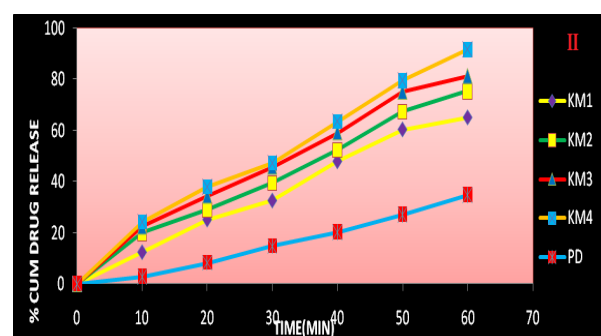
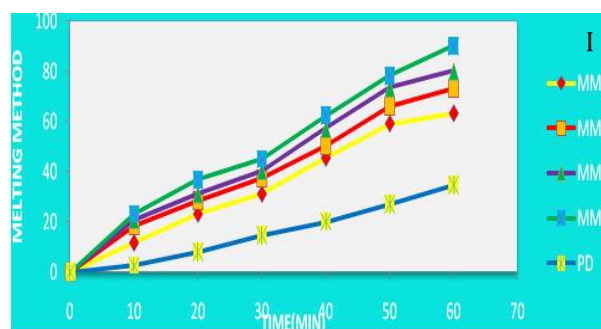
S. No	Formula Code	%Practical Yield	%Drug Content	Wetting Time (Sec)
1.	MM1	95	97.17	44
2.	MM2	95	97.44	38
3.	MM3	95.5	96.15	31
4.	MM4	95	96.66	19
5.	KM1	96.6	97.69	39
6.	KM2	96.5	96.66	35
7.	KM3	95	96.92	27
8.	KM4	95.3	95.89	16
9.	CPM1	95.6	98.46	43
10.	CPM2	94.8	95.12	39
11.	CPM3	95	95.64	29
12.	CPM4	95	98.46	18
13.	SEM1	96	97.22	36
14.	SEM2	95	97.12	30
15.	SEM3	95.6	94.22	23
16.	SEM4	96	94.3	13
17.	PM1	98	96	49
18.	PM2	98	95	43
19.	PM3	98.5	96.5	36
20.	PM4	97	97	30
Pure drug	-	-	-	95

the pure drug which was then increased with solid dispersions.

From the *in vitro* drug release profile, it could be seen that formulation SEM4 containing Urea (1:4 ratio of drug: carrier) showed higher dissolution rate 93.62% at 1hour, so it was considered as the overall best formulation. The *in vitro* drug release profile of solid dispersion formulations showed increased dissolution rate compared with the pure drug. The dissolution rate of the drug in solid dispersion formulations was increased with the increment in carrier proportion (1:4 > 1:3 > 1:2 > 1:1).

The increases in dissolution rate of the drug in solid dispersions were reported because of the enhanced wettability and hydrophilic nature of the carrier in the formulations. The best formulation was selected based on the results obtained from the wettability and *in vitro* release studies.

In vitro release studies revealed that the solid dispersions prepared using Urea by various methods showed faster drug release compared with pure drug. SEM4 (1:4) was selected as the best formulation because of its faster wetting and dissolution rate among all formulations. The results were shown in Figure 3(I-V).



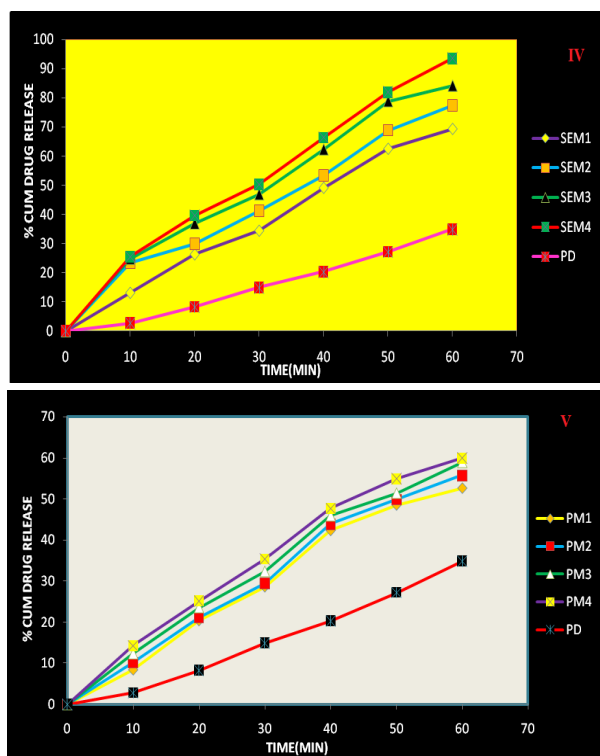


Figure 3: In vitro dissolution studies of Olmesartan medoxomil solid dispersions (I. Melting method, II. Kneading method, III. Co-precipitation method, IV. Solvent evaporation method, V. Physical mixing method)

CONCLUSION

The rate of wetting and dissolution rate of Olmesartan medoxomil from solid dispersion was found to be significantly higher than pure drug. In conclusion, development of the solid dispersions could be a promising alternative method to attain fast dissolution rate and solubility which may lead to improvement in bioavailability and hence better patient compliance.

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