JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS OF OLMESARTAN MEDOXOMIL

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Abstract

Aim: Olmesartan medoxomil is BCS class II drug which is poorly water soluble and highly permeable in nature. Lower solubility leads to poor dissolution and inadequate bioavailability. The aim of this work was to improve the solubility of poorly aqueous soluble drug Olmesartan medoximil using Poloxamer 407 and HPMC K 15 M by solid dispersion technique. Ternary solid dispersion were prepared by solvent evaporation methods. Phase solubility study of all the formulations was carried out in distilled water .). Fast dissolving tablets of Olmesartan medoximil were formulated using selected solid dispersion and superdisintegarnt. Stability studies were carried out for selected formulation. In the phase solubility study the solubility of drug carrier mixture was found in the range between 10.428 to 21.610 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. The compatibility studies indicated the conversion of crystalline form of Olmesartan medoximil to amorphous form. Fast dissolving tablets of selected formulation showed 90.8% release in 1 hour. The formulations were stable during the study period**.** From the results it can be concluded that solvent evaporation technique can be utilized to prepare solid dispersion which are successfully formulated into fast dissolving tablets.

Index Terms:- Solvent evaporation method, Olmesartan Medoximil, Fast dissolving tablets.

I. 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 may 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. [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. There are many solubility enhancement techniques used to improve drug solubility, like Solid dispersion technique which is used to enhance solubility of the poorly aqueous soluble drug incorporated into the polymeric matrix. Therefore solid dispersions were prepared to enhance solubility and dissolution of olmesartan medoximil with poloxamer 407 and HPMC K 15 M. The solid dispersions were prepared by Solvent evaporation method.

The fast dissolving solid dosage form is widely used dosage form which allows easy administration. Fast dissolving tablets which are designed to dissolve in saliva within a few seconds, and so it is called fast-dissolving tablets [5]. United States Food and Drug Administration (FDA) defined as 'A solid dosage form containing medicinal substances or active ingredients which disintegrates rapidly within a few seconds when placed up on tongue' [6]Fast dissolving drug-delivery systems were first developed in the late 20 th century as an alternative to conventional dosage form. Tablets when administered with glass of water may be inconvenient for some patients who experience difficulties in swallowing traditional oral solid-dosage forms.[7]

II. 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 HPMC K 15 M was obtained from Research- Lab, Fine Chem Ltd, Mumbai. All other chemicals and solvents were of analytical grade.

III. METHODOLOGY

Preparation Of Solid Dispersion:[8]

Solvent evaporation method: Required quantity of drug Olmesartan medoximil and carriers Poloxamer 407 and HPMC K 15 M in ratios (1:1, 1:15 and 1:2) mixture was dissolved in 5 ml methanol in a separate china dish. The solvent was allowed to evaporate on water bath at 50ºC with continuous stirring. The obtained dried powder was passed through sieve no # 100, The prepared mixtures were packed in an air tight container and stored in a desiccator until further use.

3.1 Composition of Solid Dispersion:

Table 3.1: Composition of Solid Dispersion containing olmesartan medoxomil.

Formulation Code	Ratios	Carriers (in mg)	
		Poloxamer 407	HPMC K 15 M
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

3.2 Phase Solubility Studies: [9]

Phase solubility studies was performed by a method described by Higuchi and Connors. A known excess amount of olmesartan medoxomil and carriers in (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 h.) The aliquots were filtered through Whatman filter paper. The aliquots were diluted appropriately in respective media and analyzed spectrophotometrically at 257 nm for olmesartan medoxomil. The study was performed in triplicate and the results were reported as mean ±SD (n=3).

3.3 Pre Compression Studies [10]:

3.3.1 Bulk Density

Weighed quantity of granules was transferred into a 50ml measuring cylinder without tapping and the volume occupied by granules was measured. Bulk density was measured using the following formula.

$$\mathbf{Pb = M/Vo} \quad (1)$$

Where, Pb = Bulk density

M = Mass of blend

Vo = Untapped volume (n=3)

3.3.2 Tapped Density

Weighed quantity of granules was taken into graduated measuring cylinder volume occupied by granules was noted down. The measuring cylinder was subjected to 500 taps in tapped density tester (Electro Lab USP II), the change in volume is noted down. Tapped density was measured using the following formula

$$\mathbf{Pt = M/Vt} \quad (2)$$

Where, Pt = Tapped density

M = Mass of blend

Vt = Tapped volume (n=3)

3.3.3 Compressibility Index

Compressibility is the ability of powder to decrease in volume under pressure using bulk density and tapped density. The percentage compressibility of granules were determined using the following formula

$$\mathbf{CI = Pt – Pb / Pt \times 100.} \quad (3)$$

Where, CI = Compressibility Index.

Pb = Bulk density, Pt = Tapped density, Pt = Tapped density (n=3)

3.3.4 Hausner's ratio

It is measurement of frictional resistance of the drug. It was determined by ratio of tapped density and bulk density.

$$\mathbf{H = Pt / Pb} \quad (4)$$

Where, Pb = Bulk density (n=3)

3.3.5 Angle of Repose

Weighed quantity of granules was passed through a funnel kept at a height of 2cm from the base. The powder is passed till it forms heap and touches the tip of funnel. The radius was measured and angle of repose was calculated using the following formula. (n=3)

$$\tan\theta = h/r \qquad (5)$$

Where, h and r the height and radius of the powder cone respectively.

3.4 POST COMPRESSION STUDIES:

3.4.1 Hardness of tablets [11]:

Hardness of tablets was tested using Monsanto hardness tester. Scale was adjusted to zero and the tablet held between the moving jaw and pressure was applied by these jaws until the tablet braked. Hardness of tablets is measured in terms of Kg/cm^2. Study was performed in triplicate.

3.4.2 Thickness and diameter:

By using dial meter (Mitutoyo, Japan) thickness and diameter of all prepared formulations was measured by taking the average of three readings in mm. It was reported as mean ± SD (n=3).

3.4.3 Weight variation test:

Weight variation test was carried out by using an electronic weighing balance. 20 tablets were weighed individually and the average weight was noted, and % deviation of each tablet weight was determined by the following equation:

$$\textit{Percent deviation } (PD) = \frac{W_{avg} - W_{initial}}{W_{initial}} x\ 100 \qquad (6)$$

Where,

W_{avg} = Average weight of tablet, $W_{initial}$ = individual weight of tablet.

3.4.4 Friability of tablets: [12]

10 pre-weighed tablets were allowed to fall down for 100 revolutions by using Roche friabilator. The weight loss was calculated and % friability was then calculated by:

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} x100 \qquad (7)$$

Where, W = weight of tablet.

3.5 Preparation of Fast Dissolving Tablets [13]

Tablets containing solid dispersions (equivalent to 20 mg of Olmesartan medoximil) prepared by solvent evaporation method were formulated using various excipients and evaluated for various pre compression blends. The blend was compressed on rotary press tablet, using 7 mm punch. Further subjected to various post compression studies.

Table 3.5,1: Composition of Solid Dispersion containing olmesartan medoximil

Materials (mg/tablet)	FD 1	FD 2	FD 3
SD 1:2	96	94	92
SSG	2	4	6
Magnesium Stearate	1	1	1
MCC	1	1	1
Total weight	100		

SSG= Sodium starch glycolate MCC = Microcrystalline cellulose

3.5.2 Evaluation of Fast Disintegrating Tablets

Hardness of tablets was tested using Monsanto hardness tester. Scale was adjusted to zero and the tablet held between the moving jaw and pressure was applied by these jaw until the tablet break, Friability of the tablets were determined by weighing 10 pre-weighed tablets ad it was allowed to fall down for 100 revolutions by using Roche friabilator. Weight variation test was carried out by using an electronic weighing balance. Twenty tablets were weighed individually and the average weight was noted, and % deviation of each tablet weight was determined. By using dial meter (Mitutoyo, Japan) thickness and diameter of all prepared formulations was measured by taking the average of three readings in mm. drug content was performed by weighing and triturating the tablet. The tablet triturate equivalent to 20 mg of the drug was weighed accurately, dissolved in distilled water. The content of Olmesartan medoximil was determined spectrophotometrically at 257 nm against blank using UV-visible spectrophotometer (1601, Shimadzu, Kyoto, Japan

3.5.3 *In Vitro* Dissolution Studies

In Vitro disintegration time was determined using disintegration test apparatus. A tablet was placed in each of the tubes of the apparatus. The water was maintained at a temperature of 37±0.5ºC and time taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

IV. RESULTS AND DISCUSSION

4.1 Phase solubility studies : 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.. 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 10.428 to 21.610 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 4.1 Effect of solubility of surfactant with Olmesartan medoximil

Concentration	Surfactant (%)	Solubility (mg/ml)
0.5	0.5	14.379±0.93
1		14.502±0.18
1.5		14.698±0.95
2		15.237±0.87
2.5		16.643±0.35
0.5	1	21.242±0.01
1		21.312±0.32
1.5		21.463±0.22
2		21.610±0.59
2.5		21.585±0.84
0.5	1.5	10.428±0.18
1		11.022±0.40
1.5		12.468±0.44
2		12.566±0.32
2.5		12.909±0.41
0.5	2	14.625±.66
1		15.237±0.74
1.5		15.384±0.19
2		15.899±0.39
2.5		16.563±0.87

4.3 Evaluation of fast dissolving tablets

Bulk densities and tapped densities of Olmesartan medoximil formulations were found to be in the range 0.615 to 0.658 and 0.702 to 0.714 (g/cc) respectively. Carr's index values for the prepared blends were found in the

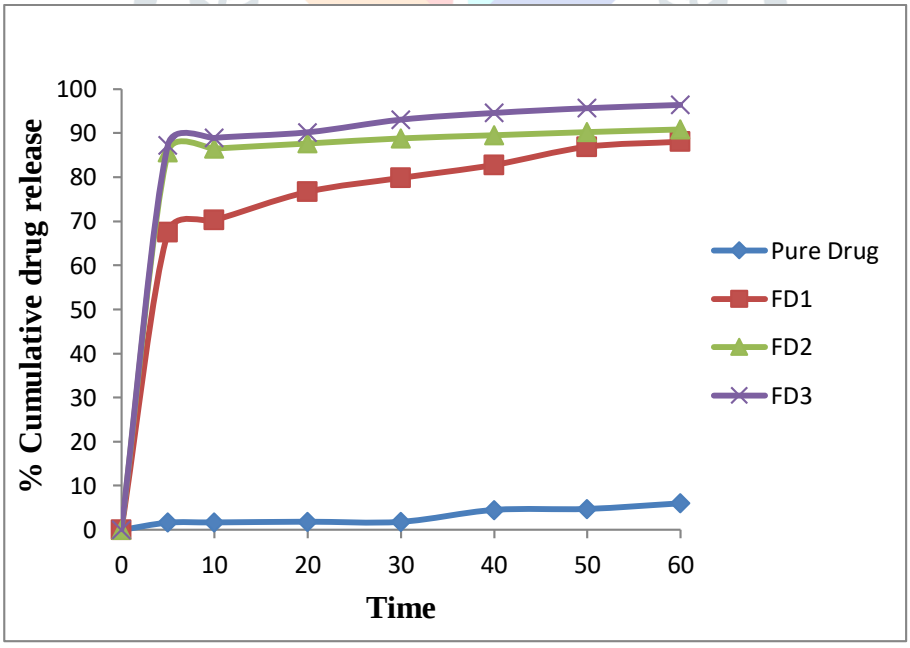
range of 13.36 to 15.75%. Hausner's ratio found to be in range of 1.16 to 1.34. The angle of repose values of all prepared formulations were in the range of 24.23±0.04°-26.98±0.01°, which indicated good flow properties of the different blends. From the results it can be concluded that the lubricated blend possessed good flow properties.

The hardness values of all prepared formulations were in the range of 2.00±0.10 kg/cm² to 2.04±0.02 kg/cm² .This ensured good handling characteristics of all batches. All the prepared tablets were evaluated for weight variation. The percent deviation from the average weight was found to be within the prescribed official standards. The percentage friability values of all prepared formulations were found in the range of 0.27 ± 0.87 to 0.41 ± 0.17%. This indicated that the % friability of prepared formulations were within the acceptable limits and tablets were mechanically stable. Tablets of each formulation were evaluated for *in vitro* disintegration time and the results are within acceptable limits. The results showed that the disintegration time of prepared tablet formulations FD1, FD2 and FD3 was less than 3 min. Thus all the formulations showed faster disintegration. The fast dissolving tablets were evaluated for *in vitro* dissolution studies in phosphate buffer pH 6.8. Formulation FD2 showed 90.88 % drug release in 1 hr.

4.4 *In Vitro* Dissolution Studies of Fast Dissolving Tablets

The fast dissolving tablets were evaluated for *in vitro* dissolution studies in phosphate buffer p H 6.8. Formulation FD2 showed 90.88 % drug release in 1 hr .

Figure 4.1 :- Comparison of *in vitro* dissolution profile of Olmesartan medoximil in pure form and FD1, FD2 and FD 3



4.5 *In Vitro* Disintegration Time

Tablets of each formulation were evaluated for *in vitro* disintegration time . The results showed that the disintegration time of prepared tablet formulations FD1, FD2 and FD3 was less than 3 min. Thus all the formulations showed faster disintegration

4.6 Evaluation of model independent kinetics parameters of solid dispersion:

The model independent kinetic parameters were estimated for solid dispersion F1 to F 15 prepared by solvent evaporation method.. The MDT of formulations F1 to F15 were ranged between 4.68 min to 23.68 min. The % DE of formulations F1 1 to F 15 were between 60.52 % to 91.39%. The formulation F 14 had shown % DE value of 91.39 % and MDT of 4.68 min. Hence it was selected as a best formulation for further study.

4.7 Evaluation of model independent kinetics parameters of fast dissolving tablets

The model independent parameters like mean dissolution time and % dissolution efficiency for the prepared fast dissolving tablets were estimated. The MDT and % DE for formulation are FD 2 3.92 min and 93.45 % respectively. So it was selected for further study.

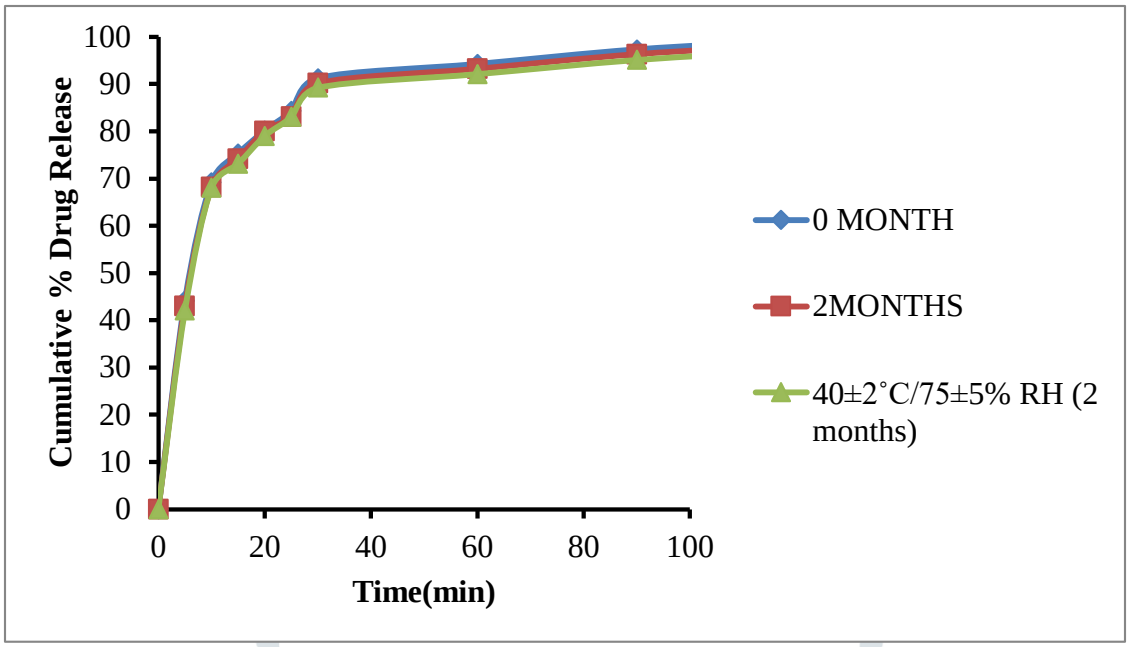
4.8 Stability Studies

The stability study on selected formulation FD 2 was carried out at room temperature and at 40° ± 2°C / 75 ± 5 % RH for 2 months. There was less variations in the dissolution profiles and appearance of stored product. It showed that the formulations were stable during the study period.

Table 4.2 : Drug content and Hardness of Olmesartan medoximil selected formulations:

Formulations	Drug content (%)	Hardness (kg/cm^2)
	FD 2	FD 2
0 month	99.35±0.12	2.01±0.94
Room temperature (2 months)	98.65±0.85	2.00±0.97
40±2˚ C/75±5% RH (2 months)	96.80±0.34	2.00±0.10

Figure 4.2 :- Stability studies of selected formulations of Olmesartan medoximil.



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

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