e-ISSN: 2320-1215
p-ISSN: 2322-0112

Research and Reviews: Journal of Pharmacy and Pharmaceutical Sciences

Solubility and Dissolution Rate Enhancement of Olmesartan Medoxomil by Solid Dispersion Technique and Development of Orodispersible Tablets

O. Kumar*[1], A. Prameela Rani [1] and V. Sai Kishore [2]

[1]Department of Biotechnology, Acharya Nagarjuna University, Nagarjunanagar-522510.

[2]Department of Pharmaceutics, Bapatla college f pharmacy, Bapatla-522101.

Research Article

Received: 19/08/2015
Revised: 02/09/2015
Accepted: 10/09/2015

*For Correspondence

O. Kumar, Department of Biotechnology, Acharya Nagarjuna University, Nagarjunanagar-522510, Tel: 9490153332; E-mail: voiceofsaikishore@yahoo.com

key words:

Olmesartan Medoxomil, Urea, Crospovidone, Orodispersible Tablets.

ABSTRACT

Solid dispersions were prepared by solvent evaporation method with different carriers such as PVP-K90, mannitol and urea in different proportions. All the solid dispersions prepared were evaluated for saturation solubility study, drug content and for dissolution studies. Among all the formulations prepared, solid dispersions prepared with Olmesartan medoxomil and Urea in 1:3 ratio showed highest drug release in 60 minutes. To study the influence of superdisintegrants on the performance of Olmesartan Medoxomil Orodispersible Tablets, a set of three formulations (F_{10}, F_{11} and F_{12}) were prepared using three different superdisintegrants *viz*, Sodium starchglycolate (5%), Croscarmalose sodium (5%), Crospovidone (5%) respectively. The dispersible tablets of Olmesartan medoxomil were evaluated for various parameters. Based on the dissolution rate, superdisintegrants can be rated as Sodium Starch Glycolate < Croscarmalose sodium < Crospovidone. The formulation prepared with Crospovidone was offered relatively rapid release of Olmesartan Medoxomil when compared with other superdisintegrants used in this investigation. The dissolution rate followed first-order kinetics. The drug release from optimized formulations was found be quite stable while stored at 25 ± 2°C, 60 ± 5% RH and at 40 ± 2 °C, 75 ± 5% RH for a

e-ISSN: 2320-1215
p-ISSN: 2322-0112

period of 3 months.

INTRODUCTION

The enhancement of oral bioavailability of poorly soluble drugs remains one of the most challenging aspects of drug development. Although salt formation, solubilization and Size reduction have commonly been used to increase dissolution rate and there by oral absorption and bioavailability of such drugs. There are some practical limitations of these techniques. One of the favourable strategy to improve the solubility and hence bioavailability of poorly water soluble drugs is the formulation of solid dispersion [1]. It refers to dispersion of an active ingredient in a carrier at solid state which is prepared by solvent evaporation method.

The drug Olmesartan medoxomil was selected for enhancement of solubility and dissolution rate. Olmesartan medoxomil is poorly water soluble (BCS class II) anti-hypertensive drugs. One of the major problems of these drugs is, low solubility in biological fluids, which results into poor bioavailability after oral administration. Due to poor solubility of drug, its bioavailability rate (26%) is limited by drug dissolution. It is a white crystalline powder and has poor flow properties and undesirable dissolution properties [2]. In the present study, an attempt was made to improve physicochemical properties by preparing solid dispersion of olmesartan medoxomil in the presence of hydrophilic carrier for the enhancement of overall physicochemical performance. Therefore, in the present study, an attempt has been made to increase solubility of Olmesartan medoxomil by solid dispersion technique.

MATERIAL AND METHODS

Olmesartan medoxomil was obtained from M/S Apotexpharma Pvt Ltd, Bangalore, India. PVP-K90, Mannitol and Urea were obtained as gift samples from Signetchem, Mumbai, India. All chemicals and solvents used were of analytical grade.

Preparation of Olmesartan medoxomil Solid dispersions

Accurately weighed quantities of Olmesartan medoxomil and the carriers PVP-K90, mannitol and urea in different proportions, as shown in **Table 1,** were dissolved in methanol, followed by evaporation of solvent using rotary evaporator thermos stated at 40°C. The solidified mass obtained in each case was scraped, crushed, pulverized, and passed through an 80-mesh sieve. All the solid dispersions were preserved in well-closed glass containers in desiccators [3]

e-ISSN: 2320-1215
p-ISSN: 2322-0112

Formulation Number	Olmesartan medoxomil (mg)	Urea (mg)	Mannitol (mg)	PVP K-90 (mg)
S F1	1000	1000		
SF2	1000	2000		
SF3	1000	3000		
SF4	1000		1000	
SF5	1000		2000	
SF6	1000		3000	
SF7	1000			1000
SF8	1000			2000
SF9	1000			3000

Table 1 Composition of Olmesartan medoxomil solid dispersions formulated with different carriers

Evaluation of Solid dispersions

Solubility studies

The solubility of Solid dispersions in water was determined by taking excess quantity of Solid dispersions and adding to screw- capped 50 ml glass vials filled with water. The vials were shaken for two hours on mechanical shaker. The solution was filtered through Whatmann filter paper No.1 and the drug concentration was determined spectrophotometrically at 258 nm [4].

Drug Content Estimation

The percentage of drug content in Solid dispersions was estimated by dissolving 80 mg of Solid dispersions in methanol, mixed thoroughly by shaking and the volume was made up to the mark within 6.8 pH phosphate buffer. The solution was filtered and the filtrate was diluted suitably with 6.8 pH phosphate buffer and absorbance was measured at 258 nm using UV/Visible spectrophotometer [5].

Dissolution studies of Solid dispersions

In-vitro dissolution studies of pure drug and Solid dispersions were carried out for 60 minutes using USP Dissolution test apparatus type II (Lab India DISSO 2000, eight stages) at 50 rpm. Solid dispersions equivalent to 20 mg of pure drug (Olmesartan medoxomil) used for dissolution study at 37±0.5^0 C in 900ml of 6.8 pH phosphate buffer as dissolution medium. Aliquot equal to 5 ml was withdrawn at regular time intervals (10, 20, 30, 40, 50, 60 min), an equal volume of fresh dissolution medium was replaced to maintain the sink condition and aliquots were measured at 258 nm UV/Visible spectrophotometer. DE_{30}%, T_{50}, T_{90} and k^{-1} values were calculated from dissolution data [6].

e-ISSN: 2320-1215
p-ISSN: 2322-0112

Preparation of Olmesartan Medoxomil Orodispersible Tablets containing superdisintegrants

Olmesartan medoxomil containing Orodispersible tablets were prepared by direct compression process and the composition was shown in **Table 2.** All the ingredients were properly mixed and passed through mesh no. 80. The resulting blend was lubricated with magnesium stearate and talc and compressed into tablets using the Cadmach sixteen stationary punching (round shaped,7mm thick) machine [7].

Formulation	Solubility (mg/ml)	% of Drug content	K (min^{-1})	T_{90} (min)	DE_{30} (%)
Pure drug	0.0038	-	0.0025	938.0	4.01
SFI	0.0645	99.87±0.04	0.0317	72.7	30.55
SF2	0.0762	99.13±0.06	0.0371	62.1	34.29
SF3	0.0889	99.94±0.03	0.0428	54.1	37.24
SF4	0.0565	99.75±0.07	0.0276	83.5	27.16
SF5	0.0652	99.11±0.05	0.0318	72.3	30.84
SF6	0.0773	99.28±0.03	0.0355	64.6	33.44
SF7	0.0453	99.16±0.06	0.023	98.7	24.91
SF8	0.0548	99.74±0.04	0.025	90.2	26.32
SF9	0.0667	99.19±0.02	0.028	82.4	28.13

Table 2. Solubility studies and drug content of Olmesartan medoxomil solid dispersions prepared by solvent evaporation technique

Evaluation of micromeritics properties of the blend

Bulk density

Blend was weighed and transferred to a measuring cylinder. Then bulk volume was noted. Bulk density was calculated by using the following formula [8]

$$\text{Bulk density} = \frac{Massofthepowder}{Bulkvolume}$$

Tapped density

Blend was weighed, transferred to a measuring cylinder, and subjected to 100 tapings. Then volume was noted as tapped volume. Tapped density was measured by using the following formula [9]

$$\text{Tapped density} = \frac{Massofthepowder}{Tappedvolume}$$

Carr's index

Carr's index was calculated by using the following formula [10]

$$\text{Carr's index} = \frac{Tappeddensity - Bulkdensity}{Tappeddensity} \times 100$$

Hausner's ratio

Hausner's ratio was calculated by using the following formula [8]

$$\text{Hausner's ratio} = \frac{Tappeddensity}{Bulkdensity}$$

e-ISSN: 2320-1215
p-ISSN: 2322-0112

Angle of repose

Required quantity of blend was taken and poured into a hollow cylinder which was placed on a graph sheet. Then the cylinder was slowly lifted. Then height and diameter of the heap formed were noted down. The angle of repose (θ) was calculated by the formula [8]

$$\text{Angle of repose, } \theta = \text{Tan}^{-1}\frac{h}{r}$$

Evaluation of Olmesartan Medoxomil Orodispersible tablets

Weight variation test

Weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average weight [9].

Disintegration Time

The disintegration time was determined in distilled water at 37±0.5^0 C using disintegration test apparatus [9] USP ED-2L (Electro lab, Mumbai).

Friability

Roche friabilator was used to determine the friability. Pre-weighed tablets were placed in friabilator and rotated at a speed of 25 rpm for 4 minutes or up to 100 revolutions. The tablets are dropped from a distance of 6 inches in each revolution. The tablets were then reweighed after removal of fines and the percentage of weight loss was calculated [9]

Hardness

Hardness of the tablet was determined using the Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning threaded bolts until the tablet fractured. Then the final reading was recorded. The hardness was computed by deducting the initial pressure from the final pressure [9]

Wetting Time

The wetting time of the tablets can be measured using a simple procedure. Five circular tissue papers of 10 cm diameter are placed in a Petri dish with a 10-cm diameter. 10 mL of water-containing amaranth a water-soluble dye is added to Petri dish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time [9]

In vitro dispersion time

Tablet was added to 10 ml of phosphate buffer solution pH 6.8 (pH of saliva) at 37± 0.5°C. Time required for complete dispersion of tablet was measured [9]

Fineness of dispersion

This test was performed by placing two tablets in 100 ml of water and stirring it gently, until the tablets get completely disintegrated. Then the dispersion is passed through a sieve screen with a nominal mesh aperture of 710 µm [9]

Drug content

Twenty tablets were powdered, and tablet powder equivalent to 20 mg of Olmesartan Medoxomil was accurately weighed and transferred into a 100-ml volumetric flask. Initially, 5 ml methanol was added and shaken for 10 min.

e-ISSN: 2320-1215
p-ISSN: 2322-0112

Then, the volume was made up to 100 ml with 6.8 phosphate buffer. The solution in the volumetric flask was filtered, diluted suitably, and analyzed spectrophotometrically at 258 nm [10].

Dissolution studies

Dissolution studies for Olmesartan Medoxomil Orodispersible tablets were performed in pH 6.8 phosphate buffer using USP dissolution test apparatus (Electrolab, Mumbai, India) with a paddle stirrer. The paddles were allowed to rotate at speed of 100 rpm. The dissolution medium was maintained at a temperature of 37±0.5 ^{o}C and samples were withdrawn at an interval of every 5-min fresh dissolution replaced the volume of the withdrawn samples medium to kept the volume of the dissolution medium as constant. The withdrawn samples were filtered and absorbance was measured at absorption maxima of 258nm using UV-visible spectrophotometer [11].

In-vitro dissolution kinetic studies

The drug release data were plotted and tested with zero order (cumulative % drug released Vs time), First order (Log % remained Vs time). The in vitro dissolution kinetic parameters, dissolution rate constants (K^{-1}), correlation coefficient (r), the times (t_{50}) for 50 % drug released (t_{50}), the times for 90 % drug released (t_{90}) and dissolution efficiency [D.E.] were calculated [12].

Stability study

The optimized formulations were subjected to accelerated stability studies as per ICH (The International Conference of Harmonization) guidelines. The optimized formulations were packed in the screw capped bottles and stored at 25 ± 2ºC, 60 ± 5% RH and at 40 ± 2 ºC, 75 ± 5% RH for 3 months [13]. Tablets were periodically removed and evaluated for physical characteristics and in-vitro drug release.

RESULTS AND DISCUSSION

Solid dispersions of olmesartan medoxomil were prepared by solvent evaporation method. The carriers like Urea, Mannitol and PVPK 90 were used in the preparation of solid dispersions. Various ratios of drug and carrier such as 1:1, 1:2 and 1:3were used in the preparation. All the solid dispersions prepared by solvent evaporation method were found to be fine free flowing powders. The results of solubility study revealed that the solid dispersions prepared with different carriers showed increased solubility compared to the pure drug. This may be due to the improved porosity, decreased primary particle size and partial amorphization of drug in solid dispersions. The drug content values were ranged from 97.19 % to 98.87%. The results of solubility study and drug content values are shown in **Table 3.**

Incorporation of hydrophilic carrier in the solid dispersions significantly enhanced the dissolution. Mixing of drug with a hydrophilic carrier results in greater wetting and increase surface available for dissolution by reducing interfacial tension between the hydrophilic drug and dissolution media. It was noted that drug carrier system sink immediately, while pure drug keeps floating on the surface for a longer time interval. The cumulative percentage of drug released from different solid dispersions was increased in the following order Olmesartan medoxomil solid dispersions prepared with Urea > Olmesartan medoxomil solid dispersions prepared with Mannitol> Olmesartan medoxomil solid dispersions prepared with PVP –K90. Among all the formulations prepared, solid dispersions prepared with Olmesartan medoxomil and Urea in 1:3 ratio showed highest drug release in 60 minutes.

e-ISSN: 2320-1215
p-ISSN: 2322-0112

Ingredients	SF_{10}	SF_{11}	SF_{12}
Olmesartan Medoxomil solid Dispersion (1:3 ratio of drug and urea)	80	80	80
Sodium Starch Glycolate (5%)	10		-
Croscarmalose sodium (5%)		10	
Crospovidone (5%)			10
Mannitol	30	30	30
Avicel pH 102	76	76	76
Talc	2	2	2
Mg streate	2	2	2
Total weight	200	200	200

Table 3. Composition of Olmesartan Medoxomil Orodispersible Tablets

To study the influence of superdisintegrants on the performance of Olmesartan Medoxomil Orodispersible Tablets, a set of three formulations (F_{10}, F_{11} and F_{12}) were prepared using three different superdisintegrants *viz*, Sodium starchglycolate (5%), Croscarmalose sodium (5%), Crospovidone (5%) respectively. The dissolution data was presented in **Table 4, 5** and **Figure1**.

Formulation code	Bulk density (gm/cm^3)	Tapped Density (gm/cm^3)	Carr's index (%)	Hausner's ratio	Angle of repose (°)
SF_{10}	0.542±0.003	0.643±0.006	15.70±0.004	1.18±0.05	28.42 ±0.02
SF_{11}	0.483±0.005	0.561±0.003	13.90±0.007	1.16±0.05	27.38 ±0.03
SF_{12}	0.422±0.002	0.487±0.004	13.35±0.003	1.15±0.04	25.14 ±0.06

Table 4. Micromeritic properties for formulation blends

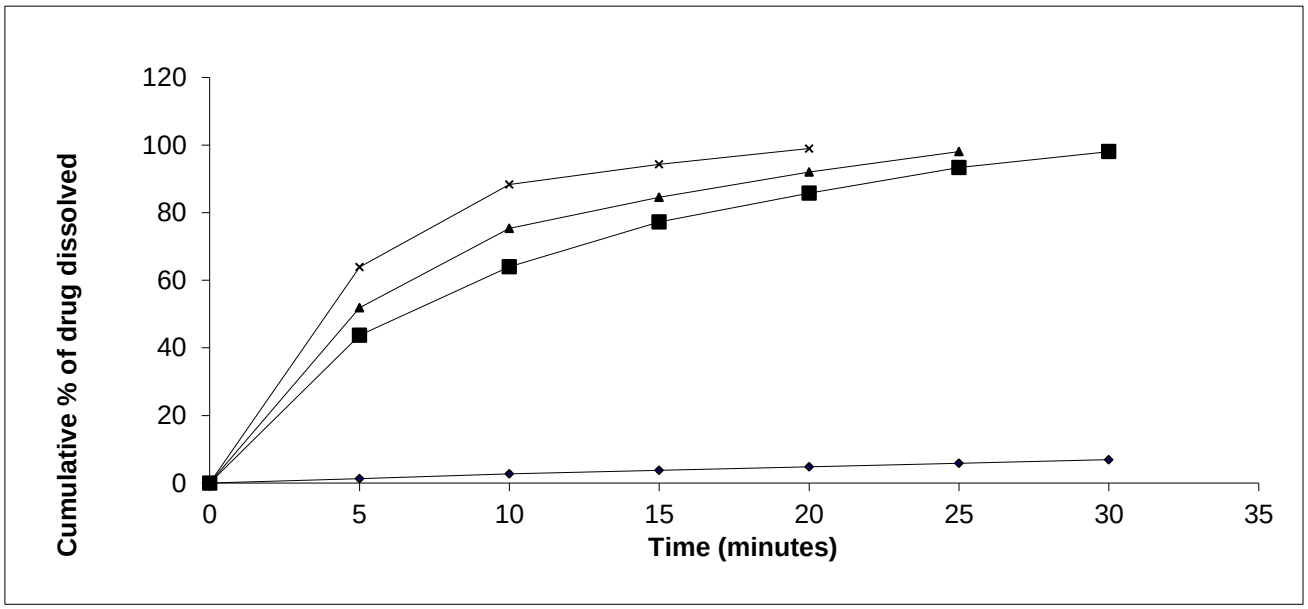
S.No.	Parameters	SF_{10}	SF_{11}	SF_{12}
1	Average weight (mg)	199±0.3	199±0.2	200±0.1
2	Drug content (%)	98.71 ±0.02	99.54±0.04	99.6 5±0.03
3	Disintegration time (sec)	152 ±0.003	140 ±0.005	120±0.007
4	Friability (%)	0.28 ±0.06	0.44 ±0.02	0.33 ±0.04
5	Hardness(kg/sqcm)	4.2 ±0.3	4.2 ±0.2	4.0 ±0.1
6	Wetting time (sec)	129 ±0.004	121 ±0.002	99±0.03
7	*In-vitro* dispersion time (sec)	251±0.005	212 ±0.007	162 ±0.004
8	Fineness of dispersion	passed	passed	passed

Table 5 Evaluation parameters of Olmesartan Medoxomil Orodispersible tablets

e-ISSN: 2320-1215
p-ISSN: 2322-0112

The *In-vitro* dissolution kinetics was presented in **Table 6.** The dissolution rate followed first-order kinetics as the graphs drawn between log % drug unreleased vs time were found to be linear. The dissolution rate of Olmesartan Medoxomil was found to be effected by nature of the superdisintegrant used in the preparation of tablets. Based on the dissolution rate, superdisintegrants can be rated as SSG < Croscarmalose sodium < Crospovidone. The formulation prepared with Crospovidone was offered relatively rapid release of Olmesartan Medoxomil when compared with other superdisintegrants used in this investigation. It showed sixteen folds enhanced dissolution efficiency compared with pure drug.

Figure 1. Dissolution profiles of Olmesartan medoxomil Orodispersible tablets



Note:
(-♦-) **Olmesartan medoxomil pure drug**
(-■-) **Olmesartan medoxomil tablets prepared with sodium starch glycolate**
(-▲-) **Olmesartan medoxomil tablets prepared with Croscarmalose sodium**
(-×-) **Olmesartan medoxomil tablets prepared with Crospovidone**

S. No.	Formulation	T_{50} (min)	T_{90} (min)	DE_{15} (%)	K (min^{-1})	Correlation coefficient values	
						Zero Order	First order
1	SF_{10}	6.0	20.0	49.23	0.11	0.8429	0.9793
2	SF_{11}	5.0	16.7	56.25	0.14	0.8220	0.9863
3	SF_{12}	3.1	10.3	66.74	0.22	0.7988	0.9886

Table 6. *In-vitro* dissolution kinetics of Olmesartan medoxomil Orodispersible tablets

The optimized formulations were stored at 25 ± 2°C, 60 ± 5% RH and at 40 ± 2 °C, 75 ± 5% RH for 3 months. Drug release from optimized formulations before and after storage under varying conditions were evaluated periodically at the regular interval of every month. The results indicated that the drug release from the optimized formulations was not changed significantly when stored at varying conditions. There were no significant changes in the

dissolution Kinetics of optimized formulations before and after storage under varying conditions. Thus, the drug release from optimized formulations was found be quite stable.

REFERENCES

1. Sanjeev Kumar, et al. Evaluation of Some Novel Techniques for Dissolution Enhancement of Poorly Water Soluble Drug Nimodipine. International Journal of PharmTech Research. 2010;2(1):950-959.

2. Mauik Patel, et al. Formulation and Assessment of Lipid Based Formulation Of Olmesartan Medoxomil. Int. J. Drug Dev. & Res. 2011;3(3):320-327.

3.Elnawawy TM, et al. Solubility enhancement of olmesartan by utilization of solid dispersion and complexation techniques. Int J Nov Drug Deliv Tech. 2012;2(4):297-303.

4.Mauik Patel, et al. Formulation and Assessment of Lipid Based Formulation of Olmesartan Medoxomil. Int. J. Drug Dev. & Res. 2011;3(3):320-327.

5.Manish R. et al. Formulation and evaluation of intraorally fast dissolving tablet of olmesartan medoxomil. Der Pharmacia Lettre. 2013;5(1):232-237.

6.Ashwini AY, et al. Enhanced solubility and dissolution rate of Olmesartan medoxomil using crystallo-co-agglomeration technique. Der Pharmacia Sinica. 2012;3(2):160-169.

7. Sasidhar RLC, et al. Solubility and Dissolution Rate Enhancement of Olmesartan Medoxomil by Complexation and Development of Mouth Dissolving Tablets. Advances in Biological Research. 2013;7(2):32-41.

8.Battue SK, et al. Formulation and evaluation of rapidly disintegrating tablet Fenoverine tablets: Effect of superdisintegrants. Drug. Dev. Ind. Pharm. 2007;33:1225-1232.

9. Sai Kishore V, et al. Formulation and Evaluation of valsartan fast dissolving tablets, Research J.Pharm.and Tech 2011;4(5):454-456.

10. Chirag Raval, et al. Enhanced oral bioavailability of Olmesartan by using novel solid self-emulsifying drug delivery systems. International Journal of advanced pharmaceutics. 2012;2(2):82-92.

11.Sasidhar RLC, et al. Solubility and dissolution rate of Olmesartan medoxomil by complexation and development of mouth dissolving tablets. Advances in Biological Research. 2013;7(2):32-41.

12. Abdelbary G, et al. Determination of the in vitro disintegration profile of rapidly disintegrating tablets and correlation with oral disintegration. Int J Pharm. 2005;292(1-2):29–41.

13. Raghavendra Rao NG, et al. Development of carbamazepine fast dissolving tablets: Effect of Functionality of hydrophillic carriers on solid dispersion technique. Asian Journal of Pharmaceutical and Clinical Research. 2010; 3(2):114-117.