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Formulatin and Development of Olmesartan Medoxomil Mouth Dissolving Tablet Using Solid Dispersion Technique

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Abstract

Olmesartan medoxomil is an antihypertensive agent administered orally, poorly water soluble drug having 26% absolute bioavailability. Low aqueous solubility is a major problem, faced during formulation development of new drug molecules. Purpose of this research was to enhance solubility of Olmesartan by using the concept of mixed hydro-trophy. Initially, solubility of Olmesartan medoxomil was determined individually in sodium acetate, sodium citrate, urea and sodium benzoate at concentration of 10, 20, 30 and 40% w/v solution using purified water as a solvent. Highest solubility was obtained in 5:20:15 ratio of urea, sodium acetate and sodium benzoate. This optimized combination was utilized in the preparation of solid dispersion by using distilled water as a solvent.

Keywords: Olmesartan Medoxomil, Hydrotropic Agent, Mouth Dissolving Tablets, *In-Vitro* Dissolution Studies.

Introduction

Orally disintegrating tablet is an emerging trend in formulation, gaining popularity due to ease of formulation and better patient compliance especially geriatric and pediatric patients.[1] Conventional tablet and capsule are difficult for swallowing, in patient group such as elderly, children, and patient mentally retarded, uncooperative, or on reduced liquid intake diet.[2,3] Hydrotrophy is a solubilization process where addition of a large amount of one solute exerts an increase in the aqueous solubility of another solute. The other solute can be a poorly soluble drug. Hydrotrophy may be cationic, anionic or a natural molecule and possesses a hydrophobic as well as a hydrophilic group. [4]

Mouth dissolving tablets are the dosage forms which disperse upon contact with the mucosal surface of the oral cavity and quickly release their components without modification or need of water before swallowing.[5] Oral cavity dissolve tablets are preferred for people suffering from dysphasia; institutional psychiatric patients as well as hospitalized patients suffering from a variety of disorders. Mouth dissolving tablets [MDT] are very beneficial for patients with difficulties in swallowing and conditions where access to water is difficult. [6]

Olmesartan medoxomil is very slightly soluble in water and as a consequence it exhibits low bioavailability after oral administration. Therefore, the improvement of Olmesartan medoxomil dissolution from its oral solid dosage forms is an important issue for enhancing its bioavailability and therapeutic efficacy. [7]

In the present study mouth dissolving tablets of Olmesartan medoxomil were formulated by using different techniques and superdisintegrants in order to reduce dose frequency and to enhance patient compliance towards therapy. Olmesartan medoxomil, a prodrug, is hydrolyzed to olmesartan during absorption from the gastrointestinal tract. Olmesartan is a selective AT_1 subtype angiotensin II receptor antagonist. [8]

Aim of the Study

The aim of the study was to formulate and evaluate Olmesartan medoxomil mouth dissolving tablet by solid dispersion technique.

Review of Literature

Jung Y.J. *et al.* (1999) improved the solubility and dissolution rate of a poorly water-soluble drug Itraconazole by a solid dispersion technique. Solid dispersion particles of Itraconazole were prepared with various pH-independent and dependent hydrophilic polymers and were characterized by differential scanning colorimetry, powder X-ray diffraction and scanning electron microscopy. The dissolution rate of Itraconazole from the tablets prepared by spray drying (SDT) was fast, with 90% released within 5 min. [9]

Tritt H. *et al*. (2004) mouth dissolving tablet of Olanzapine were prepared by effervescent formulation approach. The effervescent excipients system not only rapid disintegration of tablet in the orals cavity, but also check the slight bitter taste of medicament. Sodium bicarbonate and citric acid were used as effervescent agent and their ratio in the formulation was optimized.[10]

Shirwaiker *et al*. (2008) formulated fast dissolving tablet of atenolol by dry granulation method. Atenolol was formulated as fast disintegration tablet by using three superdisintegrants, croscarmellose sodium (Ac-Di-Sol), crospovidone (polyplasdone XL) and sodium starch glycollate. Thirteen formulations were prepared and all had the same amount of ingredients except the superdisintegrant level. All the superdisingrants were used at different concentration levels to assess their efficiency and critical concentration levels. AC-Di-Sol proved to be best amoung the three and showed satisfactory result at 3kg/cm^2. Formulations were found stable in release profile after 30 days stability studies at room temperature. [11]

Shukla M. *et al*. (2010) enhanced solubility of Glipizide by solid dispersion, hydrotropy and micellar solublization. Solid dispersion of Glipizide was prepared by solvent evaporation method. PEG (polyethylene glycol) 4000, mannitol and urea were used as carriers. Hydrotropic studies were carried out using different hydrotropic agents (sodium acetate, sodium benzoate and salicylate) and micellar solubilization was carried out using different surfactant solutions (sodium laurylsulphate, tween 80 and cetrimide). The solubility enhancement of glipizide by different solubilization technique was observed in decreasing order as hydrotropic solubilization>solid dispersion>micellar solubilization. It was observed that the solubility increased with the increase in the concentration of hydrotropic agents. [12]

Madgulkar *et al.* (2011) formulated the oral disintegrating tablet of fexofenadine hydrochloride by sublimation using camphor factorial design, in which the amount of sublimation agent camphor and superdisintegrant disodium starch glycolate were taken as formulation variables for optimizing disintegrating time, drug release within 15 minutes and friability. [13]

Gohel *et al*. (2014) reported formulation design and optimization of mouth dissolving tablet of Nimesulide using vacuum drying techniques. Granules containing nimesulide, camphor, crospovidone, and lactose were prepared by wet granulation techniques. Camphor was sublimed form the dried granules by exposure to vacuum. The porous granules were than compressed. Sublimation of camphor from tablet result in superior tablet as compared with tablet prepared from granules that were exposed to vacuum.[14]

Madan R.J. *et al.* (2015) provided a fast dissolving oral dosage form of lurasidone. By using mixed hydrotrophy method, enhancement of the solubility of lurasidone was carried out. Solubility of lurasidone was determined individually in nicotinamide, sodium citrate, urea and sodium benzoate at concentration of 10, 20, 30 and 40% w/v solutions using purified water as a solvent. Highest solubility was obtained in 15:20:5 ratio of nicotinamide, sodium benzoate and sodium citrate. This optimized combination was utilized in the preparation of solid dispersions by using distilled water as a solvent. Solid dispersions were evaluated for X-ray diffraction, differential scanning calorimetry and Fourier-transform infrared for the formulation of lurasidone. [15]

Mali R.K *et al.* (2017) developed a fast disintegrating tablet of Olmesartan Medoxomil using solid dispersion technique. A phase solubility study was performed to determine the effect of various polymers on aqueous solubility of drug. The binary SD of OLM was prepared by using poloxamer 407. The SDs was prepared by kneading, melting and solvent evaporation (SE) method by varying drug to carrier ratio. Result shows successful improvement in dissolution of poorly water-soluble drug OLM [16]

Materials and Methods

Olmesrtan medoxomil was received as a gift sample from Yarrow Chem. Ltd., Mumbai, India. The following materials were procured by SD Fine-Chem Pvt. Ltd. Mumbai and were used as received. Hydrotropic solid dispersion (HSD) agents include U-Urea, A-Sodium Acetate, and B-Sodium Benzoate. Microcrystalline cellulose (Avicel- 102), Sodium starch glycolate Crosscarmellose sodium, lactose, Magnesium stearate, Aspartame, Talc, Di-sodium hydrogen phosphate and Potassium dihydrogen phosphate were used as excepients.

Formulation of Hydrotropic Solid Dispersion (HSD) of Olmesartan Medoxomil

For preparation of hydrotropic solid dispersion, accurately weighed 1.5 gm sodium benzoate, 2 g sodium acetate and 0.50 g urea (total weight of the mixture was 5 g) were taken in a 100 ml beaker and properly mixed. Further, minimum quantity of warm distilled water, sufficient to dissolve the above hydrotropic blends was added. If minimum amount of water (approximately 5 ml) is used, lesser will be the time required to evaporate it and chemical stability of drug may not be affected adversely during removal of the water. Dissolution of the hydrotropic mixture was facilitated by agitation of a Teflon coated magnetic bead on a high–speed magnetic stirrer. After complete dissolution of above hydrotropic mixture, 1g of olmesartan medoxomil (drug to carrier ratio 1:4) was dissolved in the above solution and temp was maintained in the range of 55-60^{0}C, so as

to facilitate the water evaporation. Stirring was stopped when most of the water evaporated, this indicates the formation of hydrotropic solid dispersion, the wet solid dispersion thus obtained were spread over watch glasses and the watch glasses were kept in hot air oven maintained at 50^0C. So that remaining moisture could also be evaporated easily and a constant weight with no further weight loss could be obtained.

Preparation of Mouth Dissolving Tablet

Olmesartan medoxomil tablets were prepared by direct compression method. All the ingredients were passed through sieve # 44 separately. Then the ingredients were weighed and mixed in geometrical order. The blend thus obtained was directly compressed using 8 mm round flat punch by rotary tablet compressed machine (Cadmach, Model A13031116-17)

Table 1: Formulation of Olmesartan Medoxomil Tablet 250 mg Prepared by Direct Compression Methods

Formulation (weight in mg)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
HSD(~40mg olmesartanmedoxomil)	100	100	100	100	100	100	100	100
Crosscarmellose sodium	30	25	20	25	30	30	25	30
Microcrystalline cellulose	65	70	75	70	62	67	70	70
Crosspovidone	03	3	4	3	4	3	3	3
lactose	42	42	42	43	45	42	40	40
Aspartame	4	4	3	4	4	3	5	3
Magnesium Sterate	4	4	3	2	3	2	5	2
Talc	2	2	3	3	2	3	2	2

Evaluation Parameters

Weight Variation

Twenty tablets were chosen at a casual and average weight was determined. Then individual tablet was weight and compared with an average weight.[17]

Thickness

Thickness of the prepared tablet was measured by vernier caliper.[17]

Hardness

Hardness of the tablet was determined by Monsanto hardness tester.[17]

Friability

The friability of tablets using 10 tablets as a sample was measured using a Roche Friabilator. Tablets were rotated at 25 rpm for 4 minutes or up to 100 revolutions. The tablets were then reweighed after removal of fines and the percentage of weight loss was calculated.[18]

Wetting Time

Wetting time was determined by keeping the tablet in a Petri-dish containing 6ml of colored solution. Time to wet the upper surface of the tablet was recorded as wetting time. [18]

Drug Content

The randomly selected tablets were taken in 100ml standard flask containing phosphate buffer (pH 6.8). The flask was shaken for desired period of time to dissolve the drug from tablets. Absorbance of the resulting solution after appropriate dilution was measured on SHIMADZU 1601 double beam UV-Visible spectrophotometer at 210nm against the blank prepared. [19]

Disintegration Time

The process of breakdown of a tablet into smaller particles is called as disintegration. The *In-vitro* disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications. One tablet was placed in each of the 6 tubes of the basket. A disc was added to each tube. The apparatus was maintained at 37 ± 2^0C using pH 6.8 (simulated saliva fluid) as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 6.8 maintained at 37 ± 2^0C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded. [20]

Oral Disintegration Time

Six volunteer were selected for the study and prior to take tablet, they asked to rinse their mouth with distilled water and tablet was placed over the tongue. They were allowed to move the tablet against the upper plate of mouth with their tongue and to cause a gentle tumbling action without biting on it or tumbling it from side to side. Swallowing of the saliva was prohibited during the test and saliva was rinsed after each measurement. Average was calculated as the individual disintegration time**.** [21]

***In- vitro* Dissolution Time**

The dissolution rate study was carried out by USP-Type II rotating paddle methods. The study was done in triplicate and the mean of the determination was used to calculate the drug release from the tablet.[22]

Result and Discussion

FTIR Studies

Figure 1: FTIR Spectra of Olmesarten medoxomil

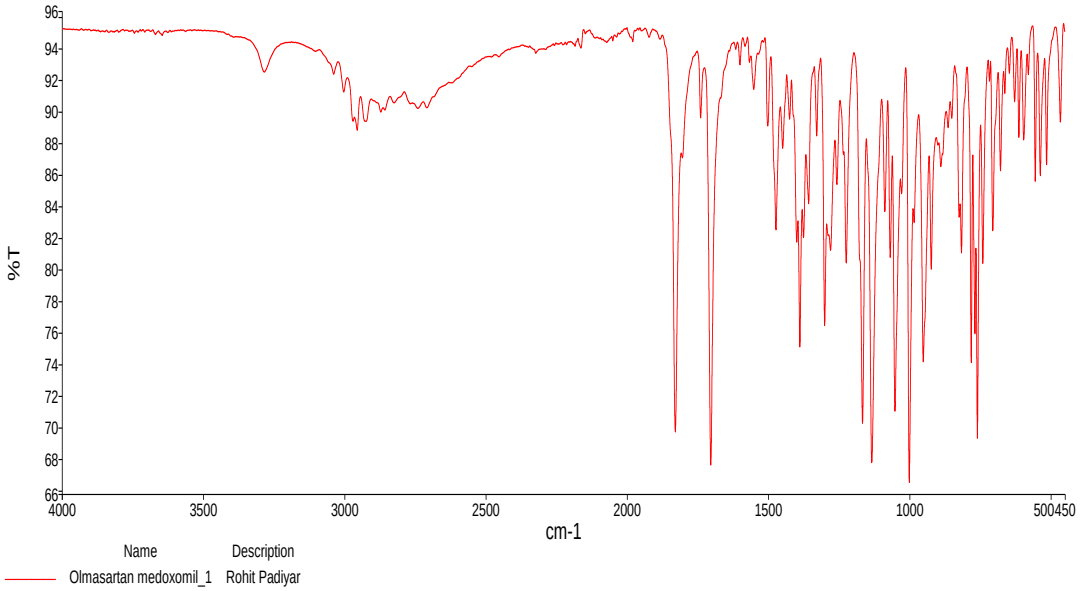


Table 2: Peak Value and Functional Group of Olmesarten medoxomil

S.NO	Peak value	Functional Group
1.	3285.87	Alcohol
2.	2956.77	Cycloalkane
3.	1829.8	Cyclopropanone
4.	1740.08	Saturated aldehyde
5.	1502.1	Aromatic compound
6.	1473.23	Aromatic hydrocarbon
7.	1375.64	Alcohol
8.	1279.88	Alcohol / phenol
9.	1150.57	Ether
10.	1001.04	Halogen
11.	781.5	n-alkanes

Weight Variation

As per I.P no tablet should deviate from the average weight by more than 7.5%. The weight variation of tablet made of all eight formulations prepared in the present studies was found to be well within the I.P 1996.

Thickness

The thickness of the formulated tablet was uniform.

Hardness

The hardness of the formulated tablets of Olmesartan medoxomil was low, but acceptable range and it was within the limit. An average of three observations was reported.

Friability

The Results shows friability of the formulated tablet was within 1% which was within the limits. Friability below 1% was an indication of good mechanical resistance.

Wetting Time

The result shows that tablets containing crosspovidone has best wetting capacity among all the formulations.

Table 3: Showing Avg. weight, Thickness, hardness, Friability and Wetting Time respectively

Sr.No.	Formul-ation	Average weight(mg)±S.D*	Avg.thickness (mm)±S.D*	Hardness (kg/cm^2)±S.D*	Friability±S.D	Wetting Time(sec)±S.D
1	F_1	249.23±1.22	4.10±0.10	3.80±0.22	0.57±0.022	21.66±1.53
2	F_2	248.14±1.45	4.05±0.15	4.12±0.25	0.55±0.025	20.00±2.00
3	F_3	249.11±1.22	4.12±0.20	4.13±0.21	0.40±0.021	35.12±1.55
4	F_4	247.14±0.88	4.30±0.30	3.76±0.18	0.40±0.018	42.01±2.12
5	F_5	249.13±1.05	4.18±0.16	4.25±014	0.48±0.014	28.12±1.53
6	F_6	246.14±1.86	4.26±0.28	4.33±0.16	0.46±0.016	35.10±2.00
7	F_7	248.16±1.53	4.20±0.30	4.53±0.10	0.78±0.010	17.00±1.00
8	F_8	247.22±1.36	4.10±0.12	4.68±0.15	0.50±0.015	22.66±2.08

*Standard Deviation

Drug Content

The drug content of the entire formulated tablet was 98.20% -99.50% which well within the I.P 1996 limit.

Oral Disintegration Time

From the tablet it is evident that formulation F_8 has least disintegration time in the mouth.

Table 4: Showing Drug Content, Disintegration Time and Oral D.T.

Sr. No.	Formulation	Drug content(%)±S.D	Disintegration Time(sec)±S.D	O.D.T±S.D (In Sec)
1	F_1	98.56±0.4041	60.20±0.58	70.20±028
2	F_2	98.08±0.5291	54.00±1.00	60.40±0.32
3	F_3	97.40±0.9073	80.12±1.10	87.20±0.50
4	F_4	98.50±0.7234	74.00±1.10	80.00±1.00
5	F_5	98.50±0.4041	51.12±1.07	28.50±0.40
6	F_6	99.50±0.5131	54.66±1.5	55.80±1.20
7	F_7	98.50±0.9018	45.37±0.5	30.00±2.00
8	F_8	99.20±0.5686	51.12±1.07	25.40±0.40

***In- vitro* Dissolution Time**

In-vitro dissolution of the formulated mouth dissolving tablets of Olmesartan medoxomil was studied in USP Type-II dissolution apparatus. Stirring rate of the paddle was 50 rpm, while volume of the dissolution fluid was 900 ml (6.8 pH phosphate buffer). Temperature of the dissolution medium was maintained at 37±1^{0}C. One tablet was used in each test. 5 ml of aliquots of dissolution medium was withdrawn at specific interval of time and equal volume of fresh dissolution medium was replaced after each withdrawal. The withdrawal sample was analyzed with the help of spectrophotometer at 258 nm.

Table 5: Dissolution Rate of Formulated Tablets by Rotating Paddle Methods

		% Cumulative Drug Released							
S.No.	Time (minutes)	F1	F2	F3	F4	F5	F6	F7	F8
1.	0	0	0	0	0	0	0	**0**	**0**
2.	5	26.46	16.66	17.85	13.45	19.56	39.57	17.45	13.45
3.	10	39.86	30.55	31.05	26.56	48.28	67.53	30.20	30.55
4.	15	59.53	57.23	38.13	38.20	70.56	86.05	37.10	38.20
5.	20	73.66	73.56	66.36	66.34	84.16	97.06	64.36	73.56
6.	25	89.81	88.23	92.54	90.54	94.38	98.92	90.23	88.23

Fig.2: % Cumulative Drug Release of Different Formulations (F_1 to F_4)

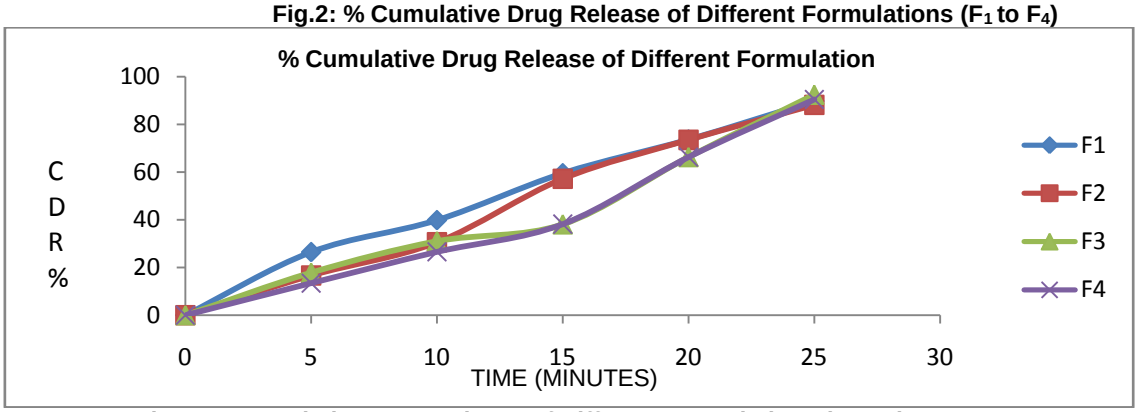
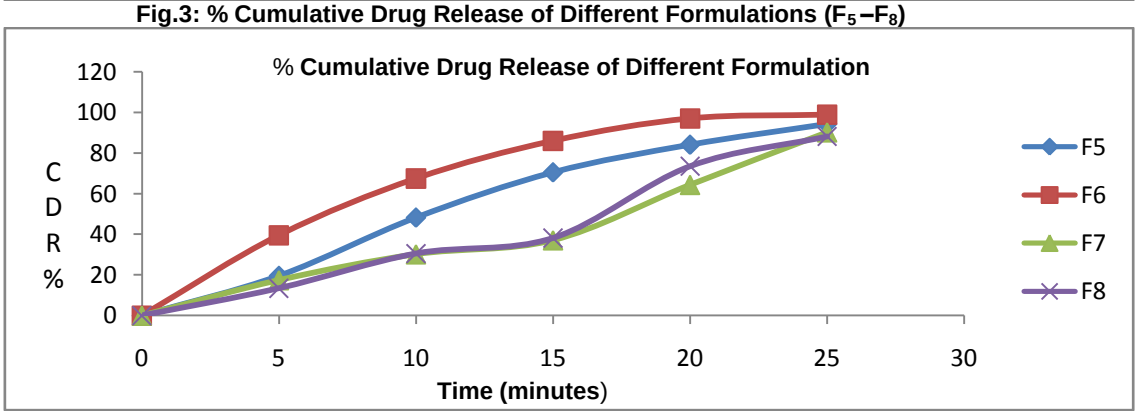


Fig.3: % Cumulative Drug Release of Different Formulations (F_5–F_8)



Conclusion

Solubility of the drug was enhanced by solid dispersion method using different hydrotropic agents like sodium acetate sodium benzoate and urea. Eight formulations of the Olmesartan medoxomil were prepared by direct compression methods and coded as F1-F8. Formulation F6 was found to be best amongst all. Weight variation of that formulation was within limit, thickness was 4.26±0.28 mm, Friability was found in acceptably range. Hardness was found 4.33±0.16 kg/cm^2, wetting time was found according to the acceptance which was essential parameter for the formulation. Drug content was found to be 99.50±0.5131 %. Oral disintegration time and *in-vitro* disintegration time were found to be 55.80±1.20 and 54.66±1.5 sec. respectively with 98.92% cumulative drug release. From the above findings the formulation F_6 selected as ideal formulation that having the combination of cross-carmellose sodium and microcrystalline cellulose with the drug utilized for the release of Olmesartan medoxomil as mouth dissolving tablet.

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