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Formulation and evaluation of intraorally fast dissolving tablet of olmesartan medoxomil

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ABSTRACT

The objective of present study is to develop the mouth dissolving tablet of an antihypertensive drug, Olmesartanmedoxomil. Mouth dissolving tablets of Olmesartanmedoxomil drug were prepared by using three different superdisintegrants like Cross carmellose sodium, Sodium starch glycolate and Crospovidone. The method of tablet preparation is direct compression method and evaluated for physicochemical evaluation parameter such as hardness, friability, weight variation, drug content uniformity, water absorption ratio, wetting time, in-vitrodisintegration time and in-vitro dissolution studies.In the present study, it was proved that the formulations containing Crospovidone have shown good in-vitro results compared to other formulations. However the formulations containing 8 % w/w concentration of any superdisintegrants have shown better optimum results, hence selected as best formulations in this study.Formulation F8 has shown excellent results in water absorption ratio. Hence F8 batch containing 8% cross povidone was found to be an optimized batch.

Keywords: Mouth dissolving tablet, Olmesartanmedoxomil,superdisintegrants, in-vitro drug release

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INTRODUCTION

For rapid onset of pharmacological effect from drugs, especially in the treatment of acute disorders, we preferred parenteral administration, but this method may not always be convenient for the patient. Therefore, there is growing interest in developing new, non-parenteral, reliable and convenient dosage forms using administration routes where a rapidly dissolved drug is immediately absorbed into the systemic circulation. Tablet formulations are generally the first choice for drug administration because of the relative ease of both production and usage. However, for acute disorders, the time to onset of action for a conventional oral tablet is generally not acceptable; this is usually attributable to gastric emptying causing a highly variable lag time between drug administration and onset of intestinal absorption[1].

Drug delivery via the oral mucosa is a promising route, whenone wishes to achieve a rapid onset of action or improved bioavailabilityfor drugs with high first-pass metabolism [2]. Thus, there isa growing interest in developing alternative dosage forms, i.e. mouth dissolving tablets, which allow a rapidly dissolving drugto absorb directly into the systemic circulation through the oralmucosa. These kinds of dosage forms are also convenient for children,elderly patients with swallowing difficulties, and in the absenceof potable liquids [3]. However, in addition to formulationconsiderations, the suitable properties of the active compound have to beappropriate in order to achieve drug delivery into systemic circulationafter intraoral administration. The parent compound has to be soluble,

stable and able to easily permeate the mucosal barrier at the administration site. Further, the dosage form has to be rapidly dissolved while retaining a sufficiently long contact time at the administration site. If dissolution of the drug is incomplete, contact time is short, and/or permeation too low, part of the dose will not be absorbed through the oral mucosa and will be swallowed, with subsequent effects on bioavailability [1].When Mouth dissolving tablets is kept in oral cavity then saliva quickly penetrates into tablet pores and causes rapid disintegration [4]. The basic approach used in development of mouth dissolving tablets is the use of superdisintegrant, which provide instantaneous disintegration of tablets after putting on tongue, thereby releasing the drug in saliva. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form [5].A number of superdisintegrants such as croscarmellose sodium, crospovidone and sodium starch glycolate are used for rapid disintegration of tablet [6].

The objective of present study is to develop the MDT of an antihypertensive drug, Olmesartan an angiotensin second inhibitor drug and thereby imparting the significance, ideal characteristics and various aspects related to mouth dissolving tablet formulation as a superior dosage form in treatment of hypertension and to improve the patient compliance. This work is used to develop ODT of drug candidate to improve bioavailability, dissolution time, disintegration time and patient compliance.

MATERIALS AND METHODS

Olmesartanmedoxomil was obtained as gift sample from Glenmark pharma, Mumbai. Croscarmellose Sodium, Sodium starch glycolate and microcrystalline cellulose were obtained from Molychem, Mumbai.Cross-povidone,Mannitol, Lactose, Talc and Magnesium stearate were obtained from S.D. Fine Chemicals. Pvt Ltd, Mumbai, India. All chemicals and solvents used were of analytical grade.

Formulation of mouth dissolving tablets:

Olmesartanmedoxomilmouth dissolving tablets were prepared by the direct compression method using different excipients. Theexcipients used were Micro crystalline cellulose, Mannitol,Croscarmellose Sodium,Sodium starch glycolateand Lactose. Compositions of variousformulations are shown in **Table 01**. All the ingredients of themouth dissolving tablets of Olmesartanmedoxomilwere weighed andmixed in mortar with the help of pestle. Then the blended materialwas slightly compressed on the 8mm flat–biconvex punch using aRimek MINI PRESS-I MT tablet machine. The total weight of the formulation wasmaintained 200mg. The hardness was adjusted to 2-4 kg/cm^2.

Table no. 1. Composition of Olmesartanmedoxomil mouth dissolving tablet

Ingredients (Quantity in mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Olmesartan	20	20	20	20	20	20	20	20	20
SSG	4	6	8	-	-	-	-	-	-
CCS	-	-	-	4	6	8	-	-	-
Cross povidone	-	-	-	-	-	-	4	6	8
Microcrystalline cellulose	50	50	50	50	50	50	50	50	50
Lactose monohydrate	104	102	100	104	102	100	104	102	100
Mannitol	10	10	10	10	10	10	10	10	10
Magnesium stearate	2	2	2	2	2	2	2	2	2
Talc	10	10	10	10	10	10	10	10	10
Total	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**

Evaluation of powder blend

Angle of repose

Angle of repose (θ) was determined using fixed funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the blend. The blends were allowed to flow through the funnel freely onto the surface. The diameter of the blend cone was measured and angle of repose was calculated using the following equation.

$$\theta = \tan{-1}(h/r)$$

Where h and r are the height and radius of the cone.

Bulk Density
Bulk density of the drug was determined by pouring gently 2gm of drug sample through a glass funnel into a 10 ml clean dry graduated measuring cylinder. The volumes occupied by the sample were recorded. Bulk density was calculated

Bulk density (g/ml) = weight of sample in gm/ volume occupied by the sample

Tapped density
Tapped density of the drug was determined by pouring gently 5gm of sample through a glass funnel into a 10ml clean dry graduated measuring cylinder. The cylinder was tapped from height of 2 inches until a constant volume was obtained. Volume occupied by the sample after tapping were recorded and tapped density was calculated.

Tapped density (g/ml) = weight of sample in gm/ volume occupied by the sample

Compressibility index
It is also one of the simple methods to evaluate flow property of a powder by comparing the bulk density and tapped density, useful empirical guide is given by Carr's compressibility.

$$\text{Carr's index} = \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}} \times 100$$

Evaluation of Mouth Dissolving Tablets
The prepared mouth dissolving tablets were evaluated for their physicochemical parameters like weight variation, hardness, thickness, friability and drug content.

In Vitro disintegration time
The disintegration time of the tablets was determined as per Indian Pharmacopoeial monograph using tablet disintegration apparatus[**7]**.

Wetting time
Five circular tissue paper of 10 cm diameter were placed in a Petri dish. 10 ml of simulated saliva pH (pH 6.8 phosphate buffer) was poured into the tissue paper placed in the Petri dish. Few drops of eosin solution were added to the Petri dish. A tablet was placed carefully on the surface of the tissue paper. The time required for the solution to reach upper surface of the tablet was noted as the wetting time**[**8].

In vitro drug release study
The drug release rate from mouth dissolving tablets was studied using the USP type II dissolution test apparatus. The dissolution test was performed using 900 ml of phosphate buffer (pH 6.8) as the dissolution medium at 50 rpm and 37 ± 0.5˚C. 5 ml of aliquots were periodically withdrawn and the sample volume was replaced with an equal volume of fresh dissolution medium. The samples were analyzed spectrophotometrically at 250 nm[9].

Uniformity of drug content
Ten tablets of each formulation were weighed and powdered. A quantity of powder equivalent to 20 mg of Olmesartanmedoxomil was taken. The amount of drug present in a 20 mg equivalent amount of powder was determined by, dissolving the powder mixture in 100 ml of methanol and suitably diluted with methanol and UV absorbance was measured at 248 nm. Drug concentration was determined from standard graph.

Water absorption ratio
A piece of tissue paper folded twice was kept in a petridish (internal diameter 5.5cm) containing 6ml of purified water. The pre-weighed tablet was placed on the tissue paper and allowed to wet completely. The wetted tablet was removed and reweighted. Water absorption ratio, R was determined according to the following equation-

$$R = 100\ (W_a - W_b)/W_b$$

Where W_b and W_a are the weight beforeand after water absorption, respectively[10].

RESULTS AND DISCUSSION

The values of angle of repose were found within the range $28^0.50' - 31^0.87'$ degrees indicating good flow properties. The values of compressibility index were found within the range 18 – 20 %. This indicates passable flow. Weight variation passes the limits as % deviations were within 10 %. The overall precompression study revealed good flow and compression properties of the powder blend. The weight variation was found within 10 % as specified for tablet weight 200mg. Hence the tablet batches have passed the tests for weight variation as per IP limits. Friability was found below 1 % .Hence tablet batches passes the friability test. Hardness was found within the range 3.4 - 3.8 identical to marketed tablets.

Table no. 2. Evaluation of mixed blend of drug and excipients

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Angle of repose (°)	28.5 ± 1.2	28.7 ± 1.1	31.87 ±0.8	31.37 ±1.1	28.78 ±0.8	28.5 ±0.3	30.82 ±0.4	28.5 ±0.7	28.9 ±0.3
Bulk density (gm/cc)	0.878 ±0.023	0.892 ±0.004	0.890 ±0.04	0.884 ±0.013	0.878 ±0..023	0.922 ±0.03	0.95 ±0.026	0.885 ±0.033	0.890 ±0.042
Tapped density (gm/cc)	1.078 ±0.02	1.115 ±0.02	1.105 ±0.03	1.089 ±0.01	1.078 ±0.02	1.054 ±0.03	1.129 ±0.03	1.064 ±0.03	1.085 ±0.02
Carr's index (I)	18.63 ± 0.7	20 ± 0.4	19 ±0.5	18.8 ±0.3	18.63 ±0.5	18.5 ±0.6	18 ±0.3	18.6 ±0.2	18.2 ±0.1

In all formulations F1 – F9, it was observed that an increase in concentration of a superdisintegrant tends to higher water absorption ratio and least wetting time. Disintegration time was inversely proportional to the concentration of superdisintegrants in cases of croscarmelose sodium and crospovidone but in case of sodium starch glycolate, as the concentration of superdisintegrant increases the disintegration time was also increased. Formulation F8 has shown good results in disintegration time, wetting time and water absorption ratio and drug release of 99.78 % in 60 minutes. Formulation F4 has shown better results in disintegration time, least wetting time and higher water absorptionratio and drug release of 98 % within 3 minutes. Formulation F9 has shown excellent results in water absorption ratio. The disintegration time and wetting time was found to be least for F9 formulation and the drug release of 98.38 % in 3 minutes. Hence F8 batch containing 8% cross povidone was found to be an optimized batch.

Table no. 3. Evaluation of Olmesartanmedoxomilmouth dissolving tablet

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Hardness (kg/cm^2)	3.6 ±0.3	3.8 ±0.3	3.6 ±0.2	3.8 ±0.33	3.4 ±0.23	3.8 ±0.3	3.4 ±0.3	3.8 ±0.2	3.8 ±0.1
Thickness (mm)	2.48 ±0.03	2.40 ±0.01	2.38 ±0.02	2.28 ±0.04	2.36 ±0.02	2.38 ±0.02	2.35 ±0.03	2.48 ±0.02	2.31 ±0.02
Diameter (mm)	8.04 ±0.02	8.08 ±0.02	8.07 ±0.03	8.13 ±0.03	8.10 ±0.01	8.13 ±0.03	8.20 ±0.02	8.20 ±0.02	8.10 ±0.02
Friability %	0.89 ±0.02	0.88 ±0.01	0.81 ±0.03	0.68 ±0.04	0.79 ±0.03	0.85 ±0.03	0.88 ±0.03	0.78 ±0.05	0.54 ±0.02
Weight variation	1.34 ±0.5	3.54 ±0.6	3.65 ±0.3	2.34 ±0.8	2.68 ±0.7	2.96 ±0.4	3.6 ±0.5	3.3 ±0.4	3.2 ±0.6
Disintegration time (sec)	34 ±2	30 ±1	28 ±1	30 ±2	32 ±3	40 ±2	40 ±2	38 ±3	27 ±0.3
Wetting time (sec)	38 ± 2	36 ±2	35 ±1	38 ±1	38 ±2	32 ±1	39 ±1	38 ±1	29 ±1
Water Absorption Ratio (%)	60 ±1.33	70.66 ±0.9	86.66±2.6	57.89±3.3	58 ±3.3	60.18 ±2.3	72 ±0.7	80 ±1.3	88.22 ±2.2
Assay (%)	95.08 ±1.34	105 ±2.32	101 ±2.2	99.16 ±1.5	97.50 ±2.4	103.33 ±1.7	105.83 ±2.6	105.83 ±2.4	102.25±1.8

Table no. 4. *In-vitro* dissolution study

Sr no	Time(min)	% drug release								
		Formulation								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	2	11.22	6.59	17.29	42.63	23.58	21.83	35.93	55.07	40.12
2	5	25.02	13.07	27.90	64.25	38.51	30.68	51.07	61.78	61.54
3	10	32.74	20.80	42.73	71.46	49.42	44.07	64.25	71.25	68.35
4	15	40.05	27.28	53.64	73.62	54.06	49.83	79.59	88.97	71.89
5	20	43.24	32.84	70.02	75.27	56.73	50.97	82.58	90.72	73.63
6	30	49.94	37.79	78.46	75.68	57.15	56.12	86.49	89.69	76.21
7	40	53.64	39.85	82.48	80.42	59.78	57.56	88.55	91.23	81.36
8	50	55.40	42.42	85.77	85.98	68.89	67.55	89.02	97.41	84.64
9	60	64.56	62.91	92.88	91.64	76.81	89.80	91.75	99.78	90.84

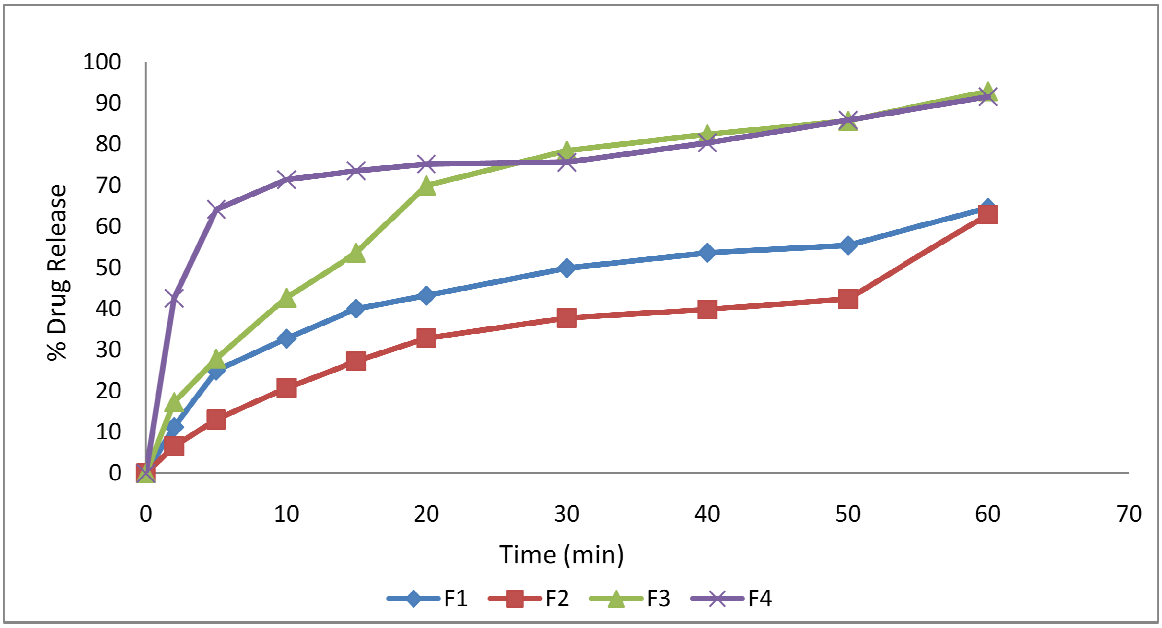

Fig no.01. Dissolution profile of batch F1-F4

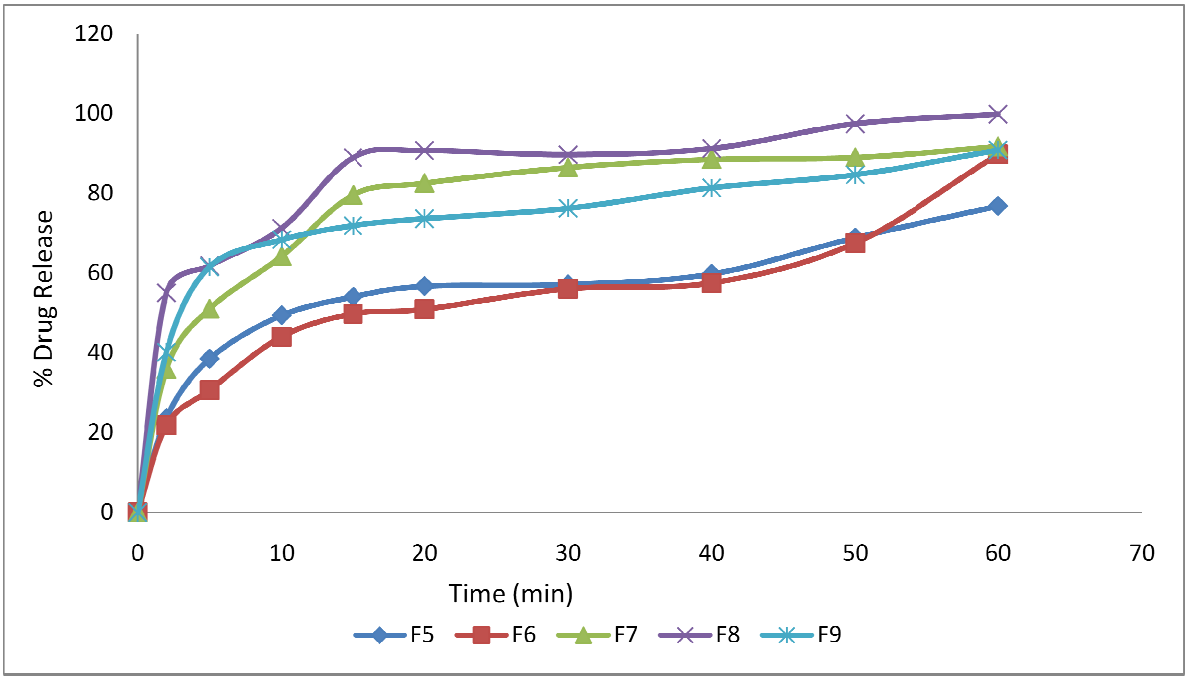

Fig no. 02. Dissolution profile of batch F5-F9

CONCLUSION

In present study, the mouth dissolving tablet of Olmesartanmedoxomil, an antihypertensive drug was formulated with an objective to improve patient compliance and achieve rapid onset of action. Three different superdisintegrantscroscarmellose sodium, sodium starch glycolate and Cross-povidone were used in formulations. Formulation F8 containing 8% cross-povidone has shown the best results for disintegration time of 27 seconds. The disintegration time is less than the marketed mouth dissolving tablet. *In-vitro* dissolution study showed 98.38 % of drug release at the end of 3 minutes. The overall results of F8 formulation were excellent. Hence formulation F8 was

concluded as an optimized formulation. Thus mouth dissolving tablets of Olmesartan can be synthesized and can have good patient compliance.

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