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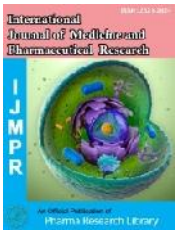

Research Article **Open Access**

Solubility and Dissolution Rate Enhancement of Olmesartan Medoxomil by Hydrotropy and Development of Oral Disintegrating Tablets

Angilicam Avinash*, Avula Sushma, Koneti Lalasa, Siddabathina Prasanth Kumar, Thumati Gowthami, Dr. M. Sreenivasulu

Narayana Pharmacy College, Chinthareddypalem, Nellore, Andhra Pradesh, India-524003.

A B S T R A C T

This research work was designed to enrich the solubility of olmesartan medoxomil by Hydrotropy technique and to develop the oral disintegrating tablets. Olmesartan medoxomil is an anti-hypertensive drug which belongs to BCS Class II having low solubility and therefore low oral bioavailability (26%). In the present study, HMs of olmesartan medoxomil with water soluble carriers like sodium acetate, sodium benzoate and urea were prepared by solvent evaporation method in different weight ratios and the optimized Hydrotropic mixture (HM) was used in the development of olmesartan medoxomil oral disintegrating tablets. HMs was evaluated for drug content and *in vitro* dissolution studies. The results revealed that the dissolution of olmesartan medoxomil HMs was improved greatly for F6 when compared with that of remaining formulations which shows 99.38% of drug release within 60 minutes. The above optimized HM was formulated as oral disintegrating tablets by direct compression using superdisintegrants like Croscarmellose sodium (CCS), (ODT1-ODT3), and sodium starch glycolate (SSG), (ODT4-ODT6). Olmesartan medoxomil oral disintegrating tablets were evaluated for pre-compression and post compression parameters. Amongst the formulations prepared (ODT1-ODT6), ODT6 was found to be effective formulation comprising of SSG which showed the drug release of 96.31% within 12 min.

Keywords: Bioavailability, croscarmellose sodium, Hydrotropy, Olmesartan medoxomil, Oral disintegrating tablets, Sodium starch glycolate, Solubility.

A R T I C L E I N F O

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***Corresponding Author**
Angilicam Avinash
Assistant Professor, Dept. of Pharmaceutics,
Narayana Pharmacy College, SPSR Nellore,
Andhra Pradesh, India-524003.
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1. Introduction

About 45% of new chemical entities coming from the discovery are poorly bioavailable. For a better oral bioavailability drug must be soluble in gastro-intestinal fluids that is, drug should be soluble in an aqueous medium and also possess permeability properties for good membrane diffusion in order to reach the bloodstream [1]. The rate of absorption and bioavailability of poorly water soluble drugs is often controlled by the rate of dissolution of the drug in the gastrointestinal tract. Many technological methods of enhancing the dissolution characteristics of slightly water-soluble drugs have been reported in various literatures [2]. These include reducing particle size to increase surface area, solubilization in surfactant systems, formation of water-soluble complexes, use of pro-drug, drug derivatization and manipulation of solid state of drug substance to improve drug dissolution, i.e. by decreasing crystallinity of drug substance [3, 4]. Hydrotropy is a solubilization process where addition of a large amount of second solute exerts an increase in the aqueous solubility of another solute [5, 6].

Hydrotropic solubilization technique is a promising approach with great potential for poorly soluble drugs. In this method, chemical modification of the drug, use of organic solvents and preparation of emulsion systems is not required [7, 8].Olmesartan medoxomil is a prodrug ester. In vivo it is completely and rapidly de-esterified to active metabolite olmesartan via an enzyme, arylesterase. Olmesartan medoxomil belongs to BCS class II [9]. Olmesartan is a specific angiotensin II type I antagonist used alone or with other antihypertensive agents to treat hypertension. Olmesartan has poor aqueous solubility and low bioavailability of 26%with a terminal half-life of approximately 13 hours.

Olmesartan medoxomil exhibits very slight solubility 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 [10]. Present study initially attempts to enhance the solubility of *olmesartan medoxomil* by hydrotropy technique using sodium acetate, sodium benzoate and urea as carriers in different ratios. Using optimized HMs oral disintegrating tablets were formulated.

2. Materials and Methods

Materials

Olmesartan medoxomil (A to Z Pharma Pvt. Ltd. Chennai), SSG (HiMedia Pvt. Ltd. Mumbai), Sodium acetate, Sodium benzoate, Urea,CCS, Citric acid, Magnesium stearate (Sd fine chemicals Ltd., Mumbai), Mannitol, Potassium dihydrogen phosphate, di-sodium hydrogen phosphate, Sodium chloride (Merck Pvt. Ltd., Mumbai.) and Talc (Otto chemicals, Mumbai).

Preparation of Olmesartan medoxomil Hydrotropy mixture: Hydrotropic Mixture containing drug and hydrotropic blend in different ratios were prepared by solvent evaporation technique. Minimum quantity of distilled water contained in a 250 ml beaker was used to dissolve the hydrotropic blend in different ratios at 90-100^{0}C. Then drug was added to this solution and stirred using magnetic stirrer, maintaining the temperature of 80-90^{o}C. Stirring was continued until semisolid mass was obtained. Then semisolid mass was dried on watch glass after almost complete drying, the powder of Hydrotropic Mixtureis passed through sieve and stored in air-tight glass bottles [11].

Evaluation of Olmesartan medoxomil Hydrotropy mixture [12]

Prepared Hydrotropy mixtures were evaluated for the following parameters:

- Percentage yield
- Drug content
- *In vitro* dissolution studies

Percentage yield

Percentage yield was calculated to know about efficiency of any method and it help in selection of appropriate method of production. The final weights of the prepared Hydrotropy mixture were taken and percentage yield was calculated by using the given formula. The results were shown in Table 7-9.

$$\%\text{yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

Drug content

Equivalent weight of prepared Hydrotropy mixture containing 100 mg drug were taken and transferred into 100 ml Standard flask Then take 1 ml from above solution and diluted up to 10 ml simulated salivary fluidp^H 6.8 and repeat the same again by take 1 ml from above solution and diluted up to 10 ml simulated salivary fluidp^H 6.8. The resulting solutions were filtered through a 0.45µ membrane filter and diluted accordingly. The absorbance of the solutions was measured at 256 nm. Percentage of drug content was calculated by using the given formula. The results were shown in Table 10-12.

$$\%\ \text{Drug content} = \frac{\text{Observed value}}{\text{Actual value}} \times 100$$

***In vitro* dissolution studies**

In vitro dissolution studies of pure Olmesartan medoxomil and Hydrotropy mixture were conducted with the USP type II apparatus (paddle type). The dissolution studies were performed using 900 ml simulated salivary fluid of p^H 6.8as dissolution medium at 37±1.0°C with 50 rpm speed. Samples of each preparation equivalent to 100 mg of drug were added into the dissolution medium. The sample of 2 ml aliquots were withdrawn periodically (15, 30, 45 and 60 min) and filtered through 0.45µ membrane filter. The withdrawn sample was replaced every time with same quantity of fresh dissolution medium. The filtered solutions were diluted suitably and the samples were analyzed for their drug content by using UV spectrophotometer at wavelength of 256 nm. Percentage of drug dissolved at

various time intervals was calculated by plotting time on X-axis against percent cumulative drug release on Y-axis. The results were shown in Table 13 and Figure 1.

Preparation of Olmesartan medoxomil oral disintegrating tablets: Olmesartan medoxomil oral disintegrating tablets were prepared by direct compression method using Olmesartan medoxomil optimized HMs prepared by solvent evaporation technique. The amount of complex equivalent to 20 mg of Olmesartan medoxomil per tablet were taken and mixed with directly compressible diluents and superdisintegrants in a mortar with the help of pestle. The blend was then compressed using 8 mm round faced punch by using tablet punching machine [13]. The total weight of tablet was 220 mg. The formula which included variable amounts of all excipients are shown in the Table 2.

Pre compression studies [14]

The powder blend was subjected for the following studies

- Angle of repose
- Bulk density
- Tapped density
- Carr's index
- Hausner's ratio

Angle of repose

The angle of repose of powders was determined by the funnel method. Accurately weighed powders were taken in a funnel. 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 powders. The powders were allowed to pass through the funnel freely onto the surface. The diameter and height of the powder cone was measured and angle of repose was calculated by using the given formula. The effect of angle of repose on flow property of powders was listed in Table 3 and the results were tabulated in Table 14.

$$\tan\theta = \frac{h}{r}$$

Where,

h = height of the powder cone

r = radius of the powder cone

Bulk density and tapped density:

A quantity of 5.5gms of powder from each formula was introduced into a 100 ml measuring cylinder. After the initial volume was observed, the cylinder was tapped continuously until no further change in volume was observed. Then bulk density (BD) and tapped density (TD) were calculated by using the given formula and the results were tabulated in Table 14.

$$BD = \frac{\text{Weight of the powder}}{\text{Initial volume}}$$

$$TD = \frac{\text{Weight of the powder}}{\text{Tapped volume}}$$

Carr's index:

The Compressibility of the powder blend was determined by Carr's compressibility index. It is indirectly related to the relative flow rate, cohesiveness and particle size. It is a simple test to evaluate the bulk density and tapped density of a powder and the rate at which it is packed. The effect of carr's index on flow property of powders was listed in Table 4. The formula for carr's Index is given below and the results were tabulated in Table 14.

$$\text{Carr}'\text{s index } (\%) = \frac{TD - BD}{TD} \times 100$$

Hausner's ratio:

The Hausner's ratio is a number that is correlated to the flow ability of a powder or granular material. It is calculated by using the given formula and the effect of hausner's ratio on flow property of powders was listed in Table 5. The results were tabulated in Table 14.

$$\text{Hausner}'\text{s ratio} = \frac{TD}{BD}$$

Post compression studies [16]

Thickness:

Tablet thickness can be measured using digital vernier calipers. 3 tablets were taken and their thickness was measured and the average thickness for each tablet was calculated. The results were tabulated in Table 15.

Hardness:

It is the force required to break a tablet by compression in the radial direction, it is an important parameter in formulation of mouth dissolve tablets because excessive crushing strength significantly reduces the disintegration time. In the present study the crushing strength of the tablet was measured using monsanto hardness tester. An average of three observations is reported. The results were tabulated in Table 15.

Friability test

Friability of the tablets was determined using Roche friability. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Pre-weighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. Conventional tablets that lose less than 1% of their weight are acceptable. The results were tabulated in Table 15.

$$\%\text{Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Weight variation

The weight variation test is done by weighing 10 tablets individually, calculating average weight and comparing the individual tablet weights to the average. The tablets meet the USP test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit. The results were tabulated in Table 15.

$$\%\text{ Weight variation} = \frac{\text{Average weight} - \text{Initial weight}}{\text{Average weight}} \times 100$$

Evaluation of Olmesartan medoxomiloral disintegrating tablets: Disintegration test

It is time taken by the tablet to breakup into smaller particles. The disintegration test is carried out in an apparatus containing a basket rack assembly with six glass tubes with the bottom containing a 10 mesh sieve. The basket is set a frequency of 28-32 cycles per minute in a medium of 900 ml which is maintained at 37 ± 2° C. The tablets were placed in the tubes and the time required per complete passage of tablet particles through 10 mesh sieve was considered as disintegration time of tablet [17]. The results were tabulated in Table 16.

Wetting time

Five circular tissue papers of 10 cm diameter are placed in a petri dish with a 10 cm diameter. Ten millimeters of simulated salivary fluid of p^H 6.8 containing 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. Three tablets from each formulation were selected randomly and the average wetting time was determined [18]. The results were tabulated in Table 16.

Water absorption ratio

A piece of tissue paper folded twice was placed in a small petri dish containing 6 ml of simulated salivary fluid of p^H 6.8. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio (R), was determined using following equation,

$$R = \frac{W_a - W_b}{W_b} \times 100$$

Where,

W_b is weight of tablet before water absorption

W_a is weight of tablet after water absorption.

Three tablets from each formulation were selected randomly and the average water absorption ratio was determined [19].The results were tabulated in Table 16.

Drug content

Five tablets were taken and powdered; the powder equivalent to 8 mg of Olmesartan medoxomil was dissolved in 100 ml of simulated salivary fluid of p^H 6.8, filtered, diluted suitably to 10 mcg/ml concentration and analyzed at 256 nm using UV-Visible spectrophotometer [18]. The results were tabulated in Table 16.

***In vitro* dissolution studies**

In vitro dissolution studies of Olmesartan medoxomil oral disintegrating tablets were conducted with the USP type II apparatus. The dissolution studies were performed using 900 ml simulated salivary fluid of p^H 6.8as dissolution medium at 37±1.0°C with 50 rpm speed. A tablet of each formulation containing 20 mg of drug was added into the dissolution medium. The sample of 5 ml aliquots were withdrawn periodically (2, 4, 6, 8, 10 and 12 min) and filtered. The withdrawn sample was replaced every time with same quantity of fresh dissolution medium. The filtered solutions were diluted and analyzed for their drug release by using UV spectrophotometer at wavelength of 256 nm. Percentage of drug dissolved was calculated by plotting time on X- axis against percent cumulative drug release on Y-axis [20].The results were tabulated in Table 17 and Figure 2.

3. Results and Discussion

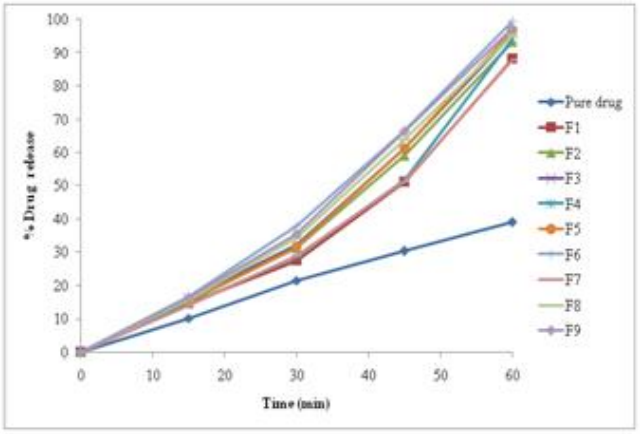

Figure 1: Comparative dissolution profile of Olmesartan medoxomil and Olmesartan medoxomil HMs containing Sodium acetate, Sodium benzoate and Urea in different ratios.

Olmesartan medoxomil hydrotropic mixtures were prepared by solvent evaporation method using Sodium acetate, Sodium benzoate and Urea as carriers in different ratios. *In vitro* dissolution profiles of Olmesartan medoxomil hydrotropic mixtures were compared with that of the pure Olmesartan medoxomil. All the formulations *viz.* F1-F9 has shown increased cumulative dissolution profiles are shown in Table 13 and Figure 1.

In addition, employing solvent evaporation technique in the preparation of Olmesartan medoxomil hydrotropic mixtures would have reduced the particle size of the drug; there by facilitating faster dissolution rate, this may be due to deposition of the drug on the surface of an inert carrier. From the results, it was revealed that the enhancement in the dissolution rate of HMs occurs due to higher amorphousness nature, ability to reduce the particle size and improved wettability of the inert carrier.

Evaluation of Olmesartan medoxomil oral disintegrating tablets

Precompression parameters:

The bulk density of all formulations, powder blend containing excipients was found to be in the range of 0.505 to 0.674 gm/ml, whereas the tapped density was observed between 0.641 to 0.724 gm/ml. From the values of bulk density and tapped density the values for compressibility index and hausner's ratio were calculated. The values for compressibility index were found between 11.61 to 15.88 %. The values for hausner's ratio were found in between 1.03 to 1.17. All these values are within the specified limit which indicates good flow properties. Angle of repose was found to be less than 30 which indicate good flow of powder. Overall these values indicate good flow properties of powder blend, uniform die fill and better compression ability.

Postcompression parameters:

Hardness test for all formulations was carried out and observations obtained were in the range of 4.66 to 5.63 kg/cm^2. Hardness for all formulations was observed to be

proper, which signify that crushing strength of all formulations was maintained after direct compression. The thickness of all formulations was found to be uniform as it was obtained in the range of 2.47 to 2.66 mm. Friability test was conducted for all formulations, all formulations indicated that % loss was less than 1%, which showed the I.P specification and reveals that all formulations have possessed good physical strength and can withstand the mechanical shocks that can be observed during handling, shipping and transportation. The % weight variation of all formulations was found to be in the range of less than ± 7.5, which complies with USP specification and signifies that there is uniformity in flow of powder blend which leads to uniform die fill. Disintegration time for all formulations was found to be in the range of 25 to 55 sec. wetting time of tablets are found in the range of 44 to 98 sec. and the water absorption ratio was found in the range of 84.42 to 97.88 %. As the porosity of formulation is increased by the super disintegrating agents and water uptake is increased due to increased capillary action, the formulation is showing less wetting time. The less wetting time helps in the quick dispersion of the formulation. When come in contact with the saliva. Disintegration study states that there was decrease in disintegration time with successive increase in concentration of superdisintegrants. Drug content of all formulations was observed between 96.50 to 99.73%. Drug content for all formulations showed uniformity which indicated that there was uniform flow and uniform distribution of drug.

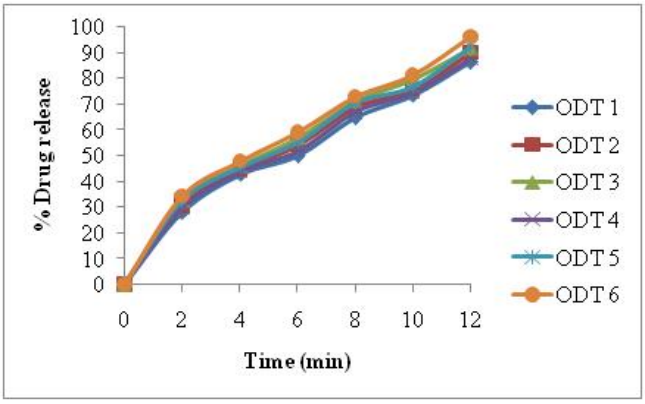

Figure 2: Comparative dissolution profile of Olmesartan medoxomil oral disintegrating tablets

Table 1: Composition of Hydrotropy mixtures of Olmesartan medoxomil

S. No.	Ingredients (gms)	Formulation code								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Olmesartan medoxomil	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
2.	Sodium acetate	1	1	2	1	1	2	–	–	–
3.	Sodium benzoate	1	2	1	–	–	–	1	1	2
4.	Urea	–	–	–	1	2	1	1	2	1
5.	Solvent (Water) (ml)	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.

Table 2: Preparation of Olmesartan medoxomil oral disintegrating tablets

Ingredients (mg)	ODT1	ODT2	ODT3	ODT4	ODT5	ODT6
OM HM complex	Equivalent to 20 mg of OM	Equivalent to 20 mg of OM	Equivalent to 20 mg of OM	Equivalent to 20 mg of OM	Equivalent to 20 mg of OM	Equivalent to 20 mg of OM
CCS	3	6	12	–	–	–
SSG	–	–	–	3	6	12
Mannitol	50.94	47.94	41.94	50.94	47.94	41.94
Citric acid	4	4	4	4	4	4
Magnesium Stearate	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5
Total weight	200	200	200	200	200	200

Table 3: Effect of angle of repose on flow property of powders

Angle of repose	Type of flow of powder
< 25	Excellent
25-30	Good
30-40	Passable
> 40	Very poor

Table 4: Effect of carr's index on flow property of powders

Carr's index	Flow
5-15	Excellent

12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
> 40	Very very poor

Table 5: Effect of hausner's ratio on flow property of powders [15]

Hausner's ratio	Flow property
1.00-1.11	Excellent
1.12-1.18	Good
1.19-1.25	Fair
1.26-1.34	Passable
1.35-1.45	Poor
1.46-1.59	Very poor
>1.60	Very very poor

Table 6: Weight variation tolerances for uncoated tablets

Average weight of tablets (mg)	Max. percentage difference allowed
130 or less	10
130-324	7.5
More than 324	5

Table 7: % Practical yield of Olmesartan medoxomil HMs containing Sodium acetate and Sodium benzoate in different ratios

S. No.	Formulation code	% Yield
1	F1	98.8
2	F2	97.42
3	F3	96

Table 8: % Practical yield of Olmesartan medoxomil HMs containing Sodium acetate and Urea in different ratios

S. No.	Formulation code	% Yield
1	F4	92.4
2	F5	88.57
3	F6	98.57

Table 9: % Practical yield of Olmesartan medoxomil HMs containing Sodium benzoate and Urea in different ratios

S. No.	Formulation code	% Yield
1	F7	86.8
2	F8	92.28
3	F9	91.14

Table 10: % Drug content of Olmesartan medoxomil HMs containing Sodium acetate and Sodium benzoate in different ratios

S. No.	Formulation code	% Drug content
1.	F1	97.44
2.	F2	96.76
3.	F3	97.27

Table 11:% Drug content of Olmesartan medoxomil HMs containing Sodium acetate and Urea in different ratios

S. No.	Formulation code	% Drug content
1.	F4	97.75
2.	F5	95.74
3.	F6	92.34

Table 12: % Drug content of Olmesartan medoxomil HMs containing Sodium benzoate and Urea in different ratios

S. No.	Formulation code	% Drug content
1.	F7	98.97
2.	F8	92.85
3.	F9	90.47

Table 13: Comparative dissolution data of Olmesartan medoxomil and Olmesartan medoxomil HM containing Sodium acetate, Sodium benzoate and Urea in different ratios

S. No.	Time (min)	% Cumulative drug release									
		Pure	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	15	10.15	14.56	15.05	16.15	14.32	15.29	16.64	14.07	15.78	16.40
2	30	21.41	27.53	31.33	32.19	28.64	31.70	37.82	28.88	34.39	35.37
3	45	30.35	51.04	58.99	61.30	51.77	61.32	66.70	51.28	64.01	66.21
4	60	39.04	88.24	93.26	95.70	94.14	96.81	**99.38**	87.88	95.34	97.42

Table 14: Physical parameters of powder blend

S.No	Formulation code	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio	Angle of repose (^{0})
1	ODT1	0.520	0.641	11.99	1.12	27.58
2	ODT 2	0.537	0.704	13.72	1.11	27.10
3	ODT 3	0.561	0.675	15.88	1.03	27.13
4	ODT 4	0.674	0.724	12.71	1.07	27.30
5	ODT 5	0.505	0.694	12.20	1.13	26.66
6	ODT 6	0.515	0.657	11.61	1.17	26.06

Table 15: Physical parameters of Olmesartan medoxomil oral disintegrating tablets

S.No	Formulation code	Hardness (Kg/cm^2)	Thickness (mm)	% Friability	% Weight variation
1	ODT1	5.33	2.50	0.61	5.148
2	ODT 2	5.25	2.66	0.66	4.102
3	ODT 3	5.63	2.47	0.81	5.153
4	ODT 4	4.66	2.49	0.71	4.102
5	ODT 5	5.20	2.75	0.91	4.324
6	ODT 6	5.50	2.55	0.51	5.454

Table 16: Evaluation tests of Olmesartan medoxomil oral disintegrating tablets

S.No	Formulation code	Disintegration time (sec)	Wetting time (sec)	Water absorption ratio (%)	% Drug content
1	ODT1	43	86	61.22	97.03
2	ODT 2	37	60	68.25	99.05
3	ODT 3	25	44	74.68	96.76
4	ODT 4	55	98	61.70	96.50
5	ODT 5	46	67	61.22	97.30
6	ODT 6	30	53	69.84	99.73

Table 17: Comparative dissolution data of Olmesartan medoxomil oral disintegrating tablets

S. No.	Time (min)	% Cumulative drug release					
		Formulation containing CCS			Formulation containing SSG		
		ODT 1	ODT 2	ODT3	ODT 4	ODT 5	ODT 6
1	2	28.34	30.80	32.94	29.95	32.48	34.33
2	4	42.85	44.70	46.31	44.00	45.62	48.15
3	6	50.00	54.37	57.14	52.07	55.52	59.21

4	8	64.74	68.89	71.19	67.05	70.70	73.04
5	10	73.50	75.80	79.49	74.65	76.95	81.33
6	12	86.40	90.09	91.70	87.78	92.39	**96.31**

4. Conclusion

Olmesartan medoxomil solubility was enhanced by the hydrotropy technique using sodium acetate, sodium benzoate and urea as carriers. Amongst the formulations prepared (F1-F9), F6 formulation containing Olmesartan medoxomil and sodium acetate and urea in 2:1ratio was considered as optimized formulation in which percentage drug release was found to be 99.38% within 60 minutes in comparison with that of the pure drug dissolution of 39.04% only within 60 minutes. This effect may be due to fine particle size of Olmesartan medoxomil adsorbed over carrier resulting in a higher surface area of drug exposed to the dissolution media and improved wettability of the drug particles which contribute to high drug dissolution rate. Using optimized Olmesartan medoxomil HM, oral disintegrating tablets of Olmesartan medoxomil were successfully prepared by using direct compression method. The results of experimental studies revealed that the powder blend of Olmesartan medoxomil showed good flow properties, post compression parameters were within acceptable limits. Amongst the formulations prepared (ODT1-ODT6), ODT6 was found to be effective formulation comprising of SSG (12 mg); which shows the drug release of 96.31% within 12min.

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