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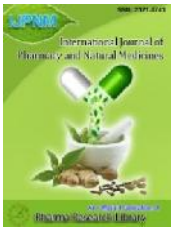

Research Article **Open Access**

Formulation and *In-vitro* Evaluation of Olmesartan Medoxomil Solid Dispersions

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A B S T R A C T

The main objective of the current research was to improve the dissolution rate and solubility of an antihypertensive drug Olmesartan Medoxomil (OM) using cyclodextrin inclusion complexation and followed by converting to orally administerable tablets using a super disintegrants. OM is a BCS Class II drug having low solubility and high permeability. Inclusion complexes of OM were prepared by solvent evaporation method at the ratio of 1:1, 1:3 and 1:5 using different cyclodextrins such as α-cyclodextrin (α-CD), β-cyclodextrin (β-CD), Hydroxy Propyl β-cyclodextrin (HP-β-CD), Methylated β-cyclodextrin (M-β-CD) and γ-Cyclodextrin (γCD). Prepared inclusion complexes were characterized for their solubility and in vitro drug release. It was observed that formulations prepared with M-β-CD at 1:5 ratio (OCD12) has shown faster drug release and higher solubility than other formulations. Hence, this formulation was converted to oral tablet using different superdisintegrants like sodium starch glycollate, crosscaramellose sodium and soluplus. Tablets were prepared by direct compression method. From in vitro dissolution study of tablets, it was observed that the tablet formulation prepared with soluplus has shown faster drug release than marketed formulation and pure drug formulation. Hence, it can be concluded that the cyclodextrin inclusion complexation and further conversion to tablet using superdisintegrants is a good technique to improve the dissolution rate and solubility of poorly soluble BCS Class II drug such as OM.

Keywords: Olmesartan medoximil, Cyclodextrins, complexation, Methylated β-cyclodextrin

A R T I C L E I N F O

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1. Introduction

Dissolution is the rate limiting step in case of poorly soluble class-II drugs in the process of drug absorption by oral route, to improve oral bioavailability of these drugs various techniques is becoming a challenge for the scientists among the various methods solid dispersion technologies are more industrially accepted methods. Hence these were experimental in the present investigation. Olmesartan medoxomil is a selective AT1 subtype angiotensin II receptor antagonist that is approved for treatment for hypertension. Olmesartan medoxomil is preferred over other antihypertensive drugs in diabetic patients where they slow the progression of nephropathy. Olmesartan medoxomil belongs to BCS class II. It is practically insoluble in water and has oral bioavailability of 26%. The unabsorbed drug may cause gastrointestinal side effects such as abdominal pain, dyspepsia, gastroenteritis, and nausea. The aim of this study was to investigate the possibility of improving the release of Olmesartan medoxomil through Solid dispersions.

2. Materials and method

Olmesartan medoxomil, α-Cyclodextrin, β-Cyclodextrin, Hydroxy Propyl β-Cyclodextrin, Methyl β-Cyclodextrin, γ-Cyclodextrin chemicals were Laboratory grade made of SD Fine chemicals Pvt.Ltd

Formulation of Cyclodextrin Inclusion Complexes.

Cyclodextrin inclusion complexes of each drug was prepared by using different grades of cyclodextrins such as α-cyclodextrin (α-CD), β-cyclodextrin (β-CD), Hydroxy Propyl β-cyclodextrin (HP-β-CD), Randomly Methylated β-cyclodextrin (M-β-CD) and γ-cyclodextrin (γ-CD) in different ratios such as 1:1,1:3 &1:5. All the complexes were prepared by solvent evaporation method. (Sanjay KD *et al*., 2002; Sruti J *et al*., 2012).

Solvent Evaporation Method:

Required quantity of each drug was taken and dissolved in sufficient quantity of methanol. To the drug solution, required quantity of carrier was added. This solution was taken in to round bottom flask, attached to the rotary flash evaporator and evaporated at 50°C, rpm was maintained at 60 for 15 min. Solid dispersions were obtained, collected and dried in the desiccator till it was completely dried.

Evaluation of prepared tablets

The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability, *In-vitro* release and drug content

3. Results and Discussion

UV Visible Spectroscopic method to estimate Olmesartan Medoxomil from *in vitro* samples

Calibration curve of Olmesartan Medoxomil was plotted by using UV visible spectroscopic method at 257nm. Linearity was observed between 5-30µg/mL. Absorbance values obtained are given in table 2 and calibration curve plotted is shown in figure 1. Regression equation obtained was used to estimate the Olmesartan Medoxomil from in vitro samples.

Preformulation Studies of Pure Drug

Micromeritic properties of Olmesartan Medoxomil obtained are given in table 2. It was observed from the results that the drug is having poor flow characteristics. The angle of repose value was found to be $45^0 50'' \pm 12''$ indicates poor flow of powder. Hence the flow character has to be enhanced in the formulation.

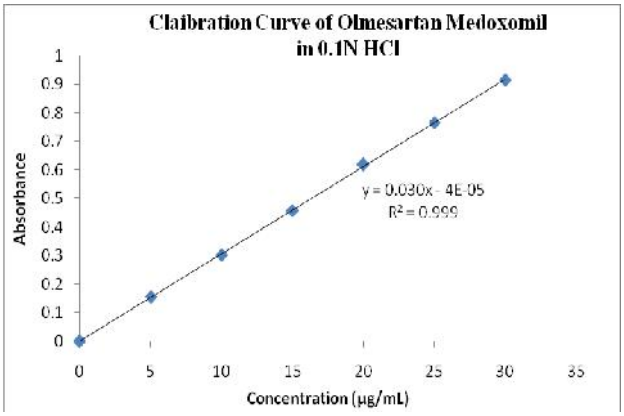

Figure 1: Calibration curve of Olmesartan Medoximol

Characterization of Olmesartan Medoxomil Inclusion Complexes

Micromeritic evaluation: The prepared formulations were characterized for their micromeritic properties. Results are tabulated in table no 3. It was observed that flow property was improved with all the formulations compared to pure drug.

Dissolution studies of Olmesartan Medoxomil Cyclodextrin Complexes

Dissolution studies were conducted for all the prepared formulations in 0.1N HCL using USP dissolution test apparatus (Apparatus 1, 100 rpm, and 37^0C). Each formulation was tested in triplicate. % Drug release values at various time intervals were calculated and results obtained are shown in Tables 5. Graphs were plotted for each carrier (Fig.2 to 7) by taking % drug release on Y-Axis and time on X-Axis. Out of all the formulations, OCD12 has shown greater drug release than the remaining carriers. This might be due to the greater solubility of the drug in the carrier and hence chosen for tablets preparation.

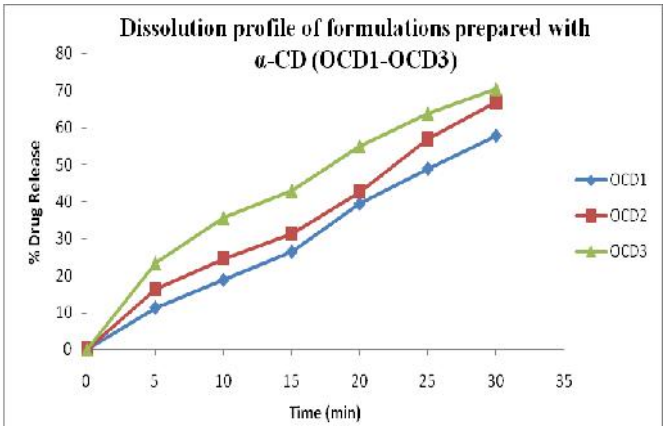

Figure 2: Dissolution profile of formulations prepared with α-CD (OCD1-OCD3)

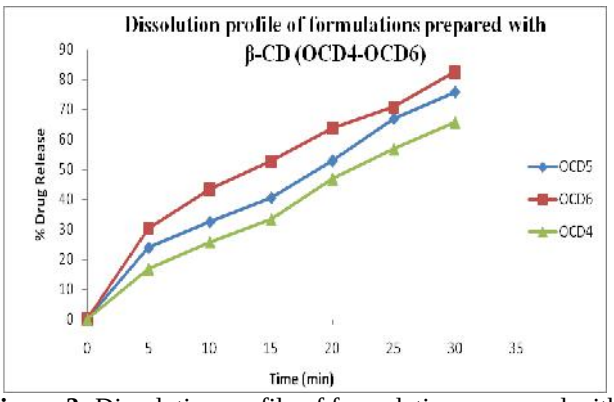

Figure 3: Dissolution profile of formulations prepared with β-CD (OCD4-OCD6)

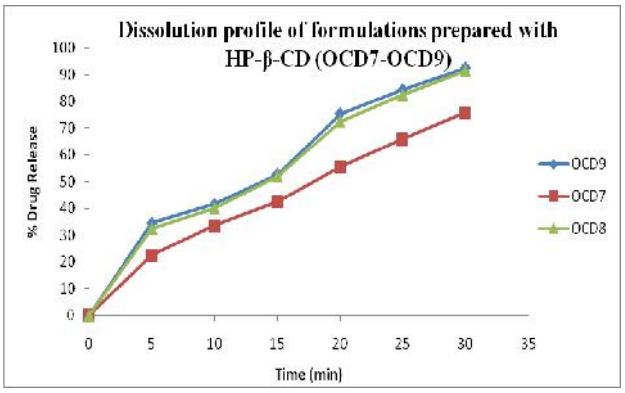

Figure 4: Dissolution profile of formulations prepared with HP-β-CD (OCD7-OCD9)

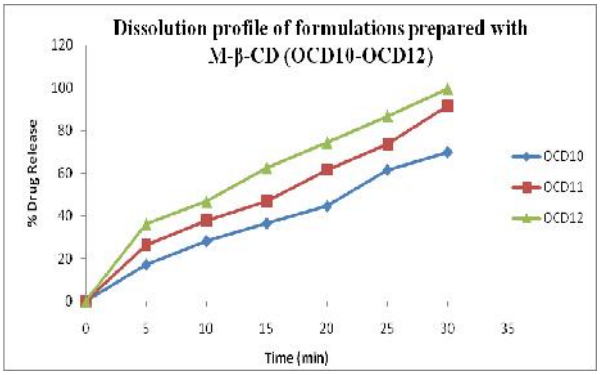

Figure 5: Dissolution profile of formulations prepared with M-β-CD (OCD10-OCD12)

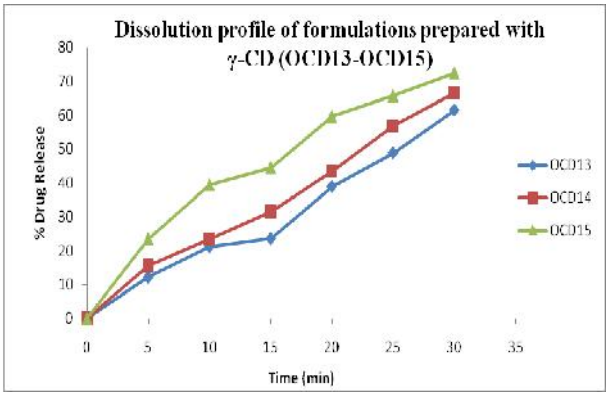

Figure 6: Dissolution profile of formulations prepared with γ-CD (OCD13-OCD15)

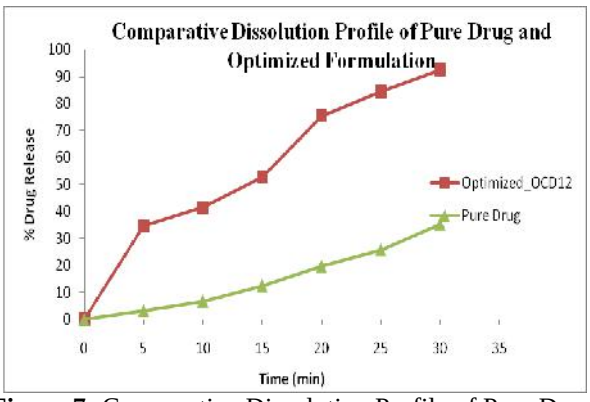

Figure 7: Comparative Dissolution Profile of Pure Drug and Optimized Formulation

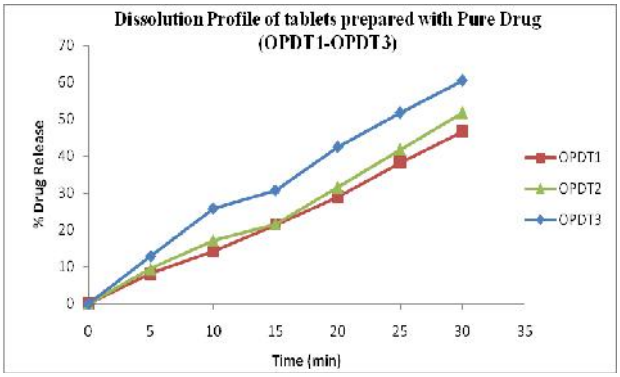

Figure 8: Dissolution Profile of tablets prepared with Pure Drug (OPDT1-OPDT3)

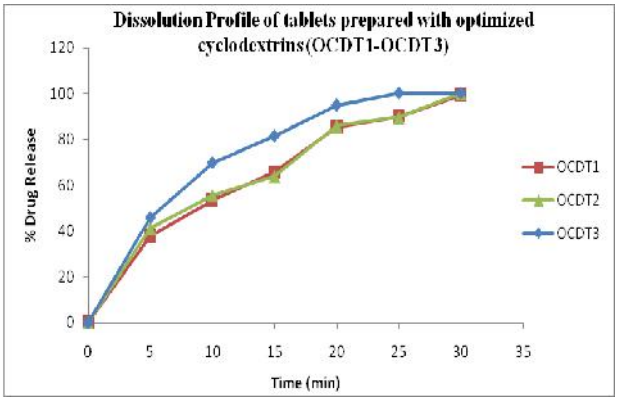

Figure 9: Dissolution Profile of tablets prepared with optimized cyclodextrins (OCDT1-OCDT3)

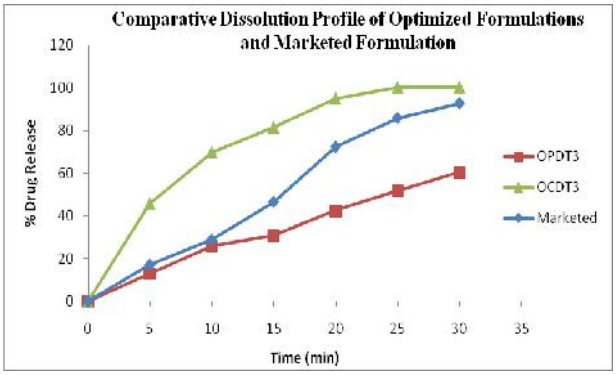

Figure 10: Comparative Dissolution Profile of Optimized Formulations and Marketed Formulation

Table 1: Compositions of Cyclodextrin Inclusion Complexes of Olmesartan Medoximol

Name of the Ingredient	OCD1	OCD2	OCD3	OCD4	OCD5	OCD6	OCD7	OCD8	OCD9	OCD10	OCD11	OCD12	OCD13	OCD14	OCD15
Olmesartan Medoxomil	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40
α-Cyclodextrin	40	120	200	--	--	--	--	--	--	--	--	--	--	--	--
β-Cyclodextrin	--	--	--	40	120	200	--	--	--	--	--	--	--	--	--
Hydroxy Propyl β-Cyclodextrin	--	--	--	--	--	--	40	120	200	--	--	--	--	--	--
Methyl β-Cyclodextrin	--	--	--	--	--	--	--	--	--	40	120	200	--	--	--
γ- Cyclodextrin	--	--	--	--	--	--	--	--	--	--	--	--	40	120	200
Ratio (Drug: CD)	1:1	1:3	1:5	1:1	1:3	1:5	1:1	1:3	1:5	1:1	1:3	1:5	1:1	1:3	1:5
Total Unit Weight (mg)	80	160	240	80	160	240	80	160	240	80	160	240	80	160	240

OCD: Olmesartan Cyclodextrins

Table 2: Absorbance values obtained for Olmesartan Medoxomil

Concentration (µg/mL)	Absorbance (at 257 nm)
0	0
5	0.154
10	0.302
15	0.458
20	0.618
25	0.765
30	0.915

Table 3: Micromeritic properties of Olmesartan Medoxomil (n=3)

BULK DENSITY (g/cm^3) (Mean ± SD)	TAPPED DENSITY (g/cm^3) (Mean ± SD)	ANGLE OF REPOSE (Mean ± SD)	CONSOLIDATION INDEX (Mean ± SD)	HAUSNER'S RATIO (Mean ± SD)
0.36 ± 0.02	**0.65 ± 0.02**	**$45^0 50'' \pm 12''$**	**44.6 ± 0.12**	**1.80 ± 0.03**

Table 4: Micromeritic properties of Olmesartan Medoxomil inclusion complexes

Parameters	Formulations														
	OCD1	OCD2	OCD3	OCD4	OCD5	OCD6	OCD7	OCD8	OCD9	OCD 10	OCD 11	OCD 12	OCD 13	OCD 14	OCD 15
Bulk Density	0.56	0.62	0.72	0.59	0.61	0.77	0.61	0.67	0.73	0.55	0.61	0.67	0.54	0.62	0.68
Tapped Denisty	0.63	0.73	0.78	0.68	0.71	0.86	0.72	0.72	0.78	0.62	0.71	0.77	0.67	0.71	0.76
Angle of Repose (º)	21.5	16.4	16.4	17.8	19.2	19.5	18.5	14.9	15.9	17.8	21.2	20.2	19.8	23.4	22.2
Carr's Index	11.1	15.1	7.7	13.2	14.1	10.5	15.3	6.9	6.4	11.3	14.1	13.0	19.4	12.7	10.5
Hausner's Ratio	1.1	1.2	1.1	1.2	1.2	1.1	1.2	1.1	1.1	1.1	1.2	1.1	1.2	1.1	1.1
Assay (%)	98.8	99.8	99.2	99.2	99.3	99.2	100.1	99.7	99.7	99.5	100.2	100.3	100.4	99.8	99.7

Table 5: % Dissolution Studies of Cyclodextrin Complexes

Time (min)	% Drug Release															
	Pure Drug	OCD1	OCD2	OCD3	OCD4	OCD5	OCD6	OCD7	OCD8	OCD9	OCD10	OCD11	OCD12	OCD13	OCD14	OCD15
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	3.2	11.3	16.2	23.4	16.9	23.9	30.2	22.5	32.5	34.5	17.2	26.4	36.2	12.2	15.5	23.5
10	6.8	18.8	24.5	35.6	25.9	32.5	43.5	33.5	40.1	41.5	28.2	37.8	46.8	21.1	23.5	39.5
15	12.5	26.4	31.2	42.9	33.5	40.5	52.8	42.5	52.1	52.8	36.5	46.9	62.5	23.6	31.5	44.6
20	19.8	39.4	42.5	54.9	46.9	52.9	63.8	55.5	72.5	75.4	44.5	61.5	74.5	38.9	43.5	59.8
25	25.9	48.9	56.8	63.8	56.9	66.9	70.8	65.9	82.5	84.5	61.5	73.5	86.9	48.9	56.9	65.8
30	35.4	57.8	66.8	70.5	65.9	75.8	82.5	75.8	91.5	92.5	69.8	91.5	99.7	61.5	66.7	72.5

Table 6: Physicochemical evaluation of Tablets

Parameters	Formulation						
	OPDT1	**OPDT2**	**OPDT3**	**OCDT1**	**OCDT2**	**OCDT3**	**Marketed**
Hardness (kP)	6.3	6.8	6.7	7.2	7.3	7.5	7.4
Thickness (mm)	3.2	3.1	3.2	3.3	3.3	3.3	3.3
Friability	0.13	0.14	0.18	0.14	0.15	0.16	0.17
Disintegration Time (Sec)	33	42	42	33	25	27	182
Assay (%)	100.3	99.7	99.7	99.8	100.1	100.2	100.3

Table 7: *In-Vitro* Drug Release of Tablet

Time (min)	% Drug Release						
	OPDT1	**OPDT2**	**OPDT3**	**OCDT1**	**OCDT2**	**OCDT3**	**Marketed**
0	0	0	0	0	0	0	0
5	8.2	9.5	12.9	37.8	41.2	45.8	17.1
10	14.2	17.2	25.8	53.4	55.6	69.8	28.9
15	21.5	21.6	30.8	65.9	63.9	81.5	46.7
20	28.9	31.6	42.5	85.6	85.9	94.9	72.4
25	38.4	41.9	51.8	90.2	89.7	100.2	85.9
30	46.8	51.9	60.5	99.7	100.1	100.2	92.7

4. Conclusion

In the current study, an attempt was made to enhance the bioavailability of poorly water soluble drugs such as Olmesartan Medoxomil by inclusion of drug in cyclodextrins and by converting the best formulation to tablets using various superdisintegrants From the results obtained the following conclusion can be drawn: From the results of precompression parameters, it can be concluded that formulations of all the drugs have shown enhanced drug micromeritic properties. Formulations of all the drugs prepared have shown enhanced drug release than pure drug. In case of Olmesartan Medoxomil cyclodextrin complexes prepared with Methylated – β- Cyclodextrin has shown faster drug release than other cyclodextrin complexes. Tablets prepared with soluplus have shown fastest drug release than marketed and pure drug tablets. From the results of stability studies conducted for three optimized formulations of each drug, it can be concluded that all the formulations were stable during the study period it can be concluded that bioavailability of final optimized formulation was higher than the marketed formulation as well as pure drug. Hence, it can be concluded that, cyclodextrin complexation followed by converting to tablets using superdisintegrants could be a promising

strategy in improving dissolution of insoluble drugs and formulating immediate release solid dosage forms.

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