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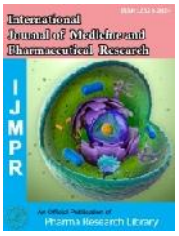

Research Article **Open Access**

Formulation and *In-vitro* Evaluation of Macitentan Solid Dispersions

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A B S T R A C T

Cyclodextrin inclusion complexation is one of the promising approaches to enhance the drug dissolution rate and solubility. As the drug is included in the hydrophilic cavity of cyclodextrins, the solubility and dissolution rate of poorly soluble drug can be expected to be improved. The main objective of the present investigation was to improve the dissolution rate and solubility of an antihypertensive drug Macitentan using cyclodextrin inclusion complexation and followed by converting to orally administerable tablets using a super disintegrates. Cyclodextrin Drug Inclusion complexes (1:1, 1:3 and 1:5) of macitentan were prepared by solvent evaporation method 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 (γ-CD). Prepared inclusion complexes were evaluated for their solubility and in vitro drug release. It was observed that formulations prepared with HP-β-CD at 1:5 ratio (MCD9) has shown faster drug release and higher solubility than other formulations. As drug release of this is higher than other formulations, it was further converted to oral tablet using various superdisintegrants such as crosscaramellose sodium, sodium starch glycollate and soluplus. Similarly tablets were prepared using pure drug as such and keeping other excipients at same level. Comparative evaluation of prepared tablets was done. From in vitro dissolution data of tablets, it was observed that the cyclodextrin tablet formulation (MCDT3) prepared with soluplus has shown faster drug release than marketed formulation and pure drug formulation (MPDT3). Hence, it can be concluded that the cyclodextrin inclusion complexation and further conversion to tablet using superdisintegrants is a promising approach to improve the solubility and dissolution rate of poorly soluble drug like macitentan.

Keywords: Macitentan, Cyclodextrins, α-cyclodextrin, glycollate, HP-β-CD

A R T I C L E I N F O

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1. Introduction

Drug delivery through oral route is the convenient method in dosage form design. 60% of potential drugs suffer from poor water solubility. Dissolution is the rate limiting step for poorly soluble class-II drugs. Solid dispersion technologies were found to be very successful for enhancing the dissolution rate and bio availability of BCS class-II drugs by using approved excipients and GRAS (Generally recognized as safe) materials. The poorly water-soluble drugs often show an erratic dissolution profile in gastrointestinal fluids, which consequently results in variable oral bioavailability and low absorption rate. The efforts to improve dissolution and solubility of poorly soluble drugs are one of the most important tasks in drug development. The aim of this study was to investigate the possibility of improving the release of Macitentan through Solid dispersions.

2. Materials and Methods

Macitentan, 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.

MCD: Macitentan Cyclodextrins

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 Macitentan from *in vitro* samples

Calibration curve of Macitentan was plotted by using UV visible spectroscopic method at 275 nm. Linearity was observed between 10-70 µg/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 Macitentan from in vitro samples.

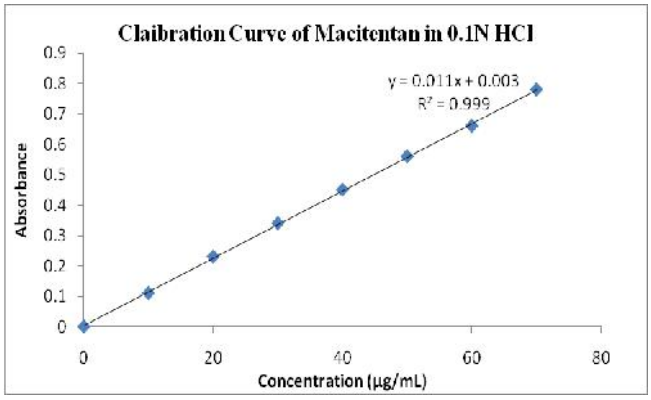

Figure 1: Calibration curve of Macitentan

Preformulation Studies of Pure Drug

Micromeritic properties of Macitentan obtained are given in table 6.3. It was observed from the results that the drug is having poor flow characteristics. The angle of repose value was found to be $45^0 20' \pm 11''$ indicates poor flow of powder. Hence the flow character has to be enhanced in the formulation.

Characterization of Macitentan Inclusion Complexes

Micromeritic evaluation: The prepared formulations were characterized for their micromeritic properties. Results are tabulated in table no 4. It was observed that flow property was improved with all the formulations compared to pure drug.

Dissolution studies of Macitentan 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, MCD9 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 preparation of tablets.

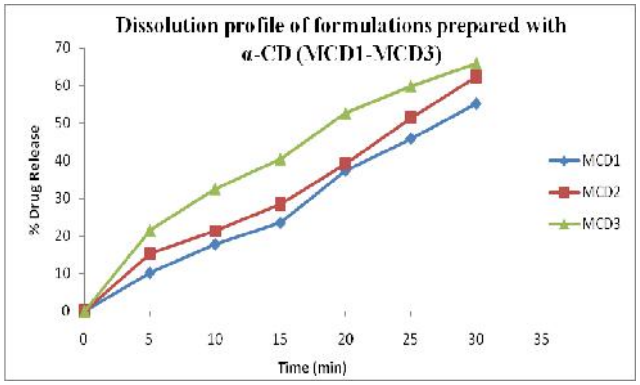

Figure 2: Dissolution profile of formulations prepared with α-CD (MCD1-MCD3)

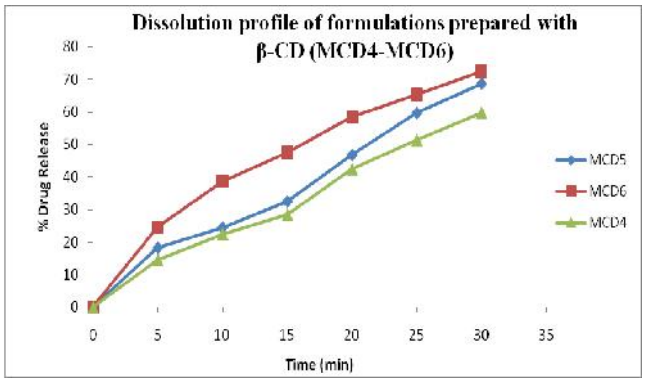

Figure 3: Dissolution profile of formulations prepared with β-CD (MCD4-MCD6)

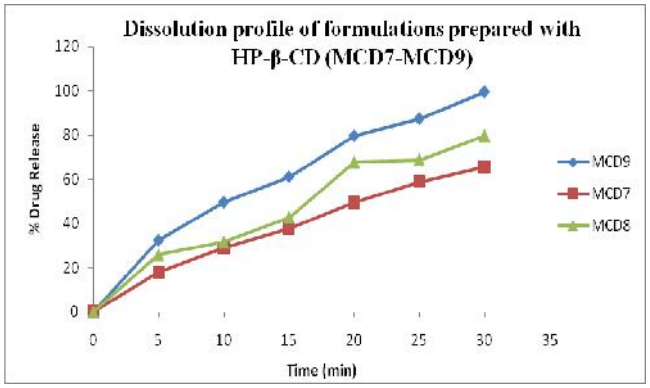

Figure 4: Dissolution profile of formulations prepared with HP-β-CD (MCD7-MCD9)

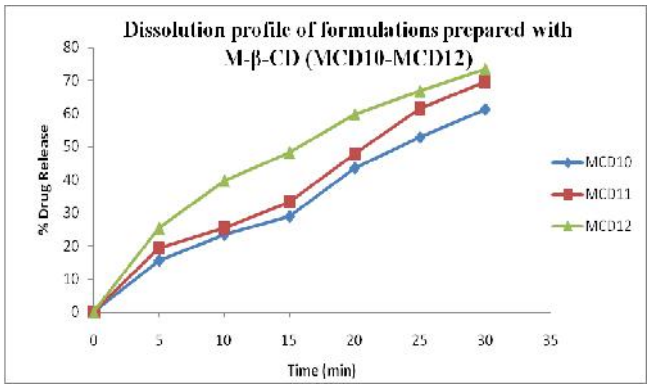

Figure 5: Dissolution profile of formulations prepared with M-β-CD (MCD10-MCD12)

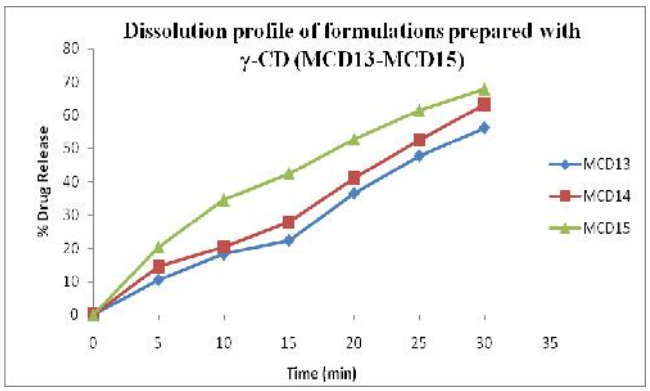

Figure 6: Dissolution profile of formulations prepared with γ-CD (MCD13-MCD15)

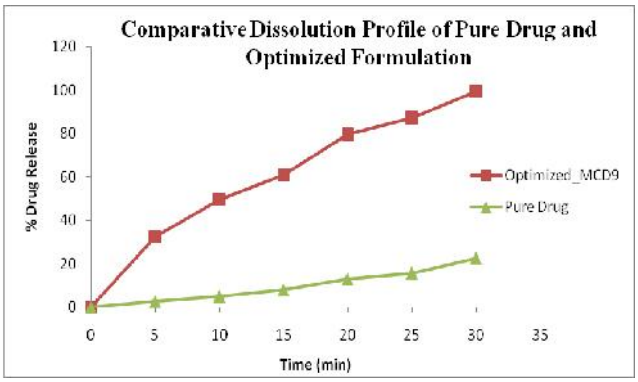

Figure 7: Comparative Dissolution Profile of Pure Drug and Optimized Formulation

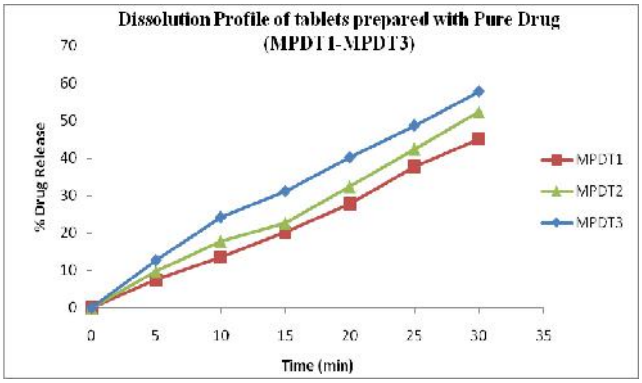

Figure 8: Dissolution Profile of tablets prepared with Pure Drug (MPDT1-MPDT3)

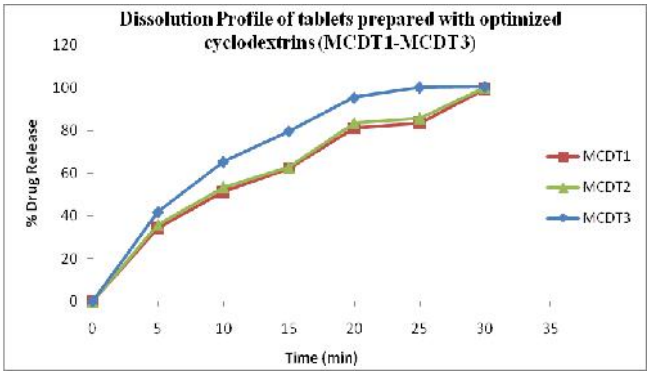

Figure 9: Dissolution Profile of tablets prepared with optimized cyclodextrins (MCDT1-MCDT3)

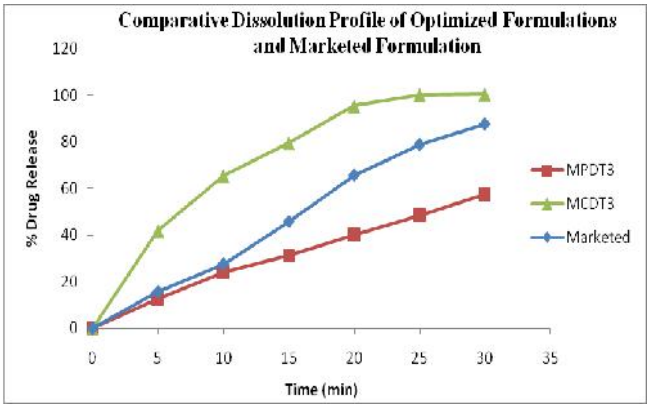

Figure 10: Comparative Dissolution Profile of Optimized Formulations and Marketed Formulation

In-Vitro Drug Release of Tablets:

Dissolution study results of prepared tablets and marketed formulation are tabulated below and graph is shown in table 7. It was observed that formulation prepared with soluplus as superdisintegrant has shown faster drug release than other formulations. Dissolution rate has been significantly improved with cyclodextrin complexes and comparatively higher than marketed formulation.

4. Conclusion

In the current study, an attempt was made to enhance the bioavailability of poorly water soluble drug such as Macitentan 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 Macitentan, cyclodextrin complexes prepared with HP– 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 and all the formulations were stable during the study period. 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. The results generated in this study described the relationship between formulation variables and dissolution profiles.

Table 1: Compositions of Cyclodextrin Inclusion Complexes of Macitentan

Name of the Ingredient	MCD 1	MC D2	MC D3	MC D4	MC D5	MC D6	MC D7	MC D8	MC D9	MC D10	MC D 11	MC D 12	MC D 13	MC D 14	MCD 15
Macitentan	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
α-Cyclodextrin	10	30	50	--	--	--	--	--	--	--	--	--	--	--	--
β-Cyclodextrin	--	--	--	10	30	50	--	--	--	--	--	--	--	--	--
Hydroxy Propyl β-Cyclodextrin	--	--	--	--	--	--	10	30	50	--	--	--	--	--	--
Methyl β-Cyclodextrin	--	--	--	--	--	--	--	--	--	10	30	50	--	--	--
γ- Cyclodextrin	--	--	--	--	--	--	--	--	--	--	--	--	10	30	50
Ratio (Drug: CD)	01:01	01:03	01:05	01:01	01:03	01:05	01:01	01:03	01:05	01:01	01:03	01:05	01:01	01:03	01:05
Total Unit Weight (mg)	20	40	60	20	40	60	20	40	60	20	40	60	20	40	60

Table 2: Absorbance values obtained for Macitentan

Concentration (µg/mL)	Absorbance (at 275 nm)
0	0
10	0.11
20	0.23
30	0.34
40	0.45
50	0.56
60	0.66
70	0.78

Table 3: Micromeritic properties of Macitentan (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)
0.38 ± 0.03	**0.65 ± 0.04**	**$45^0 20'' \pm 11''$**	**41.5 ± 0.13**	**1.70 ± 0.02**

Table 4: Micromeritic properties of Macitentan inclusion complexes

Parameters	Formulations														
	MC	MC	MC	MC	MC	MC	MC	MC	MC	MCD	MCD	MCD	MCD	MCD	MCD

	D1	D2	D3	D4	D5	D6	D7	D8	D9	10	11	12	13	14	15
Bulk Density	0.58	0.62	0.74	0.59	0.63	0.75	0.61	0.68	0.75	0.52	0.61	0.69	0.54	0.62	0.68
Tapped Density	0.63	0.71	0.78	0.68	0.71	0.78	0.69	0.72	0.79	0.64	0.71	0.78	0.67	0.71	0.78
Angle of Repose (º)	22.2º	15.2º	15.4º	16.2º	17.3º	18.5º	17.9º	14.8º	15.4º	16.9º	18.7º	14.9º	17.2º	21.2º	18.2º
Carr's Index	7.9	12.7	5.1	13.2	11.3	3.8	11.6	5.6	5.1	18.8	14.1	11.5	19.4	12.7	12.8
Hausner's Ratio	1.1	1.1	1.1	1.2	1.1	1.0	1.1	1.1	1.1	1.2	1.2	1.1	1.2	1.1	1.1
Assay (%)	99.8	100.1	97.8	100.2	99.8	98.4	99.5	100.2	99.7	99.7	99.2	98.9	99.7	100.1	100

Table 5: % Dissolution Studies of Cyclodextrin Complexes

Time (min)	**% Drug Release**														
	Pure Drug	MC D1	MC D2	MC D3	MC D4	MC D5	MC D6	MC D7	MC D8	MC D9	MC D 10	MC D 11	MC D 12	MC D 13	MC D 14	MC D 15
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	2.5	10.2	15.3	21.5	14.5	18.3	24.6	17.8	25.8	32.5	15.6	19.4	25.4	10.5	14.5	20.4
10	4.9	17.8	21.3	32.5	22.5	24.5	38.7	28.9	31.6	49.7	23.4	25.4	39.7	18.2	20.4	34.5
15	7.9	23.5	28.5	40.5	28.5	32.5	47.5	37.9	42.9	61.2	28.9	33.4	48.2	22.4	27.9	42.5
20	12.9	37.4	39.2	52.6	42.5	46.8	58.4	49.7	67.8	79.8	43.5	47.9	59.7	36.5	41.2	52.7
25	15.7	45.9	51.5	59.8	51.3	59.7	65.4	58.9	68.9	87.5	52.7	61.5	66.7	47.8	52.6	61.4
30	22.5	55.2	62.3	65.8	59.8	68.7	72.5	65.7	79.8	99.7	61.2	69.7	73.4	56.2	63.4	67.8

Table 6: Physicochemical evaluation of Tablets

Parameters	**Formulation**						
	MPDT1	**MPDT2**	**MPDT3**	**MCDT1**	**MCDT2**	**MCDT3**	**Marketed**
Hardness (kP)	5.6	5.8	5.7	6.2	6.8	6.7	6.2
Thickness (mm)	2.8	2.7	2.8	2.8	2.8	2.8	2.8
Friability	0.11	0.12	0.12	0.11	0.1	0.12	0.12
Disintegration Time (Sec)	30	35	41	25	26	21	160
Assay (%)	100.1	99.8	99.8	99.7	100.1	100.1	98.9

Table 7: In-Vitro Drug Release of Tablets

Time (min)	**% Drug Release**						
	MPDT1	**MPDT2**	**MPDT3**	**MCDT1**	**MCDT2**	**MCDT3**	**Marketed**
0	0	0	0	0	0	0	0
5	7.5	9.7	12.7	34.5	35.7	41.8	15.7
10	13.5	17.8	24.2	51.4	53.4	65.4	27.6
15	20.2	22.7	31.2	62.4	62.7	79.7	45.8
20	27.8	32.4	40.2	81.2	83.4	95.4	65.8
25	37.8	42.5	48.7	83.5	85.7	100.2	78.9

30	45.2	52.4	57.8	99.7	100.2	100.5	87.8

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