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FORMULATION AND EVALUATION OF METHYLDOPA BILAYER FLOATING TABLETS FOR THE TREATMENT OF HYPERTENSION

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ABSTRACT

Aim: Present study aim is formulations and evaluations of bilayered Methyldopa tablets by natural polymers

Method: Bilayered Methyldopa tablets were prepared by direct physical compression method using Guar Gum, Xanthan Gum (Natural), Sodium bicarbonates has a gas generating agent. The developed bilayered tablets are evaluated for physicochemical characters, buoyancy *in vitro* study, drug content, drug dissolution, Kinetic models, and drug stability studies.

Results: the results are showing satisfactory and within the limits. The bilayered tablets consisting of CIR3 and CSR4 showing good floating property and drug release was found in a sustained manner for 12 hours and follows Higuchi kinetics. The optimised CIR3 and CSR4 bilayered tablet was more stable at various storage conditions.

Conclusion: Methyldopa bilayered floating tablets were developed successfully by natural polymers and were stable for three months.

Keywords: Methyl dopa, Gaur gum, Xanthan Gum, Buoyancy and bilayered tablets

INTRODUCTION

The dosage forms that are going to be placed in stomach and releases the drug for long period of time is named as Gastro Retentive Drug Delivery Systems (GRDDSs) with different techniques called bioadhesive, floating, swelling dosage form **[1]**. Bilayered tablets were developed with the intention to provide sustained and controlled

delivery of the drug **[2, 3]**. Basically, this bilayered dosage form consists of two layers namely immediate release to provide immediate release to get immediate effect and sustained layer to maintain constant drug levels in the blood for long time.

Methyldopa, is an antihypertensive drug and considered the choice of drug in the hypertension which occurs or induces during pregnancy. Usually, this drug is considered safe for all age groups such as infant, neonate & mother **[4, 5]**. Methyldopa has narrow absorption window with a 25% bioavailability after its oral administration. It shows highest solubility in stomach condition **[6, 7]**. It has a short half life considerably about 2 hours. So, there is a need to administer this drug frequently three to four times daily in order to meet optimum plasma drug levels in the body. Based on above parameters and characteristics, methyldopa was selected as a ideal drug for the development of gastric retentive dosage forms.

MATERIAL AND METHODS

Methyldopa was gifted from Dr. Reddy's, India and polymers were received as pharmaceutical grade purchased from S.D. Fine chemicals.

Formulation development of Methyldopa bilayered Tablets

Methyldopa bilayered tablets were developed by preparing immediate release layer and sustained release layers individually. Both immediate and sustained release tablets were subjected for various *in vitro* evaluation tests and selected an optimized formulation for each layer. Then, both the optimized formulations were compacted and compressed to get a final Methyldopa bilayered tablet.

Formulation of the Methyldopa immediate release layer

The Methyldopa immediate release tablets are geared up by mixed up of drug with diverse superdisintegrants (Crospovidone and Croscarmellose sodium) according to the **Table 1**. The drug Methyldopa–super disintegrant mixture then combined with MCC up to ten minutes. Then, lubrication was done with magnesium stearate by incorporated in to the above mixture and finally added talc and compressed as a tablet by using tablet punching machine with 8mm flat faced punches. Further, several quality control tests was applied on the tablets such as hardness, friability, thickness, weight variation and tablet disintegration time.

Development of Methyldopa sustained release layer

The Methyldopa sustained release layer tablets designed by employing wet granulation technique by blending API drug with innate polymers, xanthan gum and guar gum as given in **Table 2**. Poly vinyl pyrolidone K30 was employed as a binder to get the wet mass and then it was sieved using 30# to produce granules. Then, these

granules were subjected for drying. Then, the granules mixing up with lubricant magnesium stearate &it can be compressed as a tablet by using punching machine with 8 mm punches**.** Further, the tablets were applied for several evaluation tests FLT, TFT and dissolution studies.

Table 1: Composition of the Methyldopa immediate release tablets

Ingredients (mg)	CIR1	CIR2	CIR3	CIR4	CIR5
Methyldopa	250	250	250	250	250
MCC	40	38	34	40	38
Crospovidone	4	6	8	-	-
Croscormellose sodium	-	-	2	4	6
Mg.Stearate	2	2	2	2	2
Talc	4	4	4	4	4
Yellow iron oxide	q.s	q.s	q.s	q.s	q.s
Total tablet weight (mg)	300	300	300	300	300

Table 2: Composition of the Methyldopa sustained release tablets

Ingredients (mg)	CSR1	CSR2	CSR3	CSR4	CSR5	CSR6	CSR7	CSR8	CSR9	CSR10
Methyldopa	250	250	250	250	250	250	250	250	250	250
Guar gum	20	25	30	35	40	-	-	-	-	-
Xanthan gum	-	-	-	-	-	20	25	30	35	40
$NaHCO_3$	20	20	20	20	20	20	20	20	20	20
DCP	35	30	25	20	15	35	30	25	20	15
Crospovidone	10	10	10	10	10	10	10	10	10	10
Mg.Stearate	5	5	5	5	5	5	5	5	5	5
PVP K-30	10	10	10	10	10	10	10	10	10	10
Total tablet weight (mg)	350	350	350	350	350	350	350	350	350	350

Compression of Methyldopa bilayer Tablet

The Methyldopa bilayered dosage forms developed using direct compression method, the tablet punching machine is with 12 mm flat faced**.** First the die cavity was packed up with sufficient quantity of the sustained release material, and then compacted it slightly. Upon this sustained layer, placed the appropriate quantity of the immediate release layer drug powder mixture and punched it in a tablet punching machine at hardness of 6–7kg/cm^2.

Evaluation of Methyldopa Bilayered Floating Tablet

The Methyldopa bilayered tablets are evaluated for uniformity of weighed 20 tablets, for hardness test Monsanto tester was used, for friability study Roche friabilator was used, for drug content determination by assay method and dissolution study was done with USP- type 2 apparatus and the samples were analysed UV spectrophotometer at 282 nm.

The floating characteristic study was conducted in 100 ml beaker filled with 0.1N HCl. Both FLT and TFT were evaluated by this method.

RESULTS AND DISCUSSION

Methyldopa bilayered floating tablets were developed to give immediate release layered

as well as sustained release layer tablets to obtain the loading dose and maintenance dose, respectively, and to produce the long term therapeutic action **[8-9]**. From the compatibility studies by DSC, concluded that there was no interaction found in drug with physical mixture **(Figure 1)**. Five formulations were developed as immediate release tablets and ten formulations were developed as sustained release tablets. The immediate release tablet formulations (CIR 1-5) were adapted to physicochemical characterization. Tablet weight of the entire immediate release layered tablets consisting in the range of 299.3 - 302.4 mg, and thickness between 3.1 and 3.5 mm, hardness ranging between 5.0-5.9 kg/cm^2. All the tablets exhibited disintegration time between 48-58 sec. The results were shown in **Table 3**. Among all the five immediate release formulations, CIR3 formulation was considered as the optimized formulation **(Figure 2)**.

All the sustained release formulations (CSR 1-10) instituted to physicochemical analysis. The amount of drug present in all the sustained layered tablets consisting in the range of 92.41-99.86 %. Weights of all the sustained release layer tablets consisting in the range of 349.1 -353.4 mg, and thickness (mm) between 3.1 and 3.8 and friability values were in the range 0.22-0.36, hardness ranging between 4.9-5.3 kg/cm^2. As the polymer concentration increases the FLT was also increased **[10-12]**. Results were shown in **Table 4**.

Dissolution study revealed that CSR4 formulation showed a sustained drug release up to 12 hours. So, CSR4 batch tablets were considered the optimized one among all the ten SR formulations **(Figure 3 & Figure 4)**. The drug release kinetics were applied on the optimized batch and the results showed that, it was followed Higuchi model **[13-15]**. The selected immediate release layered composition (CIR3) and sustained release layered composition (CSR4) were punched to produce Methyldopa bilayered floating tablet and these bilayered tablet (CBF) were intended to various evaluation tests **(Table 5)** including FLT, TFT and it was followed Higuchi model release kinetics **(Table 6)**. Further, it was intended for stability studies at various storage conditions for three months and it was stable for a period of 3 months **(Table 7)**.

Table 3: *In vitro* characterization of Methyldopa IR tablets

Formulation	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Disintegration time (sec)
CIR1	302.4	5.3±0.50	3.5±0.05	58
CIR2	301.2	5.1±0.43	3.3±0.08	56
CIR3	300.1	5.0±0.01	3.5±0.03	48
CIR4	299.3	5.4±0.15	3.4±0.01	57
CIR5	301.4	5.9±0.45	3.1±0.03	55

Table 4: *In vitro* characterization of Methyldopa SR tablets

Formulation	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Drug content (%)	FLT (sec)	TFT (h)	Drug release (%)
CSR1	351.2	5.1±0.10	3.6±0.05	0.22	94.18	25 ± 1	>12	93.56
CSR2	352.4	5.1±0.23	3.7±0.08	0.31	95.32	23 ± 3	>12	94.95
CSR3	349.1	5.1±0.21	3.6±0.03	0.25	97.14	27 ± 5	>12	95.05
CSR4	350.1	5.0±0.25	3.5±0.01	0.32	99.86	18 ± 4	>12	99.96
CSR5	351.2	4.9±0.15	3.8±0.03	0.23	92.41	35 ± 2	>12	93.98
CSR6	353.4	5.2 ±0.23	3.7±0.02	0.33	94.84	45 ± 7	>12	89.20
CSR7	352.3	5.3±0.10	3.8±0.01	0.24	96.28	47 ± 8	>12	90.98
CSR8	349.6	5.1±0.22	3.1±0.03	0.26	97.52	62± 2	>12	76.65
CSR9	351.4	5.2±0.25	3.5±0.04	0.29	99.04	37 ± 4	>12	96.32
CSR10	352.3	5.2±0.28	3.7±0.08	0.36	98.56	49 ± 9	>12	84.19

Table 5: *In vitro* characterization of Methyldopa bilayered floating tablets

Formulation	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Drug content (%)	FLT (sec)	TFT (h)	Drug release (%)
CIR3 & CSR 4	650	6.0±0.10	3.5±0.05	0.35	99.02	25 ± 1	>12	99.36

Table 6: The correlation coefficient (R^2) values for optimized formulation

Zero order	First order	Higuchi	Peppas
0.9325	0.8121	0.9905	0.8718

Table 7: Stability studies optimized batch

Parameters	Storage conditions		
	At 2-8°C	Room temperature	At 40°C
% Cumulative Drug Release	94.32%	99.12	93.13%
Drug Content Uniformity	95.03%	99.05%	94.46%
Color Change	No change	No change	No change

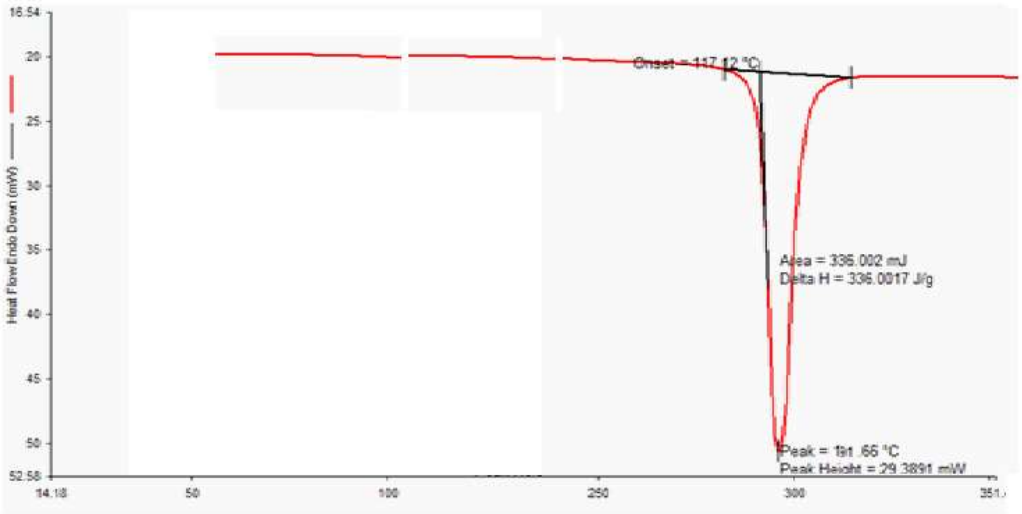

Figure 1: DSC thermogram for Methyldopa + Excipients

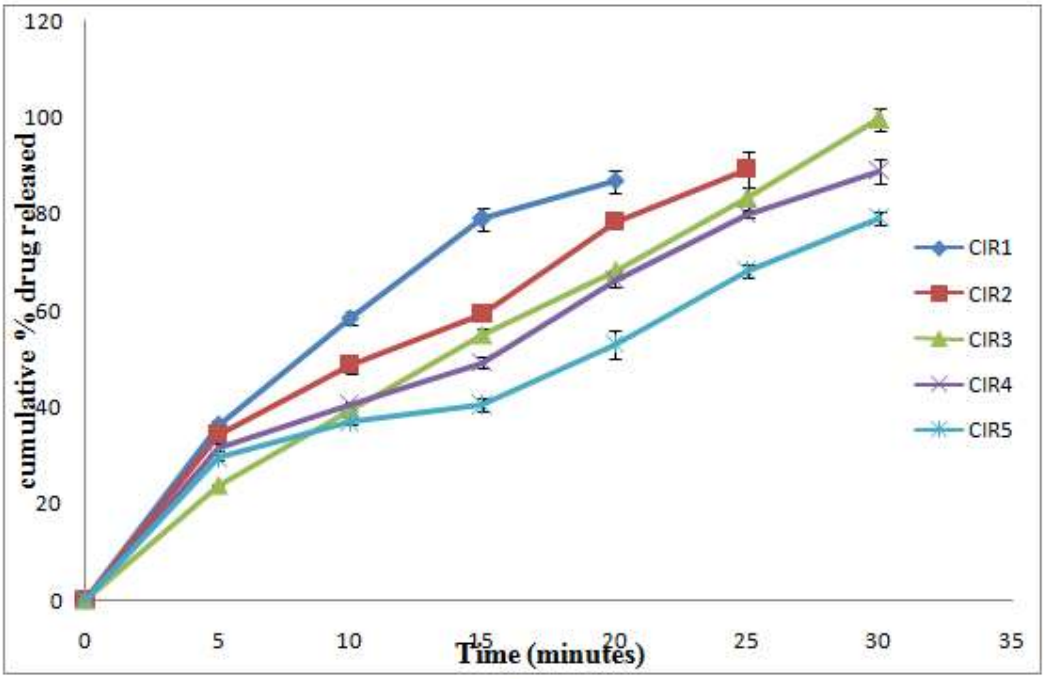

Figure 2: Drug release profiles of Methyldopa immediate release tablets (CIR1-CIR5) (Mean ± SD)

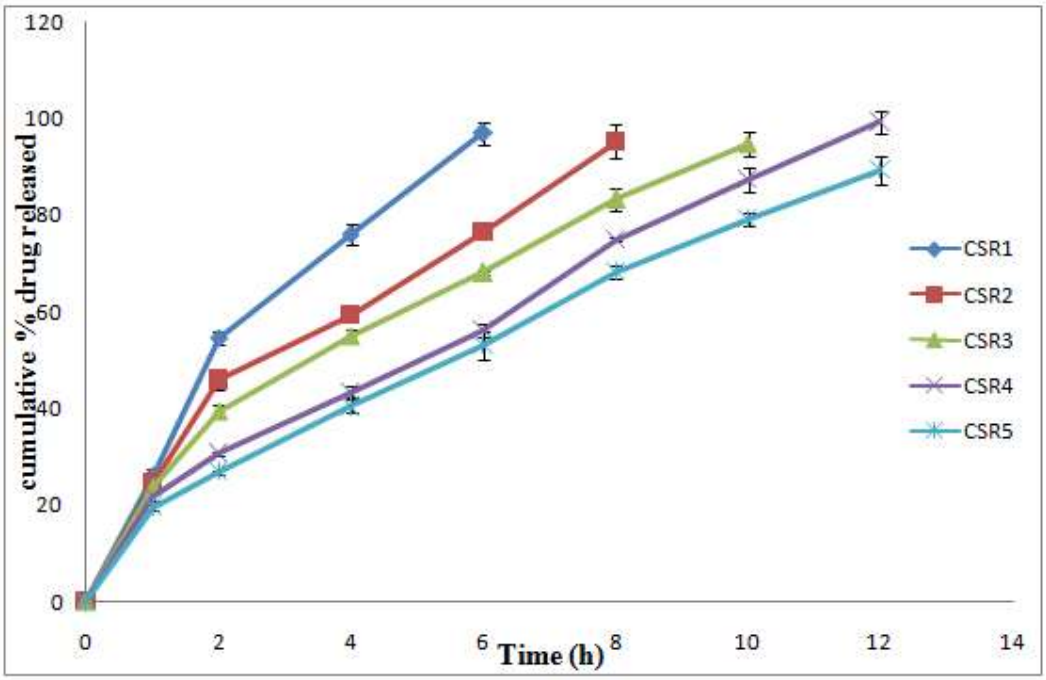

Figure 3: Drug release profiles of Methyldopa sustained release tablets prepared with guar gum (CSR1-CSR5) (Mean ± SD)

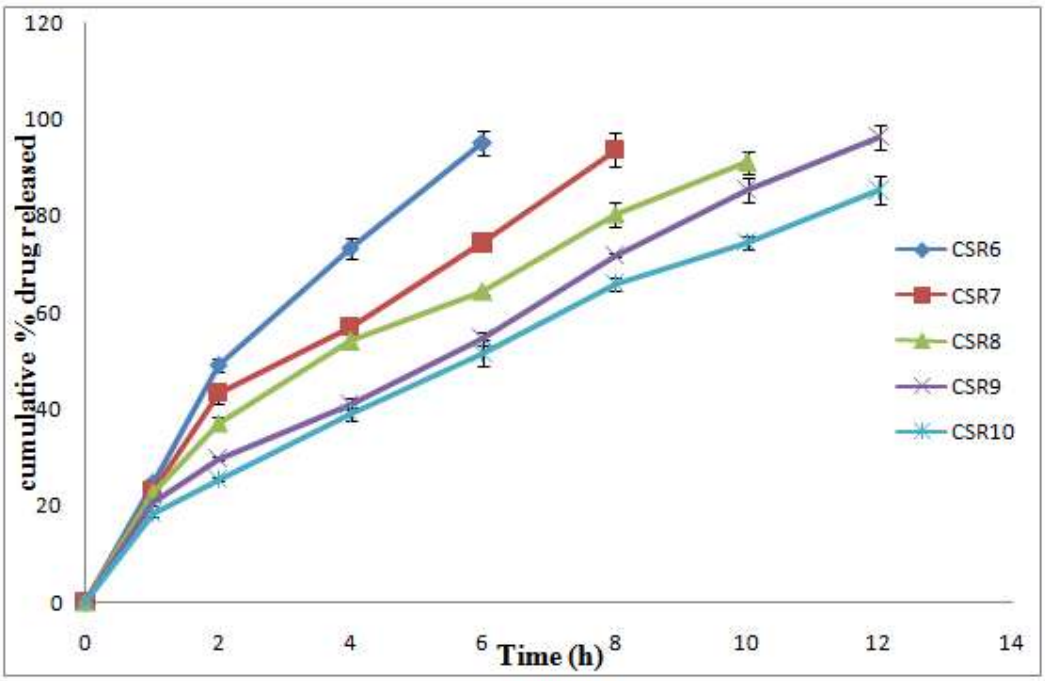

Figure 4: Drug release profiles of Methyldopa sustained release tablets prepared with xanthan gum (F6-F10) (Mean ± SD)

CONCLUSION

Methyldopa floating bilayered tablets were developed successfully and all the tablet formulation were intended for various physical evaluations and all are showing acceptable ranges with the pharmacopeia specifications. F4 was selected as an optimized tablets and it was stable for three months at various storage conditions.

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Conflict of interest

Authors have no conflict of interest.

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