Formulation and Evaluation of Gastroretentive Effervescent Floating Tablets of Methyldopa

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ABSTRACT :
The present study was aimed at the formulation and evaluation of gastroretentive effervescent floating tablets of Methyldopa to enhance its gastric residence time and improve bioavailability. Methyldopa, an antihypertensive agent, exhibits poor bioavailability (approximately 25%) due to its narrow absorption window in the upper gastrointestinal tract. Therefore, developing a floating drug delivery system provides a promising approach to prolong drug release and ensure maximum absorption in the stomach.Floating tablets were prepared by direct compression method using various polymers. The solubility studies revealed that Methyldopa is slightly soluble in water and methanol, but highly soluble in dilute hydrochloric acid, confirming its suitability for gastric retention systems. FTIR studies showed no significant drug–excipient interaction, indicating compatibility and stability. All formulations exhibited acceptable physical parameters including hardness (4.5–4.8 kg/cm^2), friability (<1%), and uniform weight and thickness.The floating lag time for all formulations was below 3 minutes, and formulations F3, F6, F8, and F9 showed a total floating duration of more than 12 hours. Among them, formulation F6 (containing higher concentration of Guar gum and Eudragit S100) was found to be the optimized batch with a floating lag time of 1.88 minutes and total floating duration exceeding 12 hours. The in vitro drug release of F6 extended up to 12 hours with 99.98% cumulative release, following Higuchi release kinetics and non-Fickian diffusion mechanism.Thus, the study concluded that the optimised formulation (F6) of Methyldopa gastroretentive effervescent floating tablets provides prolonged gastric residence, controlled drug release, and enhanced bioavailability, offering a promising approach for effective and sustained management of hypertension.
Keywords: Methyldopa, gastroretentive effervescent floating tablets, polymers, FTIR Studies, IN vitro drug release studies

I. INTRODUCTION

Gastroretentive drug delivery systems (GRDDS) have gained considerable attention in recent years as an effective approach to prolong gastric residence, especially for drugs with narrow absorption windows, high solubility in acidic pH, or local action in the stomach. Among various GRDDS approachessuch as mucoadhesion, high-density systems, swelling systems, and floating systemseffervescent floating tablets are particularly advantageous due to their simplicity of formulation, reproducible floating behaviour, enhanced patient compliance, and ability to maintain the dosage form buoyant in gastric fluids for extended periods.[1]Floating tablets utilize a combination of swellable hydrophilic polymers and gas-generating agents to achieve low density and immediate buoyancy. Upon contact with gastric fluid, the generated carbon dioxide becomes entrapped within the gel matrix, enabling the tablet to float and prolong its retention in the stomach. The present study focuses on the formulation and systematic evaluation of Methyldopa floating tablets prepared using different concentrations of polymers and effervescent agents.[2] The prepared tablets were assessed for key parameters such as floating lag time, total floating duration, swelling behaviour, hardness, drug content, and in vitro drug-release profile to identify the optimal formulation capable of sustaining drug release while maintaining buoyancy.[3]Methyldopa is a centrally acting antihypertensive drug widely used for the management of moderate to severe hypertension, particularly in pregnant women due to its proven safety profile. After conventional oral administration, significant portions of the drug pass unabsorbed through the distal intestine, resulting in reduced systemic availability and inconsistent therapeutic outcomes. Therefore, enhancing its gastric residence time is a promising strategy to overcome these drawbacks and achieve improved pharmacokinetic performance.[4]

II. EXPERIMENTAL WORK

MATERIALS

Methyldopa was procured from Hetero Labs, HYD. Guar gum, Ethyl cellulose and Eudragit RS 100 was obtained from Synpharma Research Labs, Hyderabad. Other chemicalsand the reagents used were of analytical grade.

METHODOLOGY

Fourier Transform Infrared (FTIR) spectroscopy

The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.[5]

Formulation development of Tablets:

Table-1: Formulation composition for floating tablets

Wet granulation method

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Methyldopa (mg)	250	250	250	250	250	250	250	250	250
Guargum	100	200	300	-	-	-	-	-	-
Ethl cellulose	-	-	-	100	200	300	-	-	-
Eudragit	-	-	-	-	-	-	100	200	300
PVPK30	10	10	10	10	10	10	10	10	10
$NaHCO_3$ (mg)	30	30	30	30	30	30	30	30	30
Mag. Stearate (mg)	3	3	3	3	3	3	3	3	3
Talc (mg)	3	3	3	3	3	3	3	3	3
MCC pH102 (mg)	QS	QS	QS	QS	QS	QS	QS	QS	QS
Total weight (mg)	600	600	600	600	600	600	600	600	600

Floating tablets were prepared by wet granulation method Sodium bicarbonate, citric acid, MCC and PVPk30 were mixed in a polybag, and the mixture was passed through mesh (No. 40). Granulation was done using a solutionof polymers in sufficient solvent. The wet mass was passed through mesh No 16. Thereafter, the drug methyldopa was added to the wet granules and mixed thoroughly in a plastic bag. The granules were then dried at 50ºC for about 2 h with residual moisture content of 2 to 3% w/w. The dried granules were then mixed with magnesium stearate and talc for 2 min. Tablets were compressed at 600 mg weight on an 8-station mini rotary tableting machine with 12-mm punches. Evaluation of effervescent floating tablet formulations.[6]

Evaluation parameters

Weight variation test [7]

Twenty tablets were randomly selected and weighed, to estimate the average weight and that were compared with individual tablet weight. The percentage weight variation was calculated as per Indian Pharmacopoeial Specification. Tablets with an average weight 250 mg so the % deviation was ±5 %.[8]

Friability test

Twenty tablets were weighed and subjected to drum of friability test apparatus. The drum rotated at a speed of 25 rpm. The friabilator was operated for 4 minutes and reweighed the tablets. % loss (F) was calculated by the following formula. [8]

$$F = 100\ (W0-W)/W0$$

Where W0 = Initial weight, W = Final weight

Hardness test

The hardness of tablets was measured by using Monsanto hardness tester. The results were complies with IP specification.[9]

Thickness test

The rule of physical dimension of the tablets such as sizes and thickness is necessary for consumer acceptance and maintain tablet uniformity. The dimensional specifications were measured by using screw gauge. The thickness of the tablet is mostly related to the tablet hardness can be used as initial control parameter.[10]

Drug content

The amount of drug in tablet was important for to monitor from tablet to tablet, and batch to batch is to evaluate for efficacy of tablets. For this test, take ten tablets from each batch were weighed and powdered. Weighed equivalent to the average weight of the tablet powder and transferred into a 100 ml of volumetric flask and dissolved in a suitable quantity of media. The solution was made up to the mark and mixed well. Then filter the solution. A portion of the filtrate sample was analyzed by UV spectrophotometer.[11]

***In vitro* Buoyancy studies:**

The *in vitro* buoyancy was determined by floating lag time, and total floating time. The tablets were placed in a 100ml beaker containing 0.1N HCL. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and duration of time the tablet constantly floats on the dissolution medium was noted as Total Floating Time respectively (TFT).[12]

***In vitro* drug release studies**

900ml 0f 0.1 HCL was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c $\pm$ 0.5°c. Tablet was placed in the vessel and the vessel was covered the apparatus was operated for 12 hours and then the medium 0.1 N HCL was taken and process was continued from 0 to 12 hrs at 50 rpm. At definite time intervals of 5 ml of the receptor's fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with receptor fluid and analyzed by spectrophotometrically at 236 nm using UV-spectrophotometer. [13]

Application of Release Rate Kinetics to Dissolution Data

Various models were tested for explaining the kinetics of drug release. To analyse the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.[14]

Zero order release rate kinetics:

To study the zero–order release kinetics the release rate data are fitted to the followingequation.

$$\mathbf{F = K_o\, t}$$

Where, 'F' is the drug release at time's', and 'K_o' is the zero order release rateconstant. The plot of % drug release versus time is linear.

First order release rate kinetics:

The release rate data are fitted to the following equation

$$\mathbf{Log\ (100\text{-}F) = kt}$$

A plot of log cumulative percent of drug remaining to be released vs. time is plottedthen it gives first order release.

Higuchi release model:

To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$$\mathbf{F = k\ t1/2}$$

Where, 'k' is the Higuchi constant.

In higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model:

The mechanism of drug release was evaluated by plotting the log percentage ofdrug released versus log time according to Korsmeyer- Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$$\mathbf{M_t / M_\infty = K\ t^n}$$

Where,M_t/ M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' isthe diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0;while in case of Fickian diffusion, n = 0.5; for zero-order release

(case I I transport),n=1; and for supercase II transport, n > 1.In this model, a plot of log (M_t/ M_∞) versus log (time) is linear.[15]

III. RESULTS AND DISCUSSION

Drug – Excipient compatibility studies

All these peaks have appeared in formulation and physical mixture, indicating no chemical interaction between drug and polymers. It also confirmed that the stability of drug.

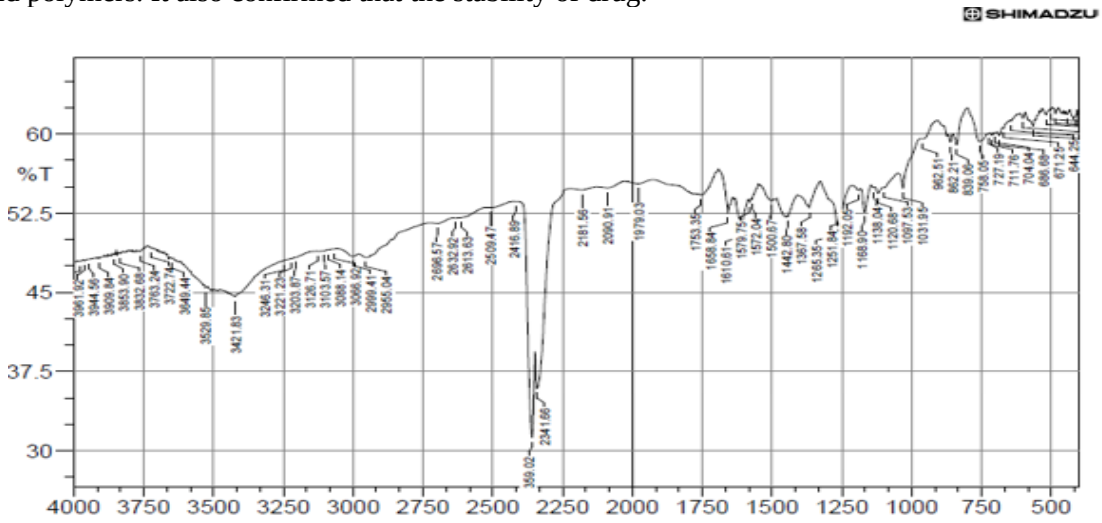

Fig-1: FT-TR Spectrum of Methyldopa pure drug.

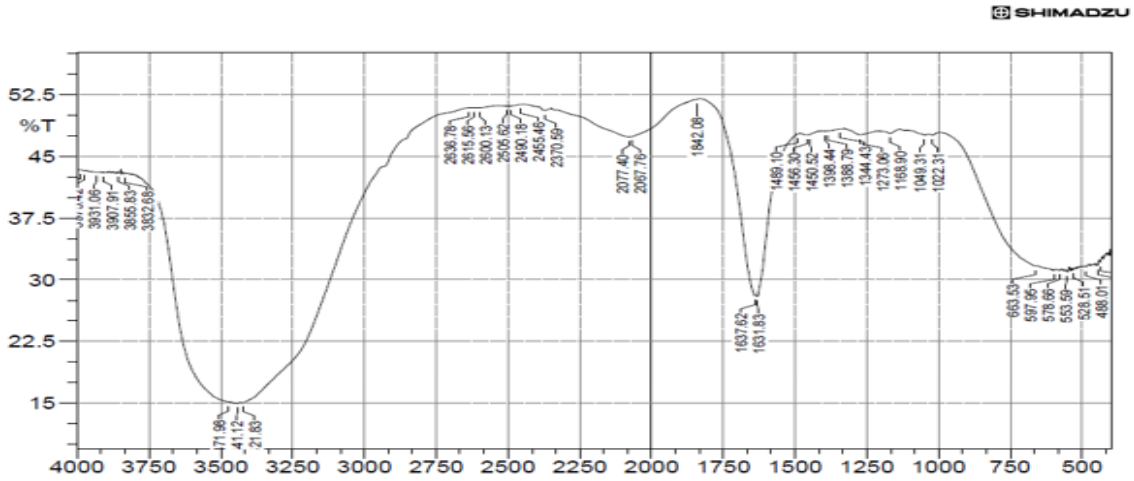

Fig-2: FT-IR Spectrum of Optimized Formulation

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and excipients were studied. The characteristic absorption of peaks was obtained as above and as they were in official limits (±100 cm-1) the drug is compatible with excipients.

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.44 ± 0.08 to 0.58 ± 0.05 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.52± 0.03 to 0.66 ± 0.06 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging from 8.82 ± 0.06 to 15.38 ± 0.05 which show that the powder has good flow properties. All the formulations have shown the hausner's ratio ranging from 0 to 1.25 indicating the powder has good flow properties.

Post compression Parameters For tablets:

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the tablets.

All the parameters such as weight variation, friability, hardness, thickness and drug content, were found to be

within limits.

Weight variation and thickness:

All the formulations were evaluated for uniformity of weight using an electronic weighing balance and the results are shown in table 7.3. The average tablet weight of all the formulations was found to be between 298.4 ± 1.34 to301.8 ± 0.75**.** The maximum allowed percentage weight variation for tablets weighing >250 mg is 5% and no formulations are exceeding this limit. Thus, all the formulations were found to comply with the standards given in I.P., and the thickness of all the formulations was also found to comply with the standards, which were found to be between 3.61 ± 0.01 to 3.91 ± 0.03.

Hardness and friability:

All the formulations were evaluated for their hardness, using the Monsanto hardness tester, and the results are shown in Table 7.3. The average hardness for all the formulations was found to be from 4.5 ± 0.14 to 4.8 ± 0.09 $Kg/cm^{2,}$ which was found to be acceptable.

Friability was determined to estimate the ability of the tablets to withstand the abrasion during packing, handling and transporting. All the formulations were evaluated for their percentage friability using roche friabilator and the results were shown in Table 7.3. The average percentage friability for all the formulations was between 0.56 ± 0.08 and0.66 ± 0.07, which was found to be within the limit.

Table-2: *In vitro* quality control parameters for tablets

Formulation code	Weight variation (mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Flaoting lag time (min)	Duration of floating time (hr)
F1	298.5 ± 0.85	4.5 ± 0.14	0.56 ± 0.08	3.65 ± 0.03	99.11 ± 0.34	2.54 ± 0.01	8
F2	300.4 ± 0.43	4.7 ± 0.12	0.63 ± 0.05	3.84 ± 0.05	98.64 ± 0.51	2.33 ± 0.02	11
F3	299.7 ± 1.06	4.6 ± 0.13	0.58 ± 0.04	3.61 ± 0.01	99.44 ± 0.63	1.47 ± 0.01	12
F4	301.8 ± 0.75	4.7 ± 0.13	0.63 ± 0.08	3.82 ± 0.02	99.65 ± 0.43	2.32 ± 0.02	10
F5	299.3 ± 0.82	4.8 ± 0.09	0.57 ± 0.04	3.86 ± 0.03	99.34 ± 0.48	1.55 ± 0.01	10
F6	298.4 ± 1.34	4.6 ± 0.10	0.64 ± 0.09	3.74 ± 0.01	98.26 ± 0.53	1.88 ± 0.03	>12
F7	300.4 ± 0.73	4.7 ± 0.12	0.66 ± 0.07	3.78 ± 0.02	97.91 ± 0.41	1.44 ± 0.01	10
F8	298.6 ± 0.26	4.8 ± 0.08	0.58 ± 0.03	3.91 ± 0.03	99.52 ± 0.67	2.25 ± 0.02	12
F9	301.2 ± 0.43	4.7 ± 0.11	0.62 ± 0.06	3.81 ± 0.02	98.93 ± 0.34	1.42 ± 0.03	>1 2

Drug content:

All the formulations were evaluated for drug content according to the procedure described in methodology section and the results were shown in table 7.3. The drug content Values for all the formulations were found to be in the range of **(**98.26 ± 0.53 to99.52 ± 0.67**).** According to IP standards the tablets must contain not less than 95% and not more than 105% of the stated amount of the drug. Thus, all the formulations comply with the standards given in IP.

***In vitro* buoyancy studies:**

All formulations were examined for buoyancy studies, in that to determine the floating lag time and duration of floating time. The floating lag time of most of the formulations were showed within 3mins. But duration of floating time was difference, it dependence on the concentration of polymer and type of polymer. Among all the formulation F3, F6, F8, F9 were showed 12 hours or more than 12 hours.

***In-Vitro* Drug Release Studies**

The in vitro dissolution studies were carried out by USP apparatus II (paddle) using pH 1.2 buffer and maintaining temperature 37 ± 0.5^0c, 50 RPM throughout period of dissolution (12 hours) test.

Table-3: Dissolution Data of Methyldopa Tablets Prepared With Ethyl cellulose in Different Concentrations

Time (Hr)	Cumulative Percent Drug Released (n=3 ± sd)		
	F1	F2	F3
0	0	0	0
0.5	34.57 ± 2.94	25.09 ± 1.36	16.98 ± 1.18
1	52.12 ± 1.61	34.45 ± 1.52	26.67 ± 1.24
2	70.45 ± 1.43	51.28 ± 1.66	37.35 ± 1.32
3	86.56 ± 2.73	68.31 ± 2.18	50.63 ± 1.29
4	99.48 ± 1.81	79.67 ± 1.46	67.45 ± 1.51
5		88.78 ± 2.37	76.43 ± 1.55
6		99.32 ± 1.29	89.63 ± 1.60
7			98.15 ± 2.37

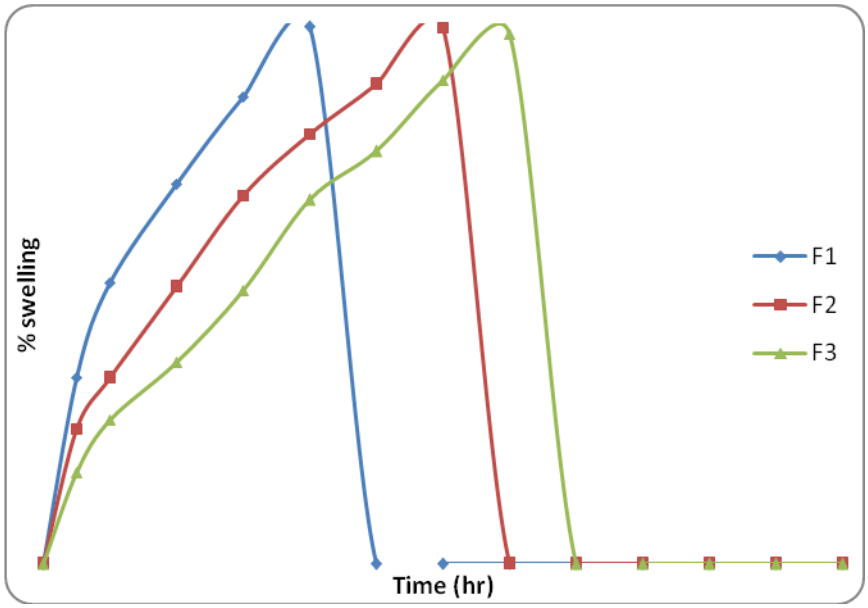

Fig-3: Dissolution profile of Methyldopa floating tablets (F1, F2, F3 formulations).

From the dissolution data, it was evident that the formulations prepared with ethyl cellulose were unable to retard the drug release up to the desired period.

Table-4: Dissolution Data of Methyldopa Tablets Prepared With Eudragit S-100in Different Concentration

Time (Hr)	Cumulative Percent Drug Released (n=3±sd)		
	F4	F5	F6
0	0	0	0
0.5	30.21 ± 1.11	24.09 ± 1.98	15.61 ± 2.04
1	42.34 ± 1.45	32.12 ± 2.15	23.22 ± 1.55
2	63.22 ± 0.88	43.21 ± 0.95	30.81 ± 1.39
3	89.22 ± 1.55	55.18 ± 1.04	39.11 ± 2.16
4	99.15 ± 2.05	62.33 ± 1.42	46.15 ± 1.72
5		73.54 ± 1.71	53.16 ± 1.51
6		82.63 ± 1.44	60.21 ± 1.83
7		99.24 ± 1.96	66.25 ± 1.88

8			72.36 ± 1.53
9			78.28 ± 1.61
10			85.52 ± 2.02
11			92.45 ± 1.29
12			99.55 ± 1.55

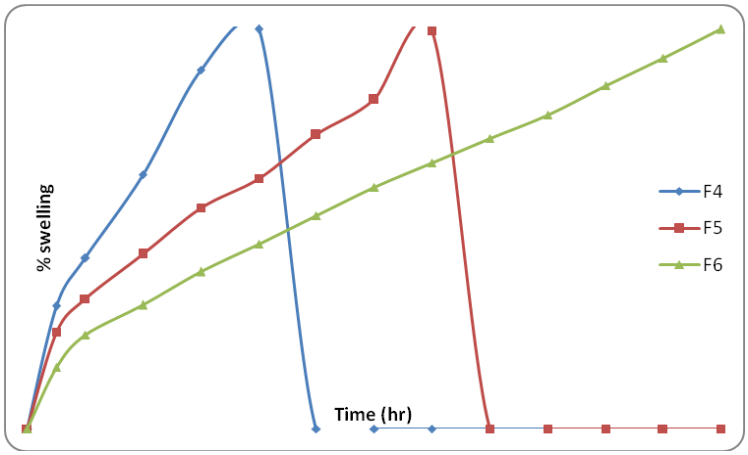

Fig-4: Dissolution profile of Methyldopa floating tablets (F4, F5, F6 formulations)

The formulations prepared with Guargum also unable to retard the drug release at lower concentration of polymer whenever increase the concentration of Guargum in the formulation (F6) it was showed maximum drug release at 12 hours (i.e . 99.55 ± 1.55)

The drug release of formulations prepared with combination of Guargum dependence on the concentration of polymer in the formulation. At low concentration, unable to retard the drug release whenever increase the concentration of polymer in formulation F6 was showed maximum drug release up to 12 hours (i.e99.98 ± 1.08) and it was showed good floating lag time and duration of floating time. When increase the concentration of polymer showed maximum drug release after 12 hours. So that formulation was not considered.

Among all the formulation, F6 formulation was considered as optimized formulation.

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first-order, Higuchi, and Korsmeyer-Peppas release models.

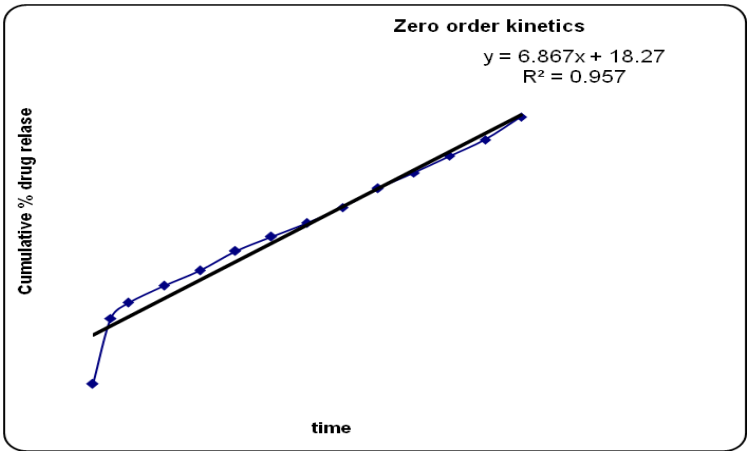

Fig-5: Zero order release kinetics graph

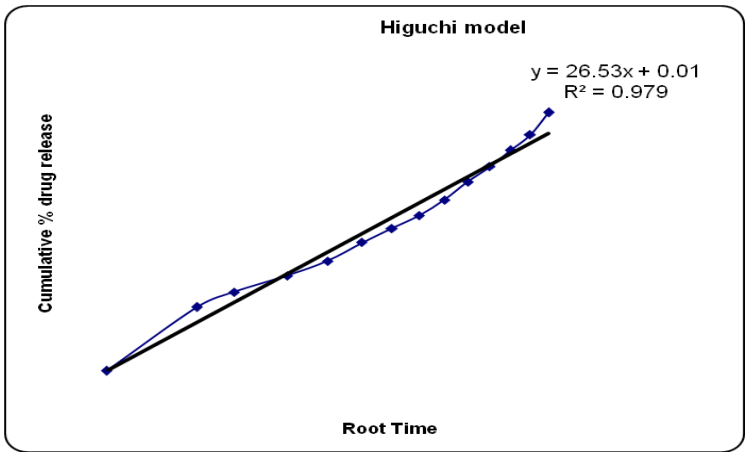

Fig-6: Higuchi release kinetics graph

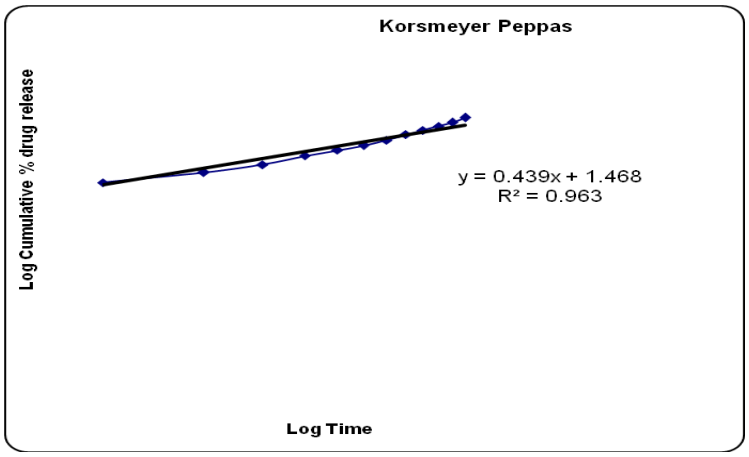

Fig-7: Korsmeyer peppas graph

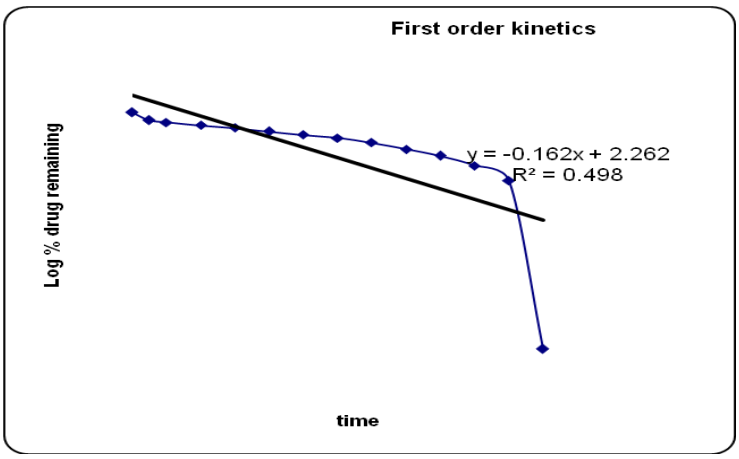

Fig-8: First order release kinetics graph

From the above graphs it was evident that the formulation F6 was followed Higuchi release kinetics.

CONCLUSION

The present study successfully formulated and evaluated gastroretentive effervescent floating tablets of Methyldopa with the objective of enhancing its gastric residence time and improving oral bioavailability. From the overall evaluation, the optimized formulation F6 can be concluded as an effective gastroretentive floating system capable of providing prolonged drug release, improved gastric residence, and potentially enhanced bioavailability of Methyldopa. Hence, gastroretentive effervescent floating tablets offer a promising and patient-friendly approach for sustained management of hypertension and improved therapeutic efficacy of Methyldopa.

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