ISSN : 2347 - 2243

Indo - American Journal of Life Sciences and Biotechnology

www.iajlb.com
Email : editor@iajlb.com or iajlb.editor@gamil.com

ISSN 2347-2243 www.iajlb.com

Indo-Am. J. of LifeSc & Bt.,2017- Vol.11, Issue.3, Aug 2019

Indo-American Journal of Life Sciences and Biotechnology

DESIGN AND OPTIMIZATION OF HYDRODYNAMICALLY BALANCED GASTRORETENTIVE DRUG DELIVERY OF INDAPAMIDE USING NATURAL AND SYNTHETIC POLYMERS

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ABSTRACT

The objective of this research was to prepare a Gastroretentive drug delivery system of Indapamide. Quick GI transit could result in incomplete drug release from the drug delivery system above the absorption zone leading to decreased efficacy of the administered dose and thus less patient compliance. Indapamide is a thiazide-like diuretic drug marketed by Servier, generally used in the treatment of hypertension, as well as decompensated cardiac failure. The main objective of this work was to investigate the possibility of improving the solubility and dissolution rate of Indapamide by preparing gastroretentive Floating Tablets using Natural and synthetic polymers By Using Wet Grannulation Technique. Then the formulation was developed by using different concentrations of polymers of gum cyamopsis, **Polyox Coagulant** and Polyox 303 as polymeric substances. The formulation blend was subjected to various preformualation studies, flow properties and all the formulations were found to be good indicating that the powder blend has good flow properties. Among all the formulations the formulations Polyox 303 as polymer were retarded the drug release up to desired time period i.e., 12 hours in the concentration of 30 mg. whereas in low concentrations the polymer was unable to produce the desired action. (F8 Formulation, 96.98 ± 1.08% Drug release). The optimized formulation dissolution data was subjected to release kinetics; from the release kinetics data it was evident that the formulation followed higuchi release kinetics.

Keywords: Indapamide, Gum cyamopsis, Methocel, Gastroretentive drug delivery system.

INTRODUCTION

Oral drug delivery is the most preferred and convenient choice as the oral route provides maximum active surface area among all drug delivery system for administration of various drugs.[1] In conventional oral drug delivery systems, there is little or no control over release of the drug and effective concentration at the target site can be achieved by irregular administration of excessive doses.

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This kind of dosing pattern result is fluctuation in therapeutic plasma concentrations, leading to marked side effects in some cases. Moreover, the rate and extent of absorption of drug from conventional dosage forms may vary greatly depending on factors such as presence of excipients, physicochemical properties of the drug, various physiological factors such as presence or absence of food, pH of gastro intestinal tract, gastro intestinal motility and so on. Uncontrolled rapid release of drug may cause local gastro intestinal or systemic toxicity. Hence, various approaches are made in designing the formulations, which will overcome the disadvantages of conventional dosage forms, which include sustained/controlled drug delivery system. The FDDS utilize matrices prepared with swellable polymers such as methocel, polysaccharides, effervescent components like NaHCO3, citric acid, and tartaric acid or chambers containing a liquid that gasifies at body temperature. The optimal stoichiometric ratio of citric acid and NaHCO3 for gas generation is reported to be 0.76:1 CO2 is released, causing the beads float in the stomach[5-7]**.** The matrices are fabricated so that upon contact with gastric fluid, CO2 is liberated by acidity of gastric contents and is entrapped in the gellified hydrocolloid. This produces an upward motion of the dosage form and maintains its buoyancy. The CO2 generating components may be intimately mixed within the tablet matrix to produce a single-layered tablet or a bilayered tablet may be compressed which contains the gas generating mechanism in one hydrocolloid containing layer and drug in the other layer formulated for the sustained release effect[8]. This concept has also been exploited for floating capsule systems[9]. The main purpose of the present research work was to formulate effervescent floating tablets of indapamide using different HPMC grade polymers and evaluate its quality and drug release profile as well to justify the formulation.

MATERIALS AND METHODS

Materials

Indapamide was procured from Dr Reddy's Laboratories Ltd., India. Gum cyamopsis, Polyox 303 and Polyox Coagulant were procured from Arvind Remedies Ltd, India. Sodium Bicarbonate and Citric Acid were procured from Merck Specialities Pvt. Ltd, India. Magnesium Stearate and Talc were obtained from Kerry laboratories, India. Microcrystalline Cellulose was procured from SD Fine Chem. Labs, India.

a) Determination of absorption maxima:

A solution containing the concentration 10 µg/ ml drug was prepared in 0.1N HCl UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400 nm.

b) Preparation calibration curve:

100mg of Indapamide pure drug was dissolved in 100ml of 0.1NHCl (stock solution)10ml of solution was taken and make up with100ml of 0.1N HCL (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1N HCL (10µg/ml). The above solution was subsequently diluted with 0.1N HCL to obtain series of dilutions Containing 2,4,6,8 and 10 µg/ml of Indapamide per ml of solution. The absorbance of the above dilutions was measured at 220 nm by using UV-Spectrophotometer taking 0.1N HCL as blank.

Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis.

Table 1: Observations for graph of Indapamide in 0.1N HCL (220 nm)

Conc [µg/ml]	Abs
0	0
5	0.158
10	0.315
15	0.503
20	0.653
25	0.812

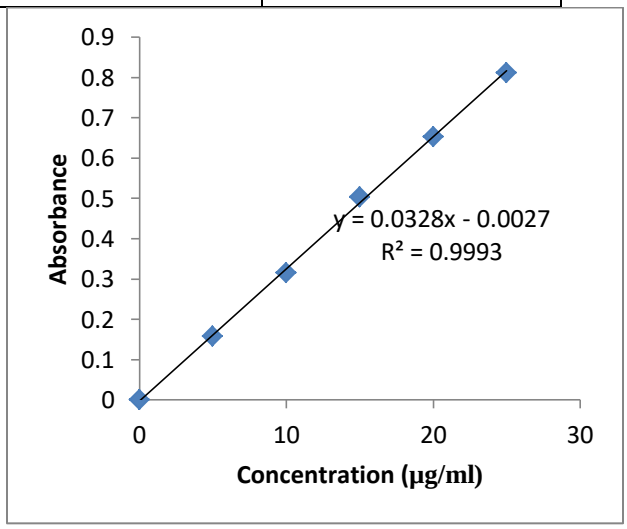

Figure 1: Standard graph of Indapamide in 0.1N HCL

Formulation development of Tablets: All the formulations were prepared by wet grannulation technique. The compressions of different formulations are given in Table 6.1 & 6.2.The tablets were prepared as per the procedure given below and aim is to prolong the release of Indapamide. Total weight of the tablet was considered as 100mg.

Procedure:

1) Indapamide and all other ingredients are individually passed through sieve no ≠ 60.
2) All the ingredients are mixed thoroughly by triturating up to 15 min.
3) The powder mixture is lubricated with talc.

4) Then add sufficient quantity of 3% PVP Solution (PVP in Iso propyl alcohol) to get the wet mass. Prepare the grannules by passsing through the sieve. the obtained grannules are dried in Hot air oven by maintaining the temperature constantly.
5) The dried grannules is lubricated with talc and Magnesium Stearate for 2 minutes in Poly ethylene bag.
6) Then punch the grannules for the get the tablets.

7) Optimization of Sodium bicarbonate concentration: Sodium bicarbonate was employed as effervescent gas generating agent. It helps the formulation to float. Various concentrations of sodium bicarbonate were employed; floating lag time and floating duration were observed. Based on the concentration of sodium bicarbonate was finalized and preceded for further formulations.

Table 2: Optimization sodium bicarbonate concentration

S.No	Excipient Name	EF1	EF2	EF3
1	Indapamide	1.25	1.25	1.25
2	Polyox 303	50	50	50
3	$NaHCO_3$	10	20	30
4	Mg.Stearate	2	2	2
5	Talc	2	2	2
6	PVP In Iso propyl alcohol 3%	Q.S	Q.S	Q.S
7	MCC pH 102	34.75	24.75	14.75
8	Total weight	100	100	100

Table 3: Formulation composition for floating tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Indapamide (mg)	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Gum Cyamopsis (mg)	15	30	45	-	-	-	-	-	-
Polyox Coagulant (mg)	-	-	-	15	30	45	-	-	-
Polyox 303 (mg)	-	-	-	-	-	-	15	30	45
$NaHCO_3$ (mg)	30	30	30	30	30	30	30	30	30

PVP In Iso propyl alcohol 3%	QS	QS	QS	QS	QS	QS	QS	QS	QS
Mag. Stearate (mg)	2	2	2	2	2	2	2	2	2
Talc (mg)	2	2	2	2	2	2	2	2	2
Avicel pH101 (mg)	49.75	34.75	19.75	49.75	34.75	19.75	49.75	34.75	19.75
Total weight (mg)	100	100	100	100	100	100	100	100	100

Evaluation parameters

Pre Compression parameters

Bulk density (D_B): Bulk density is the ratio between a given mass of the powder and its bulk volume.

Bulk density = Mass of Powder / Bulk volume of the powder

Bulk density (D_B) = W /V_0

Procedure: An accurately weighed quantity of granules (w) (which was previously passed through sieve No: 40) was carefully transferred into 250 ml measuring cylinder and measure the bulk volume.

Tapped Density (D_T)

Tapped density [69] is the ratio between a given mass of powder (or) granules and the constant (or) fixed volume of powder or granules after tapping.

Tapped density = mass of the powder/ tapped volume

Procedure: An accurately weighed quantity of granules (w) (which was previously passed through sieve No: 40) was carefully transferred into 250 ml measuring cylinder and the cylinder was tapped on a wooden surface from the height of 2.5 cm at two second intervals. The tapping was continued until no further change in volume (until a constant volume) was obtained (V_f). The tapped density was calculated by using the formula

Tapped density (D_T)=W/V_f

Hausner's ratio

Hausner's ratio [71] is an indirect index of ease of powder flow and was calculated by the formula,

Hausner's ratio = D_T/D_B

Where, D_T is the tapped density

D_B is the bulk density

Compressibility index

Compressibility index (CI) [70] was determined by measuring the initial volume (V_o) and final volume (V_f) after hundred tapping's of a sample in a measuring cylinder. It indicates the powder flow properties and expressed in terms of percentage and given in table no. 14 and calculated by using the formula

% Compressibility index = V_o - V/V_o x 100

Table 4: Carr's index value (as per USP)

Carr's index	Properties
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
2 – 35	Poor
33 – 38	Very Poor
>40	Very Very Poor

Angle of repose

Angle of repose[71] was measured by fixed funnel method. It determines flow property of the powder. It is defined as maximum angle formed between the surface of the pile of powder and the horizontal plane.

The powder was allowed to flow through the funnel fixed to a stand at definite height (h). By measuring the height and radius of the heap of powder formed (r), angle of repose was calculated by using formula given below and the calculated values obtained was shown in table no. 14

$$\theta = \tan^{-1} (h / r)$$

Where, θ is the angle of repose

h is the height in cm

r is the radius in cm

Table 5: Angle of Repose values (as per USP)

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Evaluation of post compression parameters for prepared Tablets

The designed formulation floating tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation test [67]

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 %.

Table 6: IP standards of uniformity of weight

S. No.	Average weight of tablet	% of deviation
1	≤ 80 mg	10
2	> 80 mg to <250 mg	7.5
3	≥ 250 mg	5

Friability test [8]

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.

F =100 (W0-W)/W0Where W0 = Initial weight, W = Final weigh

Hardness test

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

Thickness test [8]

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.

Drug content [8]

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 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.

***In vitro* Buoyancy studies:**

The in vitro buoyancy was determined by floating lag time, and total floating time. (As per the method described by Rosa et al) 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).

***In vitro* drug release studies**

Dissolution parameters:

Apparatus -- USP-II, Paddle Method

Dissolution Medium -- 0.1 N HCL

RPM	--	50
Sampling intervals (hrs)	--	0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
Temperature	--	37°c $\pm$ 0.5°c

As the preparation was for floating drug release given through oral route of administration, different receptors fluids are used for evaluation the dissolution profile.

Procedure:

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 receptors fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with receptor fluid and analyzed by spectrophotometrically at 220 nm using UV-spectrophotometer.

APPLICATION OF RELEASE RATE KINETICS TO DISSOLUTION DATA [9]

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 model.

Zero order release rate kinetics:

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

$$F = K_o t$$

Where, 'F' is the drug release at time't', and 'K_o' is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics: The release rate data are fitted to the following equation

$$Log (100-F) = kt$$

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

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

$$F = k t1/2$$

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 of drug 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.

$$M_t / M_\infty = K t^n$$

Where, M_t / M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the 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.

Fig 2: FT-IR Spectrum of Indapamide pure drug.

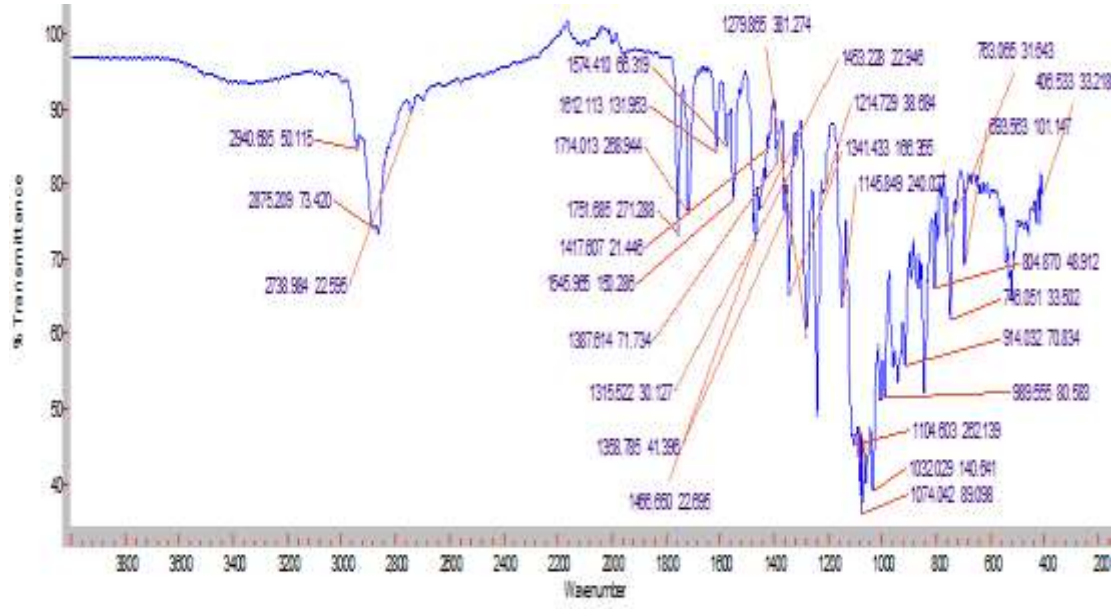

Fig 3: FT-IR Spectrum of Optimised Formulation

Table 7: Pre compression parameters of powder blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	25.11 ± 0.56	0.47 ± 0.12	0.53 ± 0.17	11.32 ± 0.14	1.12 ± 0.02
F2	27.67 ± 0.24	0.45 ± 0.18	0.56 ± 0.22	16.07 ± 0.23	1.24 ± 0.01
F3	25.54 ± 0.65	0.52 ± 0.31	0.60 ± 0.26	13.33 ± 0.41	1.15 ± 0.02
F4	26.43 ± 0.47	0.55 ± 0.24	0.62 ± 0.18	11.29 ± 0.35	1.12 ± 0.03
F5	26.34 ± 0.71	0.47 ± 0.43	0.56 ± 0.27	12.50 ± 0.24	1.19 ± 0.01
F6	27.22 ± 0.58	0.56 ± 0.16	0.63 ± 0.32	11.11 ± 0.13	1.12 ± 0.01
F7	26.18 ± 0.63	0.49 ± 0.25	0.58 ± 0.14	15.51 ± 0.23	1.18 ± 0.02
F8	25.22 ± 0.42	0.57 ± 0.33	0.66 ± 0.23	13.63 ± 0.31	1.15 ± 0.03
F9	28.05 ± 0.81	0.50 ± 0.22	0.59 ± 0.31	15.25 ± 0.22	1.18 ± 0.04

Table 8: Post compression 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
F1	102.5 ± 0.95	4.8 ± 0.01	0.57 ± 0.05	3.6 ± 0.02	98.67 ± 0.15	2.5 ± 0.02	<6 hr
F2	100.4 ± 1.05	4.7 ± 0.02	0.59 ± 0.08	3.5 ± 0.01	99.54 ± 0.13	2.1 ± 0.11	8 hr
F3	99.6 ± 0.58	4.6 ± 0.03	0.61 ± 0.12	3.5 ± 0.03	98.43 ± 0.98	2.9 ± 0.05	> 8 hr
F4	102.6 ± 0.73	4.8 ± 0.02	0.63 ± 0.09	3.6 ± 0.02	99.78 ± 0.56	2.6 ± 0.14	> 8 hr
F5	97.4 ± 0.58	4.6 ± 0.01	0.59 ± 0.10	3.6 ± 0.02	98.41 ± 1.02	2.9 ± 0.06	12 hr
F6	100.7 ± 0.82	4.8 ± 0.02	0.58 ± 0.15	3.5 ± 0.01	99.65 ± 0.38	2.4 ± 0.07	> 12 hr
F7	97.3 ± 1.23	4.8 ± 0.03	0.60 ± 0.09	3.6 ± 0.01	99.24 ± 0.26	2.2 ± 0.06	10 hr
F8	96.2 ± 1.47	4.6 ± 0.01	0.54 ± 0.12	3.7 ± 0.02	98.56 ± 0.57	2.6 ± 0.10	> 12 hr
F9	101.3 ± 0.94	4.7 ± 0.02	0.58 ± 0.13	3.6 ± 0.01	99.21 ± 0.63	2.4 ± 0.07	> 12 hr

Table 9: Dissolution Data of Indapamide Tablets Prepared With gum cyamopsis in Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED		
	F1	F2	F3
0	0	0	0
0.5	35.57	24.09	12.98
1	50.12	38.45	24.67
2	69.45	49.28	36.35
3	85.56	58.31	49.63
4	99.48	71.67	57.45
5		86.78	66.43
6		99.32	79.63
7			88.15
8			99.41
9			
10			
11			
12			

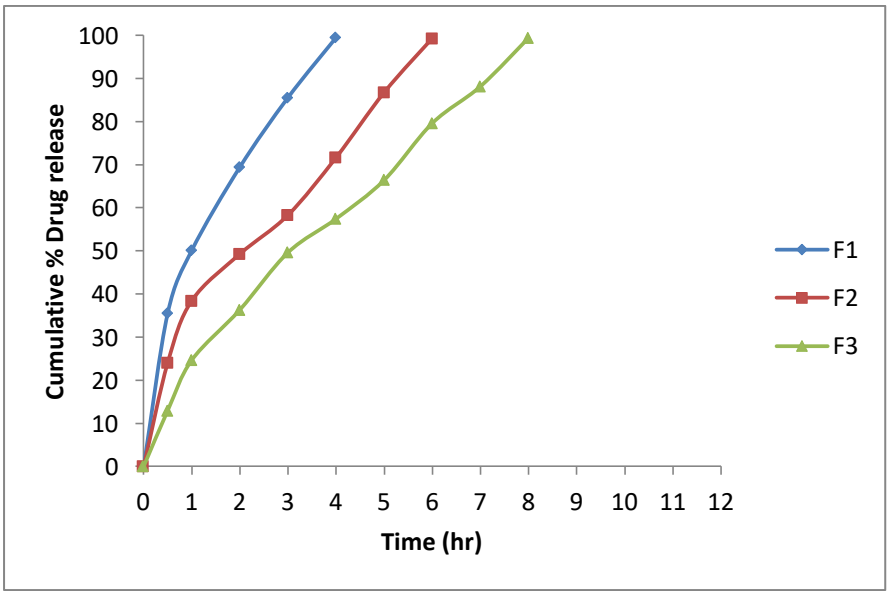

Fig 4: Dissolution profile of Indapamide floating tablets (F1, F2, F3 formulations).

Table 10: Dissolution Data of Indapamide Tablets Prepared With Polyox Coagulant in Different Concentration

TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED		
	F4	F5	F6
0	0	0	0

0.5	37.56	24.11	15.28
1	52.54	33.42	26.31
2	73.32	42.51	31.83
3	89.36	59.08	39.09
4	99.56	66.43	45.11
5		76.24	52.06
6		84.03	59.17
7		99.23	64.22
8			70.34
9			77.26
10			85.55
11			90.42
12			99.57

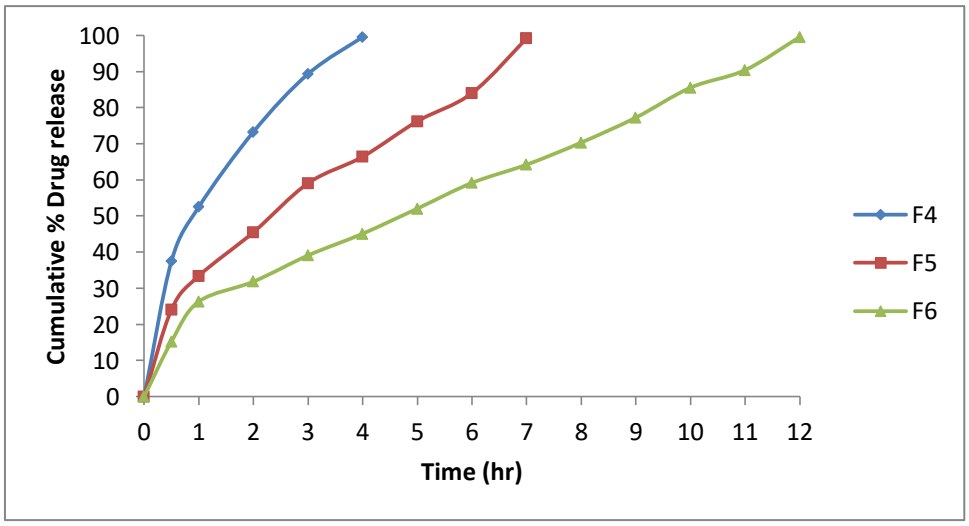

Fig 5: Dissolution profile of Indapamide floating tablets (F4, F5, F6 formulation)

Table 11: Dissolution Data of Indapamide tablets prepared with Polyox 303 in Different Concentrations

TIME **(hr)**	**CUMULATIVE PERCENT DRUG RELEASED**		
	F7	**F8**	**F9**
0	0	0	0
0.5	46.23	25.61	16.77
1	59.42	31.53	23.91

2	66.90	39.84	29.23
3	72.56	45.53	33.13
4	79.54	51.76	40.51
5	81.56	57.21	46.67
6	89.45	63.25	51.57
7	99.67	70.13	58.69
8		76.24	63.67
9		81.09	68.22
10		88.34	75.32
11		93.41	79.39
12		99.98	85.21

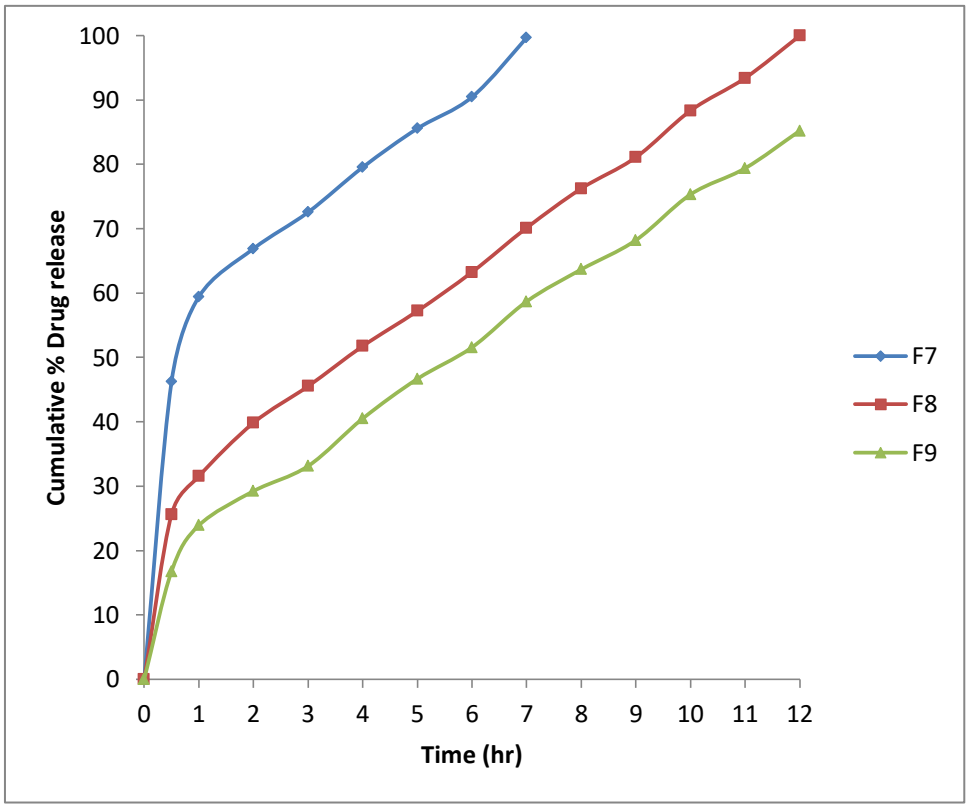

Fig 6: Dissolution profile of Indapamide floating tablets (F7, F8, F9 formulations)

Table 12: Release kinetics data for optimised formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG (%) RELEASE	LOG (T)	LOG (%) REMAIN
0	0	0			2.000
25.61	0.5	0.707	1.408	-0.301	1.872
31.53	1	1.000	1.499	0.000	1.836
39.84	2	1.414	1.600	0.301	1.779
45.53	3	1.732	1.658	0.477	1.736
51.76	4	2.000	1.714	0.602	1.683
57.21	5	2.236	1.757	0.699	1.631
63.25	6	2.449	1.801	0.778	1.565
70.13	7	2.646	1.846	0.845	1.475
76.24	8	2.828	1.882	0.903	1.376
81.09	9	3.000	1.909	0.954	1.277
88.34	10	3.162	1.946	1.000	1.067
93.41	11	3.317	1.970	1.041	0.819
99.98	12	3.464	2.000	1.079	-1.699

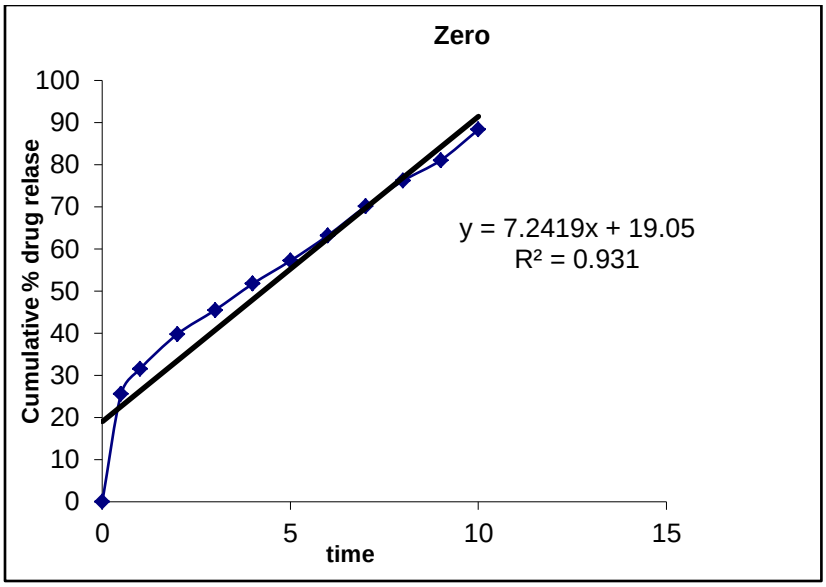

Fig 7 : Zero order release kinetics graph

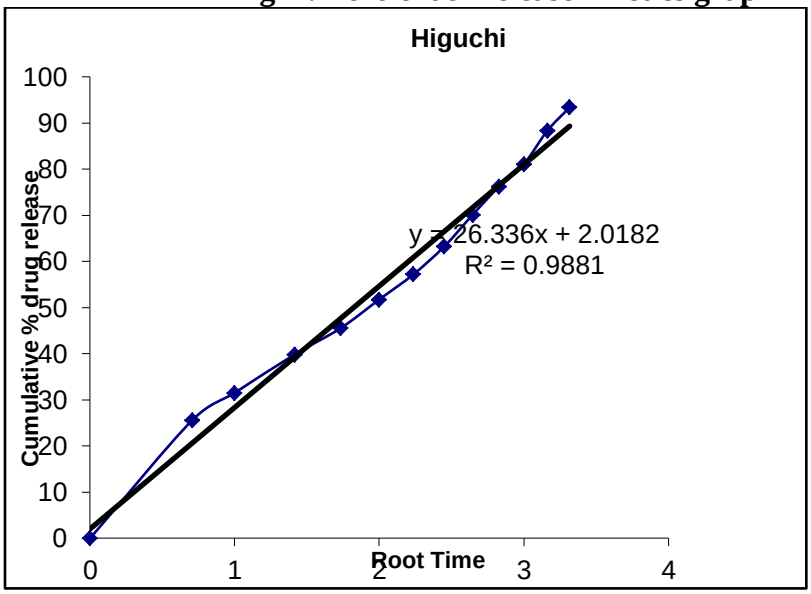

Fig 8 : Higuchi release kinetics graph

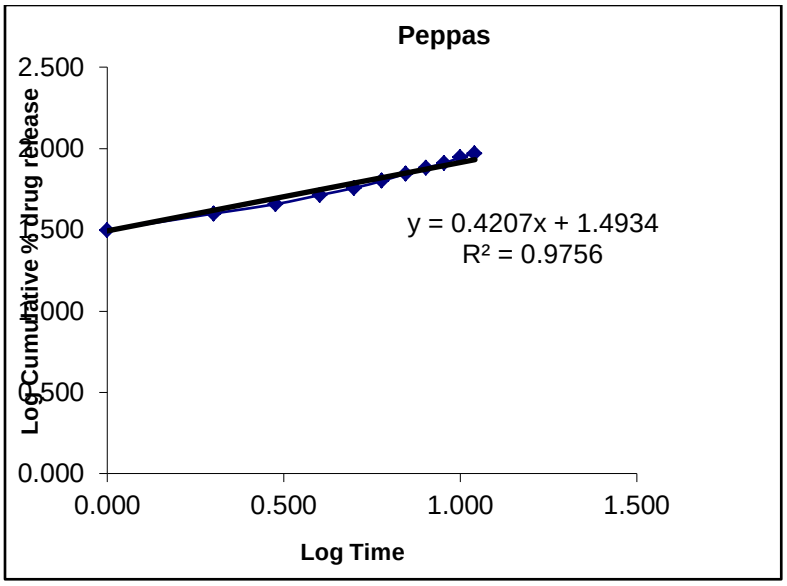

Fig 9: Kars mayer peppas graph

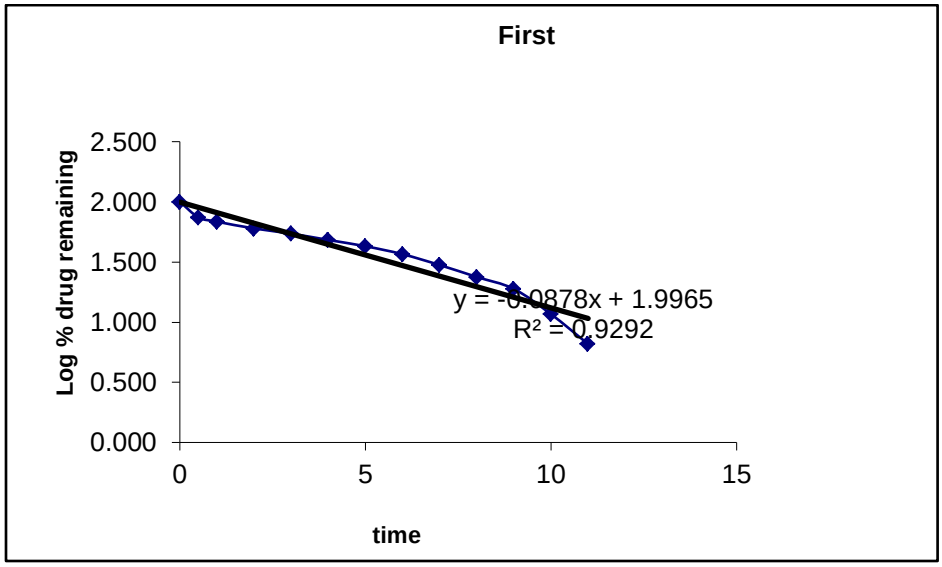

Fig 10: First order release kinetics graph

SUMMARY &CONCLUSION

Development of Gastro retentive floating drug delivery of Indapamide tablets is to provide the drug action up to 12 hours.

Gastro retentive floating tablets were prepared by direct compression method using various polymers gum cyamopsis, Polyox coagulant and Polyox 303.

The formulated gastro retentive floating tablets were evaluated for different parameters such as drug excipient compatability studies, weight variation, thickness, hardness, content uniformity, *In vitro* Buoyancy studies, *In vitro* drug

release. *In vitro* drug release studies performed in 0.1N HCL for 12hrs and the data was subjected to zero order, first order, Higuchi release kinetics and kars mayer peppas graph.

The following conclusions could be drawn from the results of various experiments

- FTIR studies concluded that there was no interaction between drug and excipients.
- The physico-chemical properties of all the formulations prepared with different polymers gum cyamopsis, Polyox coagulant and Polyox 303were shown to be within limits.
- Quality control parameters for tablets such as weight variation, Hardness, Friability, thickness, drug content and floating lag time were found to be within limits. *In-vitro* drug release studies were carried out for all prepared formulation and from that concluded F8 formulation has shown good results.
- Finally Apllied release kinetics to optimised formulation (F8) has followed Higuchi release kinetics.

Conclusion:

The present study concludes that gastro retentive floating tablets of tablets of indapamide prepared by effervescent method and using gum cyamopsis, Polyox coagulant and Polyox 303 as a retarding polymers. Among all the formulations, F8 formulation has shown optimised results. Present study concludes that gastro retentive floating system may be a suitable method for Indapamide.

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