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PREPARATION AND EVALUATION OF FLOATING MICRO BEADS FOR GASTRO RETENTIVE DRUG DELIVERY SYSTEM OF ANTIULCER DRUG

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Keywords:

Factorial designs, Percentage drug release, *In-vitro* drug release, Drug entrapment efficiency, Buoyancy, Antiulcer activity

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ABSTRACT: The objective of the present investigation was to develop an alginate-HPMC K4M microbead-based gastro-retentive drug delivery system incorporating Famotidine for the treatment of gastrointestinal ulcers. The 3^2 full factorial designs were used for the optimization of famotidine-loaded floating microbeads. Two factors were evaluated, each at 3 levels; experimental trials were performed for all nine possible combinations. The amount of HPMC K4M (X1) and rotations of stirring speed (X2) were selected as independent variables. The % entrapment efficiency, % drug release at 12 hr, and % buoyancy were selected as dependent variables. The morphological properties, mean particle size, drug entrapment efficiency, drug loading, *in-vitro* buoyancy studies, *in-vitro* drug release, and *in-vivo* antiulcer activity of microbeads were all investigated. The effect of formulation variables on the response variables was statically evaluated by applying ANOVA at a 0.05 level using the software Design Expert® 13 (Stat-Ease, USA). The average size of optimized alginate-HPMC K4M microbeads was 0.86±0.35mm, with estimated entrapment effectiveness of 71.43± 0.21%, cumulative drug release of 98.75± 0.50% and percent buoyancy of 88.82±0.26%. Alginate – HPMCK4M microbeads containing Famotidine were successfully prepared using full 3^2 factorial designs and can be utilized to treat peptic ulcers efficiently. *In-vivo*, antiulcer activity indicated that the improved microbeads formulation might prevent ulcer formation in rats' stomachs. The method presented appears to be promising for drug delivery to the stomach.

INTRODUCTION: Controlled drug release technology represents one of the frontier areas of science that involves a multidisciplinary scientific approach, contributing to human health care. These drug delivery systems have a great potential to solve the problems associated with the conventional multiple dosing systems like strict adherence to timely dosing, flip-flop plasma concentrations, associated side effects due to systemic drug accumulation, and patient non-compliance.

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Thus, there are numerous advantages such as improved efficacy, reduced toxicity, improved patient compliance and convenience *etc.* [1, 2]. Thus considerations have led to the development of oral controlled release CR dosage forms possessing gastric retention capabilities are the control of the location of a drug delivery system, especially for drugs exhibiting an absorption window in the GI tract or drugs with a stability problem, in a specific region of the GI tract offers several advantages [3].

To formulate a successful stomach-specific or gastro retentive drug delivery system, many approaches square measure currently utilized within the prolongation of the stomachic residence times (GRT) like hydrodynamic ally balanced systems (HBS) / floating drug delivery systems, low-density system, raft systems incorporating alginate gels, bioadhesive or mucoadhesive

systems, high-density systems, super porous hydrogels and magnetic systems [4]. Floating systems are low–density systems that have sufficient resistance to float on the stomach and stay afloat in the gastric without affecting the gastric emptying rate for a long time [5].

Migrating myoelectric cycle (MMC) is further divided into four phases [6]. They are

1. Phase I (basal phase)
2. Phase II (pre burst phase)
3. Phase III (burst phase)
4. Phase IV.

In controlled release drug delivery, the release of the drug proceeds at a rate profile that is not only predictable kinetically but also reproducible from one unit to another. Modified-release drug delivery systems are conveniently divided into four categories:

1. Delayed release
2. Sustained release
3. Site-specific targeting
4. Receptor targeting

Delayed-release systems use repetitive, intermittent drug dosing from one or more immediate-release units incorporated into a single dosage form. Sustained-release systems include any drug delivery system that achieves a slow drug release over an extended period, as shown in Fig. 1. If the system successfully maintains constant safe and effective drug levels in the target tissue or cells, it is considered a controlled-release system [7, 8].

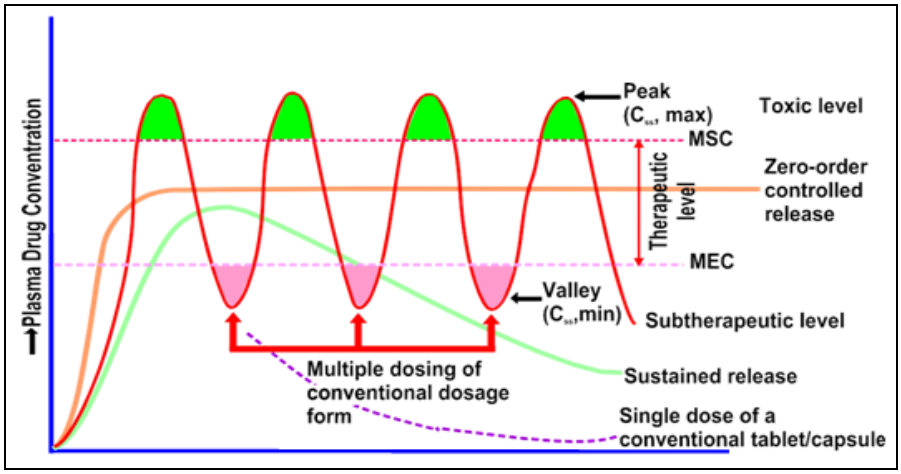


FIG. 1: A HYPOTHETICAL PLASMA CONCENTRATION-TIME PROFILE FROM CONVENTIONAL MULTIPLE DOSING AND SINGLE DOSES OF SUSTAINED AND CONTROLLED DELIVERY FORMULATIONS

Oral controlled drug delivery has faced some difficulties related to physiological adversities, like short gastric residence time (GRT) and unpredictable gastric emptying time (GET). Prolonged GRT improves the bioavailability of drugs, increases the duration of drug release, reduces drug waste, and improves the drug solubility that is less soluble in a high pH environment. This has triggered the attention towards developing various gastro retentive drug delivery technologies to deliver drugs having 'narrow absorption window' with improved bioavailability [9]. Polymers such as polylactic acid, Eudragit S and, hydroxyl propyl methyl cellulose, cellulose acetate are used in the formulation of hollow microspheres the release of the drug can be modulated by optimizing polymer concentration and the polymer-plasticizer ratio [10, 15].

The organic solvent diffuses from the emulsion droplets into the surrounding aqueous phase, and the aqueous phase diffuses into the droplets by which the drug crystallizes [11]. The main reason behind developing controlled drug delivery and increased interest in new system developments is to keep drug plasma levels within the therapeutic window for a prolonged period that ensures sustained therapeutic effectiveness [12].

GRDDS are designed to increase the gastric-retention time of drugs that are [13]:

1. Poorly soluble in high pH range.

2. Having a Narrow absorption window in GIT.

3. Not stable in Intestinal Environment.

4. Locally active in the stomach [14].

Microbeads are small, solid, free-flowing particulate carriers containing dispersed drug particles either in solution or crystalline form that allow a sustained release or multiple release profiles of treatment with various active agents without major side effects.

FMT, a potentH_2 receptor antagonist (H2RA), is generally utilized for treating stomach ulcer, Zollingo Ellison syndrome, gastroesophagal reflux disorder and other conditions of disturbances in gastric acid.

Famotidine is a H_2-receptor antagonist. Famotidine is used orally for treating active duodenal or gastric ulcers, gastroesophageal reflux disease, endoscopically diagnosed erosive esophagitis, and as maintenance therapy for duodenal ulcers. Oral Famotidine also is used for the management of pathological GI hypersecretory conditions. Famotidine is used in hospitalized individuals with pathological GI hypersecretory conditions, intractable ulcers, or when oral therapy is not feasible.

The objective of the present work was to develop gastroretentive formulation of Famotidine using natural polysaccharide sodium alginate and coating polymer (HPMC K4M), which releases the drug in the stomach and upper gastrointestinal (GI) tract and forms an enhanced opportunity for absorption in the stomach and upper GI tract rather than the lower portions of the GI tract. This led to the formulation of a sustained-release gastro retentive drug delivery system for Famotidine using suitable polymers.

MATERIAL AND METHODS:

Chemicals and Reagents: Famotidine was gifted by Piramal Healthcare Limited. Dow Chemicals generously supplied HPMC K4M. Sodium alginate was purchased from Titan Biotech Ltd, Bhiwadi (Raj.). Calcium chloride and HPMC were purchased from SD fine-chemical Ltd., Mumbai. All other reagents and solvents used were of analytical grade, and all the solutions were freshly prepared with double-distilled water.

Method:

Experiment Design: The 3^2 full factorial designs were used to optimize famotidine-loaded floating microbeads. Two factors were evaluated, each at 3 levels; experimental trials were performed for all nine possible combinations. The amount of HPMC K4M (X1) and rotations of stirring speed (X2) were selected as independent variables. The % entrapment efficiency, % drug release at 12 hr, and % buoyancy were selected as dependent variables. High and low levels of each factor were coded as +1 and -1, respectively.

The design was evaluated by a quadratic model represented by the following equation:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{11}X_1^2 + b_{22}X_2^2 + b_{12}X_1X_2 \text{ - - - - - - - (1)}$$

Where Y is the response (dependent) variable, b_0 is the intercept, b_1, b_2, b_{11}, b_{22} and b_{12} represent the regression coefficient. X_1 and X_2 stand for the main effect, X_1 X_2 are the interaction terms and shows how the response changes when two factors are simultaneously changed. X_1^2 and X_2^2 are quadratic terms of independent variables to evaluate nonlinearity.

Statistical Analysis: DESIGN-EXPERT® version 13.0 was used to perform the statistical analysis [16].

Preparation of Alginate-HPMC K4M Microbeads [17, 18]: The microbeads of drugs were prepared using the Ionotropic gelation technique. This method accurately weighed the quantity of drugs properly dispersed into 50 ml sodium alginate solution (1.50 % w/v) and thoroughly mixed at 200- 600 rpm, using a mechanical stirrer. To the resultant dispersion was added polymer (HPMC K4M) in the required concentration, and stirred for 30 min., then above bubble-free dispersion was extruded dropwise with the help of 5 ml of a hypodermic syringe with 24 gauze needle into 100 ml aqueous solution of calcium chloride 2% w/v and stirred at different rpm (200, 400 and 600). The temperature was maintained at 40°C.

Microbeads formed were filtered using a nylon cloth and repeatedly washed with distilled water. The prepared microbeads were collected, dried at room temperature, stored in desiccators, and dried at 40°C. The detailed compositions of various formulations prepared are given in **Table 1**.

TABLE 1: COMPOSITION OF MICROBEADS

Formulation code	Sodium alginate	X1 [Concentration of HPMC K4M (mg)]	Calcium chloride	Cross-linking agent	X2 [Stirring Speed (rpm)]
F1	1.50%	300	2%	1 ml	600
F2	1.50%	300	2%	1 ml	200
F3	1.50%	200	2%	1 ml	200
F4	1.50%	100	2%	1 ml	200
F5	1.50%	100	2%	1 ml	400
F6	1.50%	200	2%	1 ml	400
F7	1.50%	300	2%	1 ml	400
F8	1.50%	100	2%	1 ml	600
F9	1.50%	200	2%	1 ml	600

Percent Buoyancy Study for Floating Microbeads [19]: Formulated microbeads 100 mg were spread over the surface of 200 ml glass beaker filled with 100 ml of phosphate buffer (pH 7.4). The mixture was allowed to stay for 12 hrs overnight.

Floating microbeads were separated by decantation. Sinking Particles were again separated by filtration. Particles of both types were dried in desiccators until a constant weight was obtained. Both fractions of the microbeads were weighed, and percentage buoyancy was determined using the following formula, and the results are recorded in **Table 3**.

$$\% \text{ Buoyancy} = \{[wf / wf + ws] \times 100\}$$

Where, wf = weight of floating microbeads, ws = weight of sinking microbeads

Optimization of Formulation: The design expert was used for optimization. The Highest (%) of entrapment efficiency, cumulative drug release, and % buoyancy were the basis for selecting the optimized formulation.

Interaction between the Factors: To statistically evaluate all the results, One-Way analysis of variance ANOVA was used. P value gives the independent variables' impact on dependent responses such as entrapment efficiency, cumulative drug release, and % buoyancy. Further, the reduced model was generated by omitting non-significant terms ($p>0.05$) from the full polynomial model. The reduced polynomial model was used to evaluate the effect of independent variables on the responses.

Characterization of Famotidine Loaded Microbeads:

Measurement of Bead size: The bead size and size distribution of drug-loaded formulations were estimated by an optical microscope fitted with an ocular and stage micrometer. At least 50 microbeads from a batch were examined for estimation while experiments were carried out in triplicate.

Shape and Surface Study: SEM photographs were taken with JSM 5600 scanning Microscope (Japan) to examine beads' morphology and surface structure. The beads were deposited on brass hold on sputtered with a thin coat of gold under vacuum. The acceleration voltage used was 20kV with the secondary electron as a detector [20].

Drug Entrapment Efficiency: Drug entrapment efficiency (DEE) in floating microbeads of Famotidine was estimated by dissolving the weighed amount (100 mg) of crushed Famotidine loaded microbeads in required quantity of 0.1N HCl, pH 1.20 and analyzed using a double beam ultraviolet spectrophotometer by measuring absorbance at a wavelength of 266 nm using the calibration curve. The polymer debris formed after the disintegration of microbeads was removed by filtering through Whatman filter paper (No. 40). Each batch was examined in a triplet manner. The drug entrapment efficiency of floating microbeads was calculated by dividing the actual drug content by the theoretical drug content of microbeads[21]. The % DEE of floating microbeads was calculated using the following formula:

DEE (%) = [(Actual drug content of microbeads /Theoretical drug content of microbeads)] × 100

***In-vitro* Drug Release Study from Microbeads:** *In-vitro* dissolution study of floating microbeads of Famotidine was carried out using USP type II dissolution test apparatus (Paddle Type). The study was carried out in 900 ml of 0.1N HCl (pH 1.20). The dissolution medium was maintained in a thermostatically controlled water bath at 37±0.5^{o}C.

Microbeads containing a drug equivalent to 40 mg were spread over the surface of 900 ml of dissolution media (0.1N HCl, pH 1.20). The paddle was rotated at 50 rpm [22]. At predetermined time intervals *i.e.*, 1, 2, 4, 6, 8, 10, 12, and 15 hours 5 ml of sample was withdrawn from the dissolution apparatus and replaced with fresh dissolution media to maintain sink conditions. The withdrawn aliquots were filtered, and the drug concentration was analyzed by using UV spectrophotometer (Shimadzu 1800, Japan) at 266 nm. The study was carried out in triplicate [23].

***In-vivo* Radiographical Study:** The percent buoyancy of the floating formulations was evaluated using barium sulphate X-ray contrast medium to test their gastro retentive efficiency. The institutional animal ethical committee (Registration No. 1/BNCP/IAEC/2021/CPCSEA) was created for the purpose provided ethical approval for the handling of experimental animals and the conduct of the study. For radiographic investigation, floating microbeads containing 10% barium sulphate as a contrast agent was created. The experiment was conducted on two healthy male rabbits who were devoid of any gastrointestinal ailments or abnormalities. Overnight, the rabbits were fasted. The rabbits were given a suspension of the formulations in 25 ml of water and an X-ray image was taken right afterward [24].

Ulcer Protective Effect of Formulation in Ethanol-Induced Gastric Ulcers: The experiments were carried out on two animals (each group having six albino wistar rats). Animals in group I were given a 2 ml vehicle solution as a control, whereas animals in group II were given a 2 ml suspension of formulation (equal to 20 mg/kg famotidine) orally as a test. At a one-hour interval, all of the animals received a three-dose therapy. The percentage of protection was computed using the algorithm below.

% Ulcer Protection = Mean ulcer in control- Mean ulcer in Test / Mean ulcer in Control × 100

The ulcer index can be calculated with the use of this formula.

$$UI = (UN+US+UP) \times 10^{-1}$$

UI stands for Ulcer Index. UN stands for "average number of ulcers per animal." US stands for "average severity score." UP = Statistical comparison of the percentage of animals with ulcers.

In all the cases, values of $P < 0.05$ were considered significant. All values were presented as mean ± SEM.

RESULTS:

Yield: The percentage of practical yield of different batches found was from 98±0.5% to 66±0.68%. The highest alginate-HPMC K4M microbeads yield was obtained in formulation F8 (98±0.50%) as given in **Table 2** and shown in **Fig. 2A**.

TABLE 2: PHYSICAL CHARACTERISTICS OF MICROBEADS

Formulation code	% Production yield	Physical Appearances
F1	67±0.68	Spherical, small size
F2	72±0.50	Spherical, small size
F3	72±0.78	Elongated, large size
F4	66±0.68	Spherical, small size
F5	74±0.50	Spherical, small size
F6	72±0.78	Elongated, large size
F7	70±0.78	Elongated, large size
F8	98±0.50	Spherical, small size
F9	68±0.50	Spherical, small size

* All values are reported as mean standard deviation (n = 3).

Shape and Surface Morphology: The particle shape and surface morphology of prepared microbeads containing Famotidine was determined by optical microscope **Fig. 2B** and Scanning electron microscope (SEM).

The SEM study revealed that formulated uncoated microbeads were spherical in shape given in **Table 2**, with an apparently homogenous surface, as shown in **Fig. 3**.

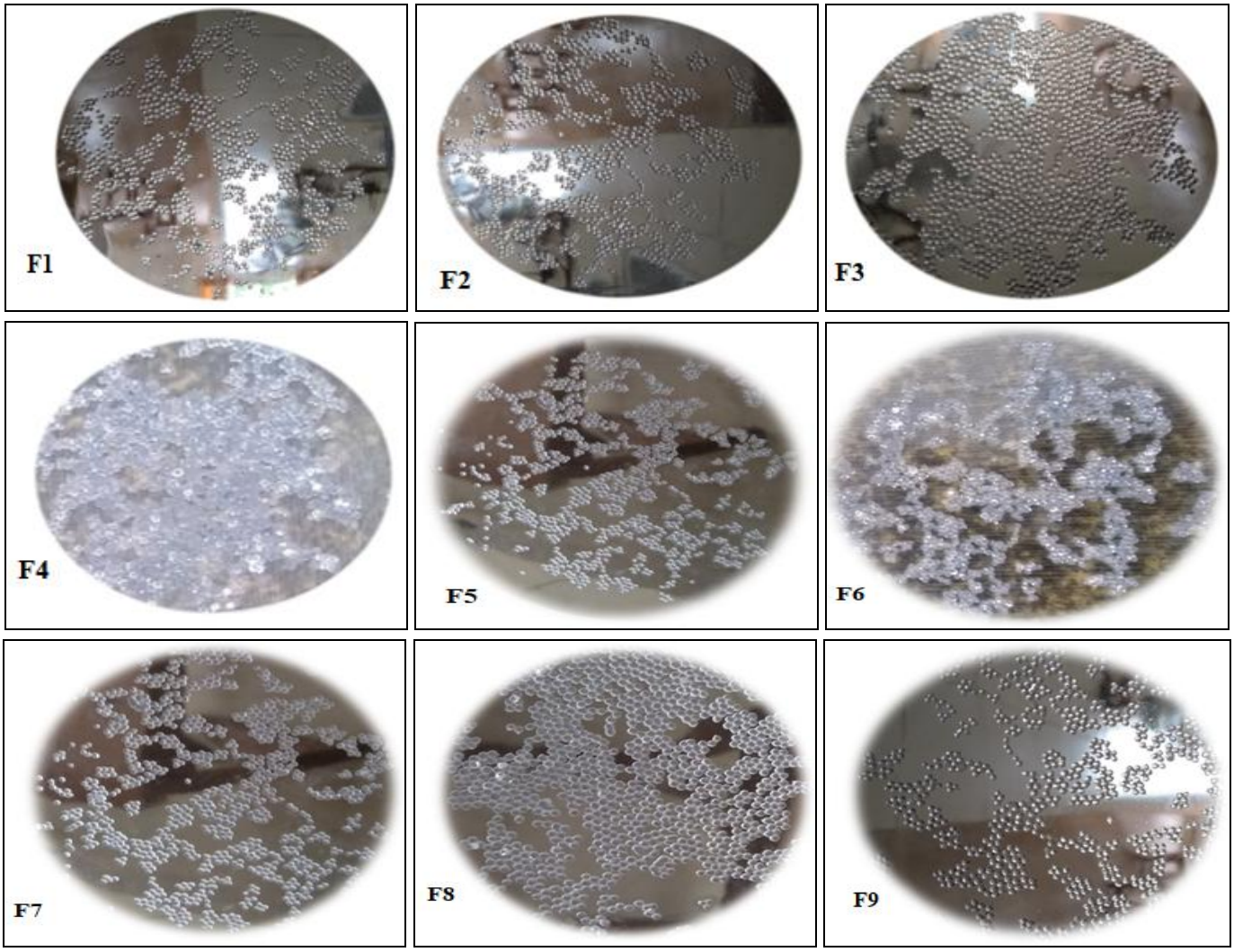


FIG. 2A: WET MICROBEADS OF FORMULATION CODE F1 TO F9

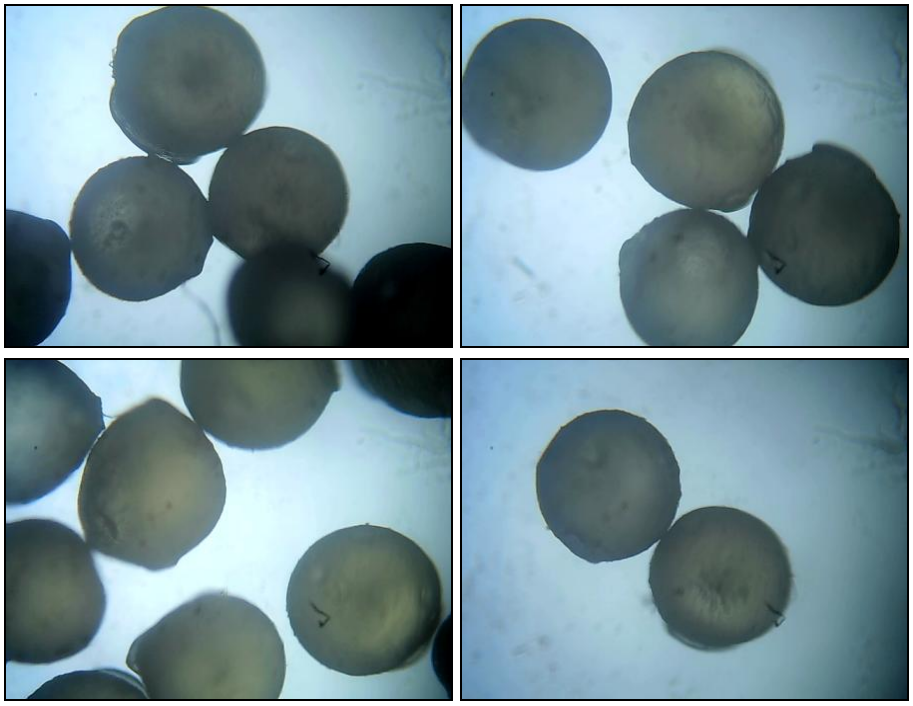


FIG. 2B: OPTICAL MICROSCOPY OF BEST BATCH WITH FORMULATION CODE F8

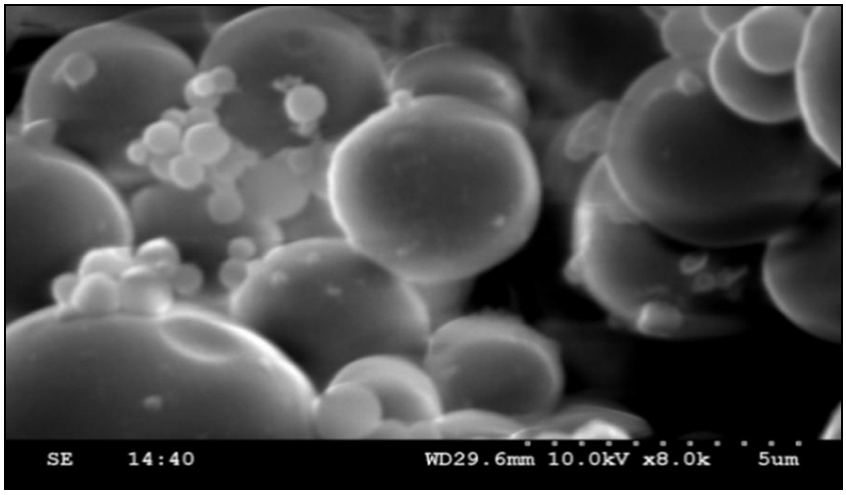


FIG. 3: SEM OF UNCOATED FAMOTIDINE LOADED ALGINATE-HPMC MICROBEADS (F8)

Particle size Analysis: The optimum particle size of alginate-HPMC K4M microbeads was found to be 0.86±0.35 mm for the F8 batch **Table 3.**

Drug Entrapment Efficiency: The drug entrapment efficiency of Famotidine-containing alginate-HPMC microbeads was found to be 63.47±0.25% to 71.43±0.21%. The maximum drug entrapment efficiency of alginate-HPMC microbeads was found to be 71.43±0.21% of best batches F8, as given in **Table 3**.

TABLE 3: COMPOSITION AND CHARACTERISTICS OF DRUG-LOADED UNCOATED MICROBEADS

Formulation Code	Entrapment Efficiency (%)	% Cumulative Drug Release	Microbeads size (mm)	%Buoyancy
F1	64.62±0.11	88.43±0.81	1.12±0.07	75.42±0.60
F2	67.64±0.21	76.21±0.33	1.81±0.03	68.72±0.61
F3	70.26±0.39	66.64±0.23	0.89±0.32	65. 96±0.70
F4	67.48±0.07	62.88±0.38	1.08±0.11	83.74±0.81
F5	65.36±0.25	92.21 ±0.68	0.96±0.015	80.79±0.75
F6	63.47±0.25	92.23 ±0.23	0.89±0.32	74.72±0.70
F7	67.78±0.13	95.35±0.68	0.83±0.05	72.65±0.93
F8	71.43±0.21	98.75±0.50	0.86±0.35	88.82±0.26*
F9	66.79±0.23	88.55±0.24	1.03±0.13	70.42±1.31

* n = 3, all values ± standard deviation

***In-vitro* Drug Release Study:** *In-vitro* famotidine drug release from microbeads was tested in 0.1 N HCl, pH 1.20. The in vitro release profile indicated a burst release phase lasting up to 1 hour, possibly due to surface-associated drug, followed by a continuous release phase as the entrapped drug slowly diffused into the dissolving media. *In-vitro* drug release experiments found that raising the concentration of HPMC K4M reduced drug release from microbeads.

The maximum cumulative percentage drug release of alginate-HPMC microbeads was found to be 98.75 ±0.50% of batches F8 after 12 hrs in 0.1 N HCl, pH 1.20 as given in **Table 3.**

Selection of Optimized Formulation and Validation of Experimental Design: The nine formulations of Famotidine loaded microbeads were prepared to study the effect of polymer concentration and speed of stirring speed. The effect of formulation variables on the response variables were statically evaluated by applying ANOVA at 0.05 level using a software Design Expert® 13 (Stat Ease, USA).

Based on the preliminary experiments, polymer concentration and stirring speed were identified. Key factors responsible for % entrapment efficiency, % drug release at 12 hours and % buoyancy of microbeads. The variation in % entrapment efficiency, % drug release at 12 hours and % buoyancy were observed on changing the concentration of polymer and stirring speed as shown in **Table 4.**

TABLE 4: CODED VALUES OF VARIABLES FOR NINE FORMULATIONS FOR THEIR RESPONSES

Sr. no.	Formulation code	X1 [Concentration of HPMC K4M (mg)]	X2 [Stirring Speed (rpm)]	R1 Entrapment Efficiency (%)	R2 %Cumulative Drug Release at 12 h	R3 %Buoyancy
1	F1	300	600	64.62±0.11	88.43±0.81	75.42±0.60
2	F2	300	200	67.64±0.21	76.21±0.33	68.72±0.61
3	F3	200	200	70.26±0.39	66.64±0.23	65. 96±0.70
4	F4	100	200	67.48±0.07	62.88±0.38	83.74±0.81
5	F5	100	400	65.36±0.25	92.21 ±0.68	80.79±0.75
6	F6	200	400	63.47±0.25	92.23 ±0.23	74.72±0.70
7	F7	300	400	67.78±0.13	95.35±0.68	72.65±0.93
8	F8	100	600	71.43±0.21	98.75±0.50	88.82±0.26
9	F9	200	600	66.79±0.23	88.55±0.24	70.42±1.31

Mathematical polynomial cubic equations were generated for all the dependent variables such as % entrapment efficiency, % drug release at 12 hours and % buoyancy to determine the relationship between the factors used and the response value obtained. The mathematical models were tested for significance. All values of the regression coefficient (R^2), SD, % coefficient of variance and results of ANOVA are shown in **Tables 5** to **7.**

A value of R^2 and the results of ANOVA for the dependent variables confirmed that the model was significant for observed response variables. The ANOVA showed the significance and goodness of fit of the regressional model. The regression model is considered significant when a p-value is less than 0.05. Since the response models were significant, the adjusted and predicted R^2 of response models were in good agreement.

TABLE 5: SUMMARY OF ANOVA RESULTS FOR % DRUG RELEASE AT 12 H

Source	Degree of Freedom (df)	Sum of Square (SS)	Mean Square (MS)	F Value	p Value	R^2	Std. Dev. (S.D.)	Coeff. of variance (% C.V.)
Model	2	1155.71	577.85	20.25	0.0021 Significant	0.8710	0.534	0.632
Residual	6	171.19	28.53					
Total	8	1326.89						

TABLE 6: SUMMARY OF ANOVA RESULTS FOR % BUOYANCY

Source	Degree of Freedom (df)	Sum of Square (SS)	Mean Square (MS)	F Value	p Value	R^2	Std. Dev. (S.D.)	Coeff. of variance (% C.V.)
Model	2	350.45	175.23	11.18	0.0095 Significant	0.7884	0.396	5.23
Residual	6	94.04	15.67					
Total	8	444.49						

TABLE 7: SUMMARY OF ANOVA RESULTS FOR % ENTRAPMENT EFFICIENCY

Source	Degree of Freedom (df)	Sum of Square (SS)	Mean Square (MS)	F Value	p Value	R^2	Std. Dev. (S.D.)	Coeff. of variance (% C.V.)
Model	3	100.24	50.17	66.43	0.0134 Significant	0.7641	0.796	3.64
Residual	5	4.53	5.47					
Total	8	104.77						

TABLE 8: REGRESSION COEFFICIENT (CODED COEFFICIENT) FOR % DRUG RELEASE AT 12 H, % BUOYANCY AND % ENTRAPMENT EFFICIENCY

Factor	Coded Coefficient		
	% drug release at 12 h	% buoyancy	% entrapment efficiency
Intercept	84.58	75.69	68.52
A-A	-16.01	8.76	0.55
B-B	8.68	-5.33	-1.10
AB			-2.34
A^2			-0.76
B2			-1.71

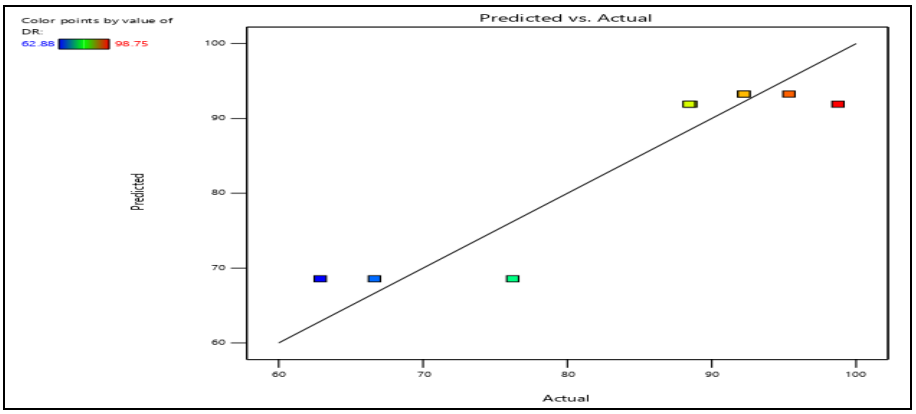
Final polynomial equations of response variables in terms of coded coefficients of the formulation parameters were obtained as shown below:

% Drug release at 12 h= $+84.58-16.01X_1+8.68X_2$

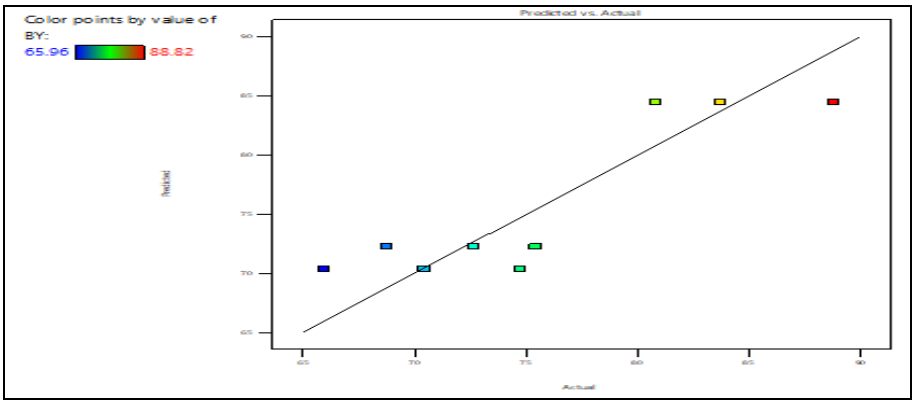
% Buoyancy= $+75.69+8.76X_1-5.33X_2$

% EE= $+68.52+0.55X_1-1.10X_2-2.34X_1X_2-0.76\ X_1^2-1.71X_2^2$

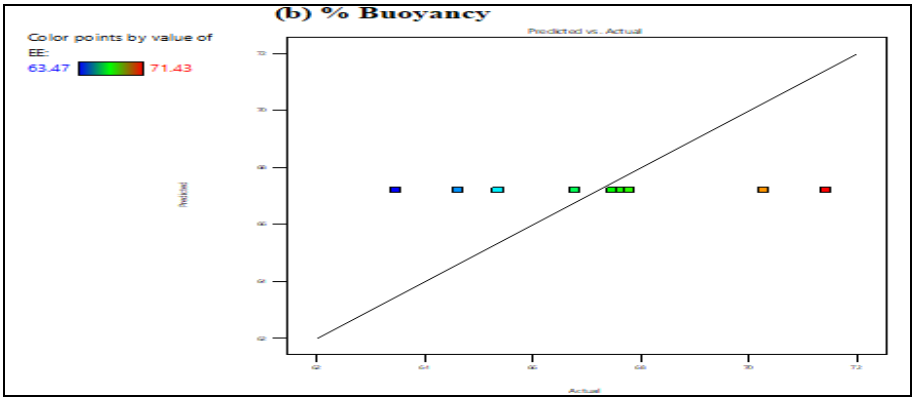
Where X_1 and X_2 represent the coded values of the polymer concentration and stirring speed (rpm) respectively, coefficients of developed models had physical meanings on response variables. Both the magnitude and sign of coefficients are important. The magnitude implies the strength, whereas the sign indicates the direction of that factor variable on the corresponding response variable. The positive value of a factor in the above equations points outs the enhancement of that response and vice versa. The model was expressed using coded coefficients as given in **Table 8,** which represents the closeness of the observed response value to the predicted response value obtained by the polynomial equation, as shown in **Fig. 4.**



(A) % DRUG RELEASE AT 12 H



(B) % BUOYANCY



(C) % ENTRAPMENT EFFICIENCY

FIG. 4 CORRELATION BETWEEN ACTUAL AND PREDICTED VALUES OF (A) % DRUG RELEASE AT 12 H (B) % BUOYANCY, AND (C) % ENTRAPMENT EFFICIENCY

To demonstrate the influence of each factor on responses graphically and to indicate the optimum level of factors, the 3D response surface plots were generated using Design-Expert® 13 software as shown in **Fig. 5** to **Fig. 7.**

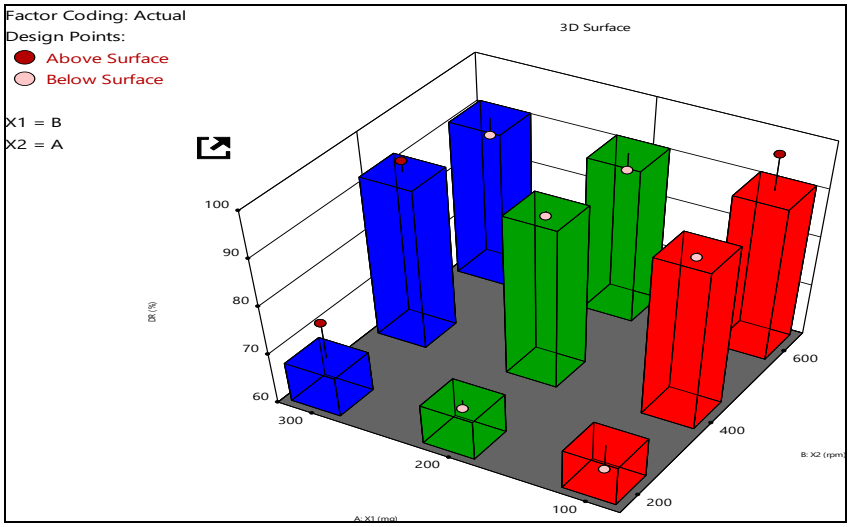


FIG. 5: 3D SURFACE PLOT OF EFFECT OF X1 AND X2 ON % DRUG RELEASE AT 12 H

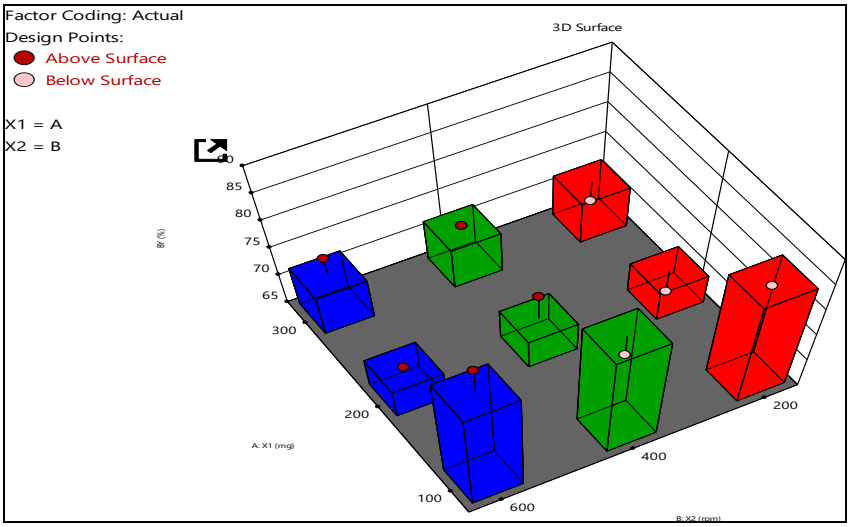


FIG. 6: 3D SURFACE PLOT OF EFFECT OF X1 AND X2 ON % BUOYANCY

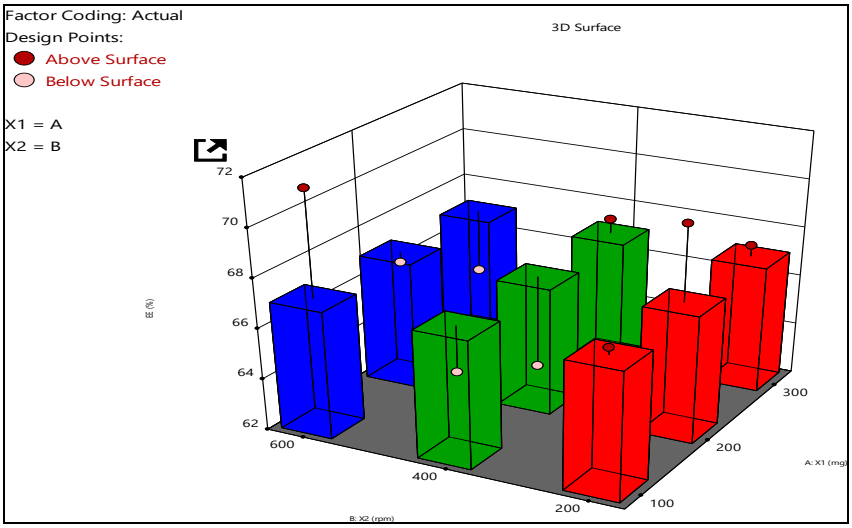


FIG. 7: 3D SURFACE PLOT OF EFFECT OF X1 AND X2 ON % ENTRAPMENT EFFICIENCY

Different Kinetic Models for Treatment of Dissolution Data: The amount of drug released from floating medications was calculated as a function of the rectangular root of time, as is customary in structures where drug release is controlled by diffusion. However, using this data in a swellable matrix system isn't completely justified because such systems are erodible and the contribution of the rest of the polymeric chains to drug shipping must be considered. As a result, analyzing drug release from a swellable matrix requires a flexible version that can recognize the contribution to average kinetics, as proposed by Ritger and Peppas in their equation as given in **Table 9.**

TABLE 9: DIFFUSION EXPONENT VALUES INDICATING DRUG RELEASE MECHANISM

S. No.	Diffusion exponent value (n)	Drug release mechanism
1	Less than 0.45	fickian release
2	0.45- 0.89	non-fickian transport
3	0.89	Case II transport
4	More than 0.89	Super case II transport

The results of kinetic treatment applied to dissolution profile of best formulation are given in **Table 10**. Graphs are shown from **Fig. 8** and **Fig. 9**. *In-vitro* drug release, Higuchi data for all formulations are given in **Table 11** and **Table 12.**

TABLE 10: KINETIC VALUES OF DISSOLUTION DATA OF BEST FORMULATION

Kinetic model	F8		
	R^2 value	Slope	Intercept
0 order	0.9350	7.2110	20.4602
Higuchi's	0.9942	28.741	-0.9310
Korsemeyer Peppas	0.5799	1.0801	0.9671

TABLE 11: *IN-VITRO* DRUG RELEASE AND HIGUCHI DATA FOR F1-F4

Time (hrs)	Square root time	Cumulative % drug released			
		F1	F2	F3	F4
0	0	0	0	0	0
1	1.00	30.66	20.22	10.21	12.22
2	1.41	35.93	27.75	14.11	15.23
3	1.73	40.26	30.45	22.49	21.46
4	2.23	46.24	36.98	25.23	30.85
5	2.24	50.12	41.54	30.19	28.84
6	2.45	56.37	48.24	37.59	35.62
7	2.65	62.66	54.51	41.65	43.44
8	2.83	68.2	60.15	48.95	46.63
9	3	75.55	65.43	52.07	52.64
10	3.16	79.54	68.23	56.72	55.32
11	3.32	84.29	72	60.07	61.11
12	3.46	88.43	76.21	66.64	62.88

TABLE 12: *IN-VITRO* DRUG RELEASE AND HIGUCHI DATA FOR F5-F9

Time (hrs)	Square root time	Cumulative % drug released				
		F5	F6	F7	F8	F9
0	0	0	0	0	0	0
1	1.00	21.48	14.45	26.74	31.82	12.55
2	1.41	31.32	30.47	34.14	40.44	22.54
3	1.73	38.78	37.34	42.77	48.63	30.22
4	2.00	45.65	46.67	49.14	54.27	38.72
5	2.24	53.14	54.78	54.63	58.78	48.73
6	2.45	58.67	63.46	62.42	68.74	56.36
7	2.65	67.45	67.55	70.56	77.28	62.85
8	2.83	73.23	72.26	79.32	83.34	67.74
9	3.00	79.45	79.94	85.22	87.57	74.63
10	3.16	87.67	85.54	89.92	92.82	81.43
11	3.32	90.14	90.98	93.35	95.58	86.76
12	3.46	92.21	92.23	95.35	98.75	88.55

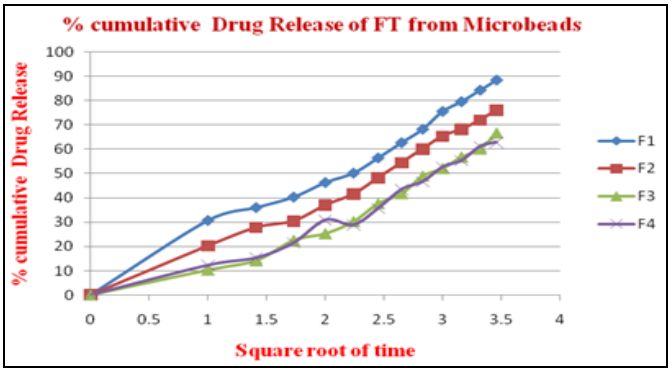


FIG. 8: HIGUCHI'S PLOT OF F1-F4

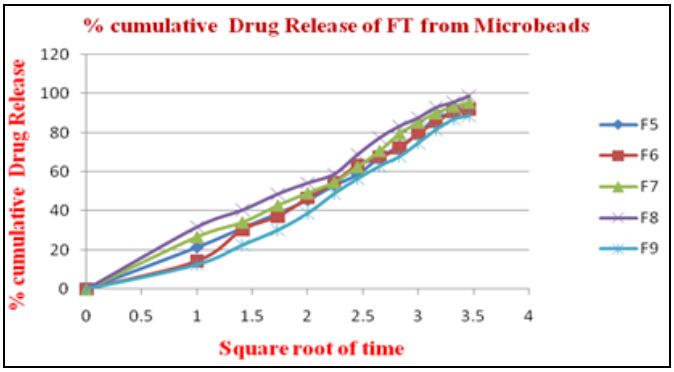
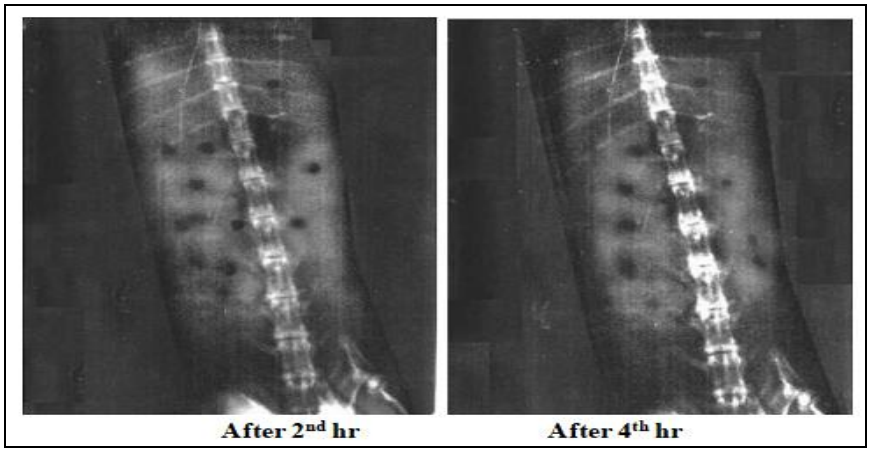


FIG. 9: *IN-VITRO* DRUG RELEASE GRAPH OF F5- F9

***In-vitro* Buoyancy Study:** *In-vitro* Buoyancy study was carried out by spreading a given quantity of microbeads over the pH 1.2 medium. Percent buoyancy was calculated. The % buoyancy of all the preliminary formulations was found to be in the range of 65.96±1.86% to 88.82±0.26%. All the microbeads showed more than eight hours of floating over the medium, as shown in **Fig. 10**. The observation values were reported in **Table 3**.

FIG. 10: % *IN-VITRO* FLOATING STUDY OF OPTIMIZED BATCH OF F8

***In-vivo* Radiographical Study:** Radiographic images (X-ray photographs) of the rabbit's stomach at specified time intervals were used to evaluate the *in-vivo* floating behaviour of famotidine microbeads loaded with 10% barium sulphate. **Fig. 11** shows radiographs taken at 2, 4, 8, and 12 hours, indicating a homogeneous distribution of microbeads throughout the gastric fluid and in vivo floating for more than 12 hours. As a result, produced microbeads were found to be effective in extending the gastric residence time (GRT) of Famotidine in the stomach to treat peptic ulcers.



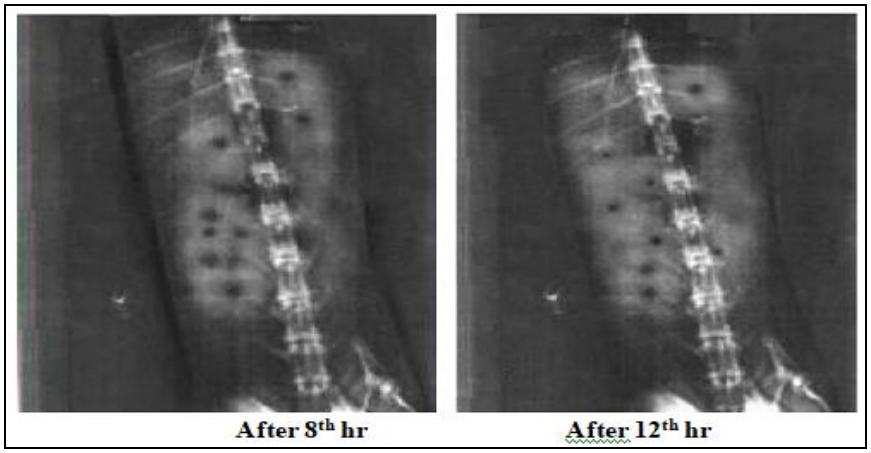


FIG. 11: RADIOGRAPHICAL STUDY OF BEST FORMULATION F8

Ulcer Protective Effect of Best Formulation: A study of the ulcer-protective effects of F8 formulations in a stomach ulcer model is absolute by 100% ethanol. The use of absolute alcohol (1ml/200gm, p.o.) per body weight in group I animals resulted in acute ulcers. The animals in group II who were given a suspension of compound F8 (2ml) before being given total alcohol for 30 minutes were shown to be protected against ulcers. Compared to the control group, oral ethanol administration resulted in hemorrhagic lesions, red streaks, and inflammation in the glandular part of the stomach, as seen in **Fig. 12.**

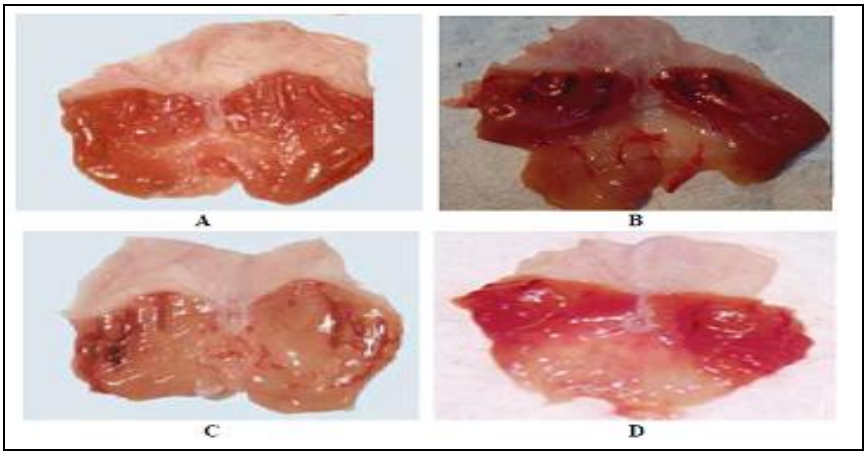


FIG. 12: IMAGES OF ULCER-INDUCED STOMACH OPENED ALONG THE GREATER CURVATURE: AFTER ORAL ROUTE OF ADMINISTRATION OF VEHICLE SOLUTION (A), AFTER ORAL ROUTE OF ADMINISTRATION OF ETHANOL (B), AFTER ORAL ADMINISTRATION OF AQUEOUS SUSPENSION OF MARKETED FORMULATION, STANDARD (C), AND BEST FORMULATION F8

DISCUSSION: Floating microbeads of Famotidine with swellable hydrophilic polymer (HPMC K4M) correctly organized the ionotropic gelation method. The prepared microbeads had an exclusive length and the % entrapment efficiency of the drug by using various formula variables, polymeric attention, and stirring fee. Increased concentration of sodium alginate increases cross-linking between alginate and calcium ions to form denser cross-linked cage structure, resulting in the generation of the more compact and smaller structure of beads, thereby increasing the polymer entrapment into alginate matrix, which result is an increase in the practical yield. On increasing the concentration of sodium alginate, the mean particle size of microbeads was found to increase because of increased cross-linking between alginate and calcium ions resulting in larger particles. The drug was uniformly dispersed in the formulation. It was observed that, due to the water-sparingly soluble nature of Famotidine, almost all the drug was entrapped in the polymer matrix, resulting in higher entrapment efficiency. Microbeads followed the polymer matrix swelling and erosion as a drug release mechanism. As the concentration of sodium alginate was increased, the cross-linking between

alginate to calcium ions increased, so a more dense cross-linked cage structure was formed, resulting in more compact structure of beads, converting microbeads into denser and smaller ones leads to increase in entrapment efficiency and the cumulative percentage drug release.

In the ANOVA study of % cumulative drug release, The Model F-value of 20.25 implies the model is significant. There is only a 0.21% chance that a large F-value could occur due to noise. P-values (0.0021) less than 0.0500 indicate model terms are significant.

In the ANOVA study of % buoyancy, The Model F-value of 11.18 implies the model is significant. There is only a 0.95% chance that a large F-value could occur due to noise. P-values (0.0095) less than 0.0500 indicate model terms are significant.

The prepared formulations have been further evaluated, and based totally on the consequences of in vitro drug launch studies, % entrapment efficiency, and % buoyancy, F8 was selected as the nice system. The best formulation (F8) accompanied Higuchi kinetics and the release mechanism changed into non-Fickian diffusion. SEM has a look at effects in microbeads having a round shape and greatest size. *In-vivo* radiographic pics had been helpful in locating the position of floating microbeads in the gastrointestinal tract and also showed that the organized microbeads could keep in the stomach for the prolonged time frame and sustained release of Famotidine. As a result, the organized buoyant microbeads might also show to be potential candidates for a couple of of-unit transport systems for intragastric drug delivery.

The in-vivo anti-ulcer assessment confirmed that animals handled with optimized formula showed tremendous ulcer safety. Accordingly, such floating microbeads of Famotidine prove to be useful for the extended gastric house of the drug, higher bioavailability, and anti-ulcer activity.

CONCLUSION: Formulation of Alginate-HPMC K4M microbeads by applying 3^2 factorial designs of batch F8 showed the better shape and surface morphology, entrapment efficiency 71.43 ±0.21% and cumulative percentage drug release 98.75 ±0.50% after 12 hrs in 0.1N HCL pH 1.20, which makes the formulation more preferable over other oral dosage formulations. These studies suggest that formulated gastro retentive drug delivery dosage of sodium alginate-HPMC K4M microbeads may be taken orally via encapsulation or converted into tablets to deliver Famotidine specifically for effective treatment of peptic ulcer.

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REFERENCES:

1. Lee TW and Robinson JR: Controlled release drug delivery systems. In: Gennaro AR, editor. Remington: The science and practice of pharmacy. 20th ed. Vol. 1. Philadelphia: Lippincott Williams and Wilkinson 2000; 903-28.
2. Gaikwad RP: Formulation and evaluation sustained release floating multi- particulate oral drug delivery system. Acta Scientific Pharmaceutical Sciences 2019; 3(5): 128-41.
3. Baviskar P, Patil P and Saudagar RB: Floating Drug Delivery System: A comprehensive review, Journal of Drug Delivery and Therapeutics 2019; 9(3): 839-846.
4. Shinde Jitendra V, Malshikare Swapnali S and Chavanrajashree S: A Review on Floating Drug Delivery System. Published in International Journal of Trend in Scientific Research and Development 2020; 4(3): 427-433.
5. Iyan Sopyan, Sriwidodo, Retno Wahyuningrum and Norisca Aliza P: A review: Floating drug delivery system as a tool to improve dissolution rate in gatric. Int J App Pharm 2020; 12(4): 51-54.
6. Vijay Sharma, Rathore DS and Amit Kumar: Floating drug delivery system. A review International Journal of Medical and Biomedical Studies 2020; 4(8): 23-30.
7. Kumar R, Gautam PK and Chandra A: Formulation and evaluation of famotidine micro balloons with enhanced anti-ulcer activity. Int J App Pharm 2018; 10(3): 131-40.
8. Mishra A, Rathore S, Marothia D and Chauhan CS: Formulation and evaluation of floating microspheres of an anti-diabetic agent. Int J Drug Dev & Res 2018; 10(2): 7-11.
9. Hajare PP and Rachh PR: Gastroretentive microballoons: a novel approach for drug delivery. International Journal of Pharmaceutical Sciences and Research 2020; 11(3): 1075-83.
10. Srivastava A, Shukla R, Sharma K, Jain H and Meshram DB: Microballoons: a gastro retentive drug delivery system. J of Drug Delivery and Thera 2019; 9(4): 625-30.
11. Srikar G, Shanthi D, Ramesh J, Kalyani V and Nagamma I: Floating microspheres: A prevailing trend in the development of gastroretentive drug delivery system. Asian Journal of Pharmaceutics 2018; 12(4): 235-42.
12. Sarjavalagi V, Prabhat K, Harshitha A, Singh S and Narayan S: Gastroretentive Drug Delivery System: A

Systematic Review. Asian J Pharm Tech 2020; 10(4): 278-84.
13. Oh T, Kim J and Ha J: Preparation of highlyporous gastroretentive metformin tablets using a sublimation method. European Journal of Pharmaceutics and Biopharmaceutics 2019; 83(3): 460-467.
14. Sarjavalagi V, Prabhat K, Harshitha A, Singh S and Narayan S: Gastroretentive Drug Delivery System: A Systematic Review. Asian J Pharm Tech 2020; 10(4): 278-84.
15. More S, Gavali K, Doke O and Kasgawade P: Gastroretentive Drug Delivery System. J Drug Del Therapeutics 2018; 8(4): 24-35.
16. Bhatt S: Design and optimization of febuxostat-loaded nano lipid carriers using full factorial design. Turk J Pharm Sci 2021; 18(1): 61-67.
17. Vijay Sharma, Rathore DS and Amit Kumar: Floating drug delivery system: A brief review International Journal of Medical and Biomedical Studies 2020; 4(8): 23-30.
18. Haridwar Lodh, Sheeba FR, Prabhat Kumar Chourasia and Harshitha Arun Pardhe: Floating Drug Delivery System, American J of Pharm Tech Res 2020; 10(4): 103-122.
19. Marbaniang D, Das R J and Pal P: Extended release floating microballoons containing *Clerodendrum colebrookianum* extract: *In-vitro in-vivo* evaluation. Indian Journal of Pharmaceutical Education and Research 2019; 53(3): 5246-54.
20. Setia M, Kumar K and Teotia D: Gastro-retentive floating beads a new trend of drug delivery system. Journal of Drug Delivery and Therapeutics 2018; 8(3): 169-180.
21. Harshal S, Chetan G, Surbhi U and Sujit P: Development and in vitro evaluation of an oral floating tablet of metronidazole. J Drug Delivery Ther 2018; 8: 83-6.
22. Chudiwal V, Shahi S, Chudiwal S and Ahale D: Innovative Technologies for Gastro-Retentive Drug Delivery Systems. Asian Journal of Pharmaceutical Education and Research 2017; 6(4): 22-28.
23. Kusuma D, Muralikrishna KS, Jyothisri S and Santhisree V: Formulation and evaluation of floating microspheres of acebutolol. Int J Pharm Sci Rev Res 2017; 46(1): 31-36.
24. Gupta P, Kumar M and Kaushik D: Pantoprazole sodium loaded microballoons for the systemic approach: *In-vitro* and *in-vivo* evaluation. Adv Pharm Bull 2017; 7(3): 461-7.

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