ORIGINAL ARTICLE

Sapindus Mukorossi Fruits Gum as Sustained Release Carrier: Optimization of Gastroretentive Drug Delivery System using Simplex Lattice Design

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Abstract

Background: Main focus of this research is to demonstrate the potential use of *Sapindus mukorossi* fruits gum in the development of drug delivery systems. Therefore, in this effort, gastroretentive tables of famotidine were prepared using simplex lattice design considering the concentration of okra gum, locust bean gum, and *S. mukorossi* fruits gum as independent variables. A response surface plot and multiple regression equations were used to estimate the result of independent variables on hardness, f_{lag} time, floating time, and drug release for 1 h, 2 h, and 8 h and for 24 h. A checkpoint batch was also ready by considering the constraints and desirability of optimized formulation to upgrade its *in vitro* performance. The significance of result was analyzed using analysis of variance and $P < 0.05$ was considered statistically significant. **Results:** Formulation mainly contains *S. mukorossi*. Fruits gum found to be satisfactory for hardness and floatability, but the combined effect of three variables was responsible for the sustained release of drug. The *in vitro* drug release data of checkpoint batch (F8) was found to be sustained well compared to the maximum suitable formulation (F6) of 7 runs. The "n" value was found to be between 0.5 and 1 telling that release of drug follows anomalous (non-Fickian) diffusion mechanism indicating both diffusion and erosion mechanism from these natural gums. Predicted consequences were nearly similar to the observed investigational values representing the correctness of the design. **Conclusions:** Research showed *S. mukorossi* fruits gum (eco-friendly natural gums) can be considered as capable SR polymers.

Key words: Famotidine, gastroretentive tablet, *Sapindus mukorossi* fruits gum, simplex lattice design

INTRODUCTION

For converting active pharmaceutical ingredients into dosage, we need some pharmaceutical excipients which may be natural either synthetic origin. With the increasing attentiveness in polymers of natural origin, the pharmaceutical world has passivity to use the most of them in their formulations. Natural origin-based polysaccharides are commonly used excipient in pharmaceutical preparations.[1] Today, a number of plant-based excipients such as guar gum, agar, acacia, alginate, cellulose, gum dammar, and gum katira.[2,3] are used in formulation development for different purposes such as diluents, binder, and release modulator. Plant origin polymer is attractive substitute for synthetic polymer because of its various advantages (biocompatible, low toxicity, eco-friendly, and low price) over synthetic products.[4,5] Okra gum, obtained from the fruits of *Hibiscus esculentus* L. (Moench),[6] Malvaceae, is a polysaccharide consisting of D-galactose, L-rhamnose, and L-galacturonic acid.[7] Locust

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bean gum (LBG) is a neutral plant galactomannan extracted from the seed (kernels) of the carob tree *Ceratonia siliqua* L. Fabaceae.[8] The okra gum and LBG show a synergistic gelation in acidic pH[9,10] and in combination with *Sapindus mukorossi* fruits gum form an original gelation which has an excellent buoyancy and useful for oral gastroretentive formulations.

Famotidine is a long-acting histamine H2 receptor antagonist used in the treatment of duodenal ulcer and benign gastric ulcer.[11] The systemic bioavailability of famotidine administered orally is 40–45%. Drug reaches peak plasma concentration in 1–3 h after oral administration with an elimination half-life of 2.5–3.5 h. This drug is more soluble in acidic pH, and its solubility decreases with increasing pH owing to its pKa (~6.5) value.[12] The beneficial delivery system would be gastroretentive drug delivery system (GRDDS) which remain in the gastric region for several hours and significantly prolong the gastric residence time of drugs.[13] Hence, the goal has been set to evaluate the potential of *S. mukorossi* fruits gum in combination with okra gum and LBG for GRDDS of famotidine using simplex lattice design (SLD).

MATERIALS AND METHODS

Okra gum (pod mucilage)

The fresh *Abelmoschus esculentus* fruits were collected and washed with water. The fruits were crushed and soaked in water for 5–6 h, boiled for 30 min, and left to stand for 1 h to allow complete release of the mucilage. The mucilage was separated using a multilayer muslin cloth and was precipitated by adding acetone (3 times the volume of filtrate). The precipitate obtained was collected, dried in an oven at 40°C, and passed through a sieve #80 to obtain discrete powder.[14]

S. mukorossi fruits gum

For the isolation of mucilage, the fruits were washed properly with distilled water to remove any dust particles. Pulp of fruits was peeled off from the fruits and was sliced into small pieces and soaked in distilled water for 24 h. The soaked pulp of fruits was further ground in a grinder and kept for 24 h for the release of mucilage. The material was squeezed through 8-fold muslin cloth to separate the marc from filtrate. Then, acetone was added to the filtrate in a ratio (1:2) to precipitate the mucilage. The mucilage was separated and dehydrated in hot air oven at 40°C, crushed, and passed through British Standard Sieve no. 80 (Mesh size 180 µm). The reddish-brown powder was kept in a desiccator until further use.

SLD

A SLD was implemented to improve the preparation variables of GRDDS of famotidine.[15] The SLD for a 3-component system is symbolized by an equilateral triangle in two-dimensional space [Figure 1]. In this design, 3 factors were assessed by varying their concentrations consecutively and keeping their overall concentration constant. Seven batches (F1-F7) of tablet formulations were prepared, one at each vertex (A, B, and C), one at the halfway point between vertices (AB, BC, and AC), and one at the center point (ABC). Each vertex represents a formulation containing the maximum amount of 1 component, with the other 2 components at a minimum level. The halfway point between the 2 vertices represents a formulation containing the average of the minimum and maximum amounts of the two ingredients. The center point represents s a formulation containing one-third of each ingredient. Concentrations of *S. mukorossi* fruits gum (A), okra gum (B), and LBG (C) were selected as independent variables. Hardness (kg/cm^2), floating lag time (f_{lag} time, sec), drug release for 1 h (%), drug release for 2 h (%), drug release for 8 h (%), and drug release for 24 h (%) were taken as response values (dependent variables). The response values obtained were analyzed using multiple regression analysis to find their relationship with the factors used.

Formulation of gastro retentive matrix tablets

A weighed quantity of drug, polymers, effervescent combination, and diluent [Table 1] were passed through sieve #80, mixed and triturated in a mortar for 10 min to obtain a uniform mixture. Powder was lubricated with magnesium stearate and talcum powder for 3 min.

Powder mass was compressed with multistation tablet punching machine using 8 mm concave punches (Model no: K-10402NP, Ahmedabad, India). The dimensional specifications were measured using thickness gauge (Okimoto); weight variation test was conducted as per pharmacopeia of India specifications. Hardness of the tablet was measured using Pfizer type hardness tester.

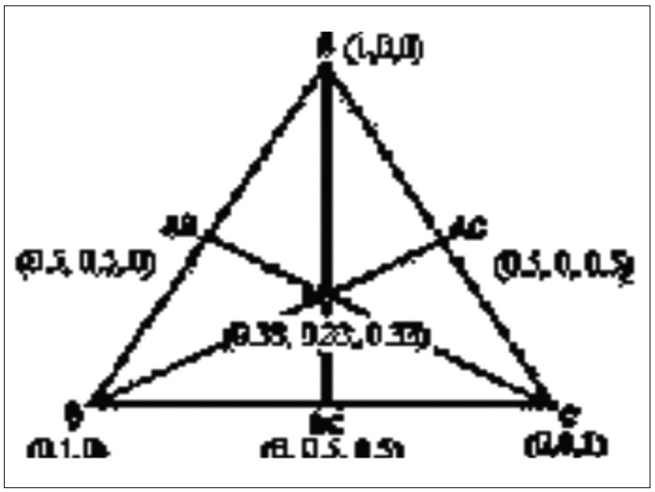

Figure 1: Equilateral triangle representing simplex lattice design

Evaluation

Drug content estimation

Standard calibration curve of famotidine was constructed using ultraviolet (UV)-visible spectrophotometer (Systronics-2201, New Delhi, India). Drug solution was prepared in methanol at the concentration range of 10–50 µg/mL, sonicated, and filtered using 0.45 µ (Millipore) membrane filter. The drug content of standard drug solution and tablet formulation was measured at 266 nm against methanol as a blank solution.[16] This method was found to have good repeatability and reproducibility, and relative standard deviation was not more than 2%. The working curve equation for famotidine was y = ×0.0315 with correlation coefficient value, $R^2 = 0.99933$.

In vitro floatability

In vitro floatability[17] of the formulation was determined by placing weighed tablet matrices in the USP dissolution testing Apparatus II (Thermonik Campbell electronic-DR-08, India), in 900 mL of simulated gastric fluid (0.1N HCl) at 37 ± 0.5°C, rotated at 75 rpm. The time required for the tablet to rise to the surface and float was determined as flag time. Floating time was the time, during which the tablet floats (including f_{lag} time) in simulated gastric fluid dissolution medium.[18,19]

Swelling index

The extent of swelling was measured in terms of percent weight gain by the tablet.[20,21] Each tablet formulation was kept in a beaker containing 100 mL of simulated gastric fluid; the tablet was withdrawn, blotted with tissue paper, and reweighed. Then, for every 1 h, weights of the tablets were noted and the process was continuous till the end of 6 h. The percentage weight gain by the tablet was calculated using the formula.

$$SI = \{(Mt\text{-}M_0)/M_0 \times 100$$

Where SI is swelling index, Mt is the weight of tablet at time "t," and Mo is the weight of tablet at time "t" =0.

Dissolution studies

The release rate of famotidine from floating matrix tablets was determined using USP XXIV dissolution apparatus (Thermonik Campbell electronic-DR-08, India) Type-II (paddle) method for 24 h. The study was carried out using 900 mL of simulated gastric fluid (0.1 N HCl) at 37 ± 0.5°C at 75 rpm. Aliquot volume of 5 mL was withdrawn from the dissolution apparatus hourly for 24 h, and the samples were replaced with fresh prewarmed dissolution medium. The withdrawn samples were suitably diluted with methanol and filtered, and drug content was determined using UV-spectrophotometer.[22,23]

Kinetic modeling on drug release profile

The dissolution profile of most satisfactory formulation (F6) of 7 runs and a checkpoint batch (F8) were evaluated using mathematical models to describe the kinetics of the drug release. The kinetics of drug release was evaluated for Higuchi, Korsmeyer–Peppas, first-order and zero-order models to check the phenomena controlling the drug release from tablets.[24,25] The goodness of fit was evaluated using the correlation coefficient values (r^2).

Statistical analysis

The statistical assessment of SLD responses was performed using analysis of variance (ANOVA) and by applying the Student – *t*-test. Model terms are significant if the calculated "*t*" value is less than the critical value of "*t*" (0.05).

Table 1: Formulations of famotidine according to SLD

Ingredients	Formulation code							
	F1	F2	F3	F4	F5	F6	F7	F8
Drug (famotidine)	20	20	20	20	20	20	20	20
S. mukorossi fruits gum	0	33.33	100	0	16.7	66.7	16.7	72.10
Okra gum	0	33.33	0	100	66.7	16.7	16.7	0
Locust bean gum	100	33.33	0	0	16.7	16.7	66.7	27.89
Sodium bicarbonate	40	40	40	40	40	40	40	40
Tartaric acid	10	10	10	10	10	10	10	10
Polyvinylpyrrolidone	15	15	15	15	15	15	15	15
Magnesium stearate	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1
Lactose QS	200	200	200	200	200	200	200	200

SLD: Simplex lattice design, *S. mukorossi: Sapindus mukorossi*

RESULTS AND DISCUSSION

Formulation of gastroretentive matrix tablets

Formulation the drug release characteristics was varied according to the types and proportion of matrix forming polymers in the formulation. *S. mukorossi* fruits gum was selected as a hydrophilic matrixing agent.[26] LBG and okra gum were considered as gelling agents, and they impart sufficient integrity to the tablets and works as release modifiers. Okra gum is insoluble in gastric pH but enormously swells which helps in retarding the drug release. Sodium bicarbonate generates CO_2 gas in the presence of tartaric acid on contact with dissolution medium. The gas generated is trapped and protected within the gel (formed by hydration of *S. mukorossi* fruits gum), thus decreasing the density of the tablet.[27] As the density of the tablet falls below 1 (density of water), the tablet becomes buoyant.

SLD

The general equation for the response-based SLD for three component systems consisting terms for pure component and mixtures of component.[28]

$$R = B_0+b_1A+b_2B+b_3C \quad (1)$$

Where R is the response variable and A, B, and C are the proportions of formulation components. b_0 is the arithmetic mean response of the 7 runs and b_1, b_2, and b_3 are estimated coefficient for the factor A, B, and C, respectively. The coefficients can be calculated from the responses of "R" using a multiple regression equation. The fitted equations relating the hardness, flag time, and drug release for 1 h, drug release for 2 h, drug release for 8 h, and drug release for 24 h to the transformed factor were used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e., positive or negative).

Effect of independent variables on hardness

$$R1 \text{ (Hardness)} = +5.52*A+3.40*B+5.73*C \quad (2)$$

Although the statistical results infer ("F" value of 5.21 and $P = 0.0769$ [<0.05]), the linear model equation is not significant for hardness the values of regression coefficient infers, and the concentration of *S. mukorossi* fruits gum (A) and LBG (C) has equally contributed for the hardness [Figure 2a]. As *S. mukoross*i fruits gum (A) and LBG (C) has sufficient cohesiveness, fibrous integrity makes them to undergo binding and contributed for hardness.[29,30]

Effect of independent variables on f_{lag} time

$$R2 (f_{lag} \text{ time}) = +30.61*A+158.92*B+55.76*C \quad (3)$$

The linear equation for flag time indicates that the factor "A" has a more significant effect on flag time than "B" and "C" [Figure 2b]. This is further evident with the model terms for flag time being significant with "F" value of 10.44 and $P = 0.0258$ (<0.05) on a linear model. Floating lag time was found to increase at a higher level of okra gum and decreases as the level of *S. mukorossi* fruits gum increases. This is due to high swelling property of the later. Hence, a higher proportion of *S. mukorossi* fruits gum is important in the formulation to decrease the flag time. This is also evident from the results of swelling index determination (221.95–257.15 (%) for F1 to F7 at the end of 6 h). Swelling index increases with increase in the concentration of *S. mukorossi* fruits gum signifying its importance for decrease in flag time.[29-31]

Effect of independent variables on drug release

The extent of coefficients observed for 1, 2, 8, and 24 h release found from the results of multiple linear regression analysis is expressed in equations 4, 5, 6, and 7, respectively. The release rate and percentage drug release for the 7 batches (F1-F7) showed a varied difference (i.e., 85.26–94.98%) as shown in Table 2. Formulation F2 prepared using only *S. mukorossi* fruits gum, bushed before 8 h, and fails to sustain the drug release till 24 h. This highest value of percentage release observed in initial hours is due to little value of both the independent variables (B and C), thus weakening the gel strength.

Drug release for 1 h and 2 h

$$R3 \text{ (drug release for 1 h)} = +9.76362*A+8.8436*B+3.39562*C \quad (4)$$

$$R4 \text{ (drug release for 2 h)} = +17.89*A+11.19*B+5.75*C \quad (5)$$

The equations 4 and 5 conclude that the "A" has extra promising outcome on increase in drug release and the factor "B" and "C" in delaying drug release for 1 and 2 h. Although the model terms are not significant ($P = 0.1218$ and 0.1315 [<0.05] for 1 h and 2 h drug release), it is understood that the water solubility of *S. mukorossi* fruits gum assistances in increasing drug release and the water insolubility but the swellability of LBG and okra gum is responsible for it.[32] Optimum concentration of *S. mukorossi* fruits gum must be there in the formulation for immediate release of drug at initial hours.

Drug release for 8 h and 24 h

The concentration of *S. mukorossi* fruits gum has a significant part in improving the drug release for 8 and 24 h and opposite is correct with a concentration of okra gum and LBG. As the concentration of okra gum and LBG rises, it causes a rise in viscosity of the swollen gel matrix, which declines the water diffusion into the core layer. The decrease in hydration of matrix contributes more interference for drug

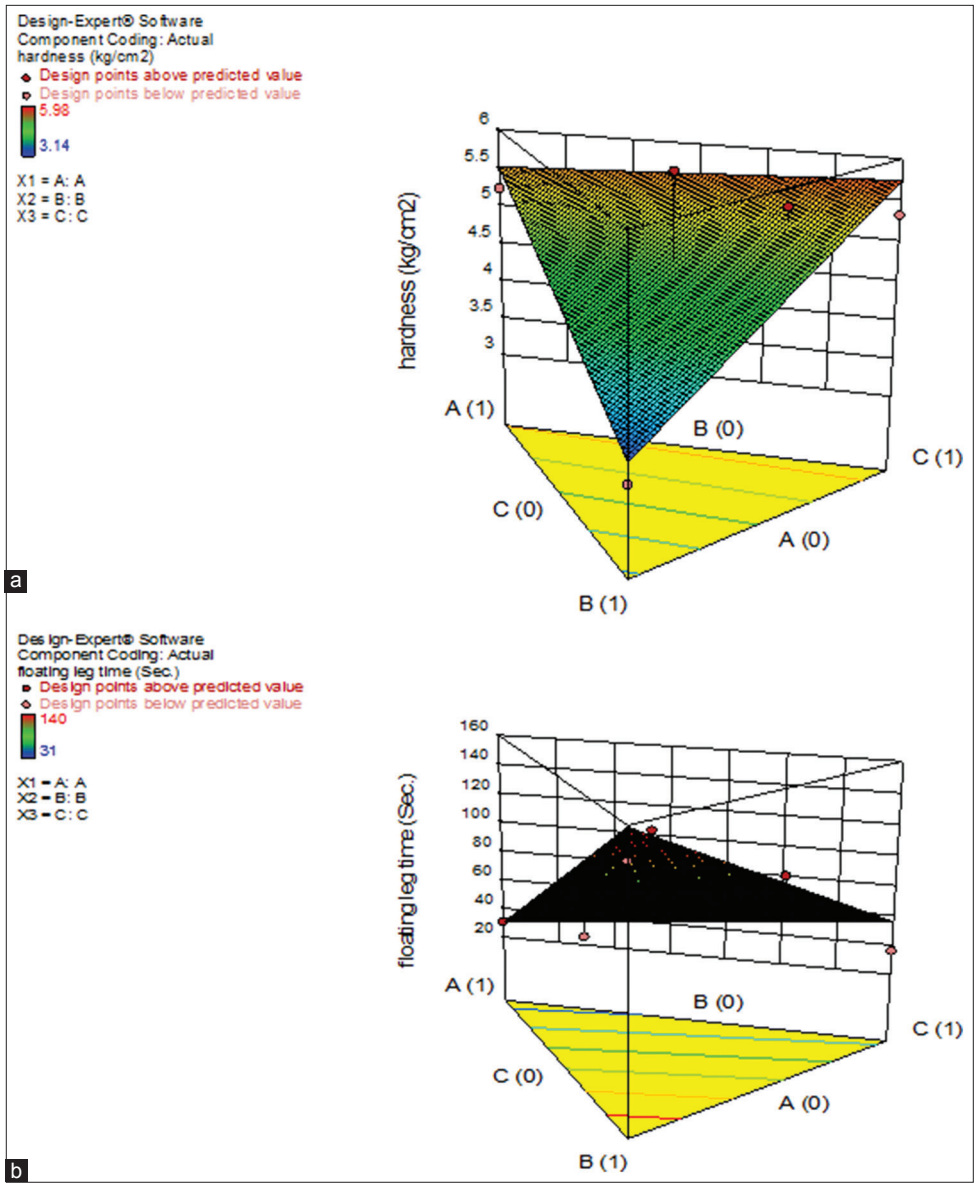

Figure 2: (a) Response surface plots showing the effect of concentration of *Sapindus mukorossi* fruits gum, okra gum, and locust bean gum on hardness (kg/cm^2) and (b) floating lag time (sec)

Table 2: Characterization of famotidine gastro retentive formulation

Formulation code	Responses (dependent variables)					
	Hardness (kg/cm^2)	Flag time (s)	Drug release for 1 h (%)	Drug release for 2 h (%)	Drug release for 8 h (%)	Drug release for 24 h (%)
F1	5.31	36	4.81	9.11	31.19	86.36
F2	5.98	98	5.13	10.2	36.32	85.55
F3	5.24	31	12.11	23.13	78.51	-
F4	3.14	140	11.2	15.83	39.13	89.46
F5	3.99	140	6.15	7.01	40.31	85.26
F6	5.08	37.23	6.63	9.15	41.08	94.98
F7	5.48	90.11	5.31	6.85	38.89	86.11

diffusion and accordingly reduction in release rate.[33] This can be further elucidated with the help of response surface plot [Figure 3].

$$R5 \text{ (drug release for 8 h)} = +67.15*A+35.34*B+28.42*C \quad (6)$$

$$R6 \text{ (drug release for 24 h)} = +95.68*A+86.82*B+84.68*C \quad (7)$$

The model terms for R5 (8 h release) and R6 (24 h release) were established to be significant with an F = 5.0 and 1.39, and $P = 0.0794$ and 0.3745 (<0.05) correspondingly. These outcomes visibly indicate that the percentage drug release is powerfully dependent on all the designated independent variables. This equation concludes that the thoughtful combination of *S. mukorossi* fruits gum, okra gum, and LBG is essential[34] to control and sustain the drug release for 24 h. Table 3 shows the outcomes of the ANOVA, which was performed to identifying significant factors.

Based on this investigation, formulation F6 was arbitrarily selected as an optimized batch which releases the drug satisfactorily till the end of 24 h in spite of its high flag time of 37.23 ± 13.79 s. To overcome the drawbacks of F6 formulation, a checkpoint batch F8 prepared by considering the constraints and desirability to improve [Table 4] its' *in vitro* performance. The investigational outcomes of formulation F8 for flag time, total floating time, and swelling index were found to be 37.11 ± 4.16 s, >24 h, and 20.4.0 ± 5.30% (up to 6 h), respectively. The *in vitro* drug release data were found to be sustained well compared to the most satisfactory formulation (F6) of 7 runs [Figures 4 and 5]. Predicted results were almost similar to the observed experimental values indicating the accuracy of the design [Table 5]. All preparations were found to be buoyant for more than 24 h.

Kinetic modeling on drug release profile

The release profile and kinetics of drug release are important because they correlate the *in vitro* and *in vivo* drug responses

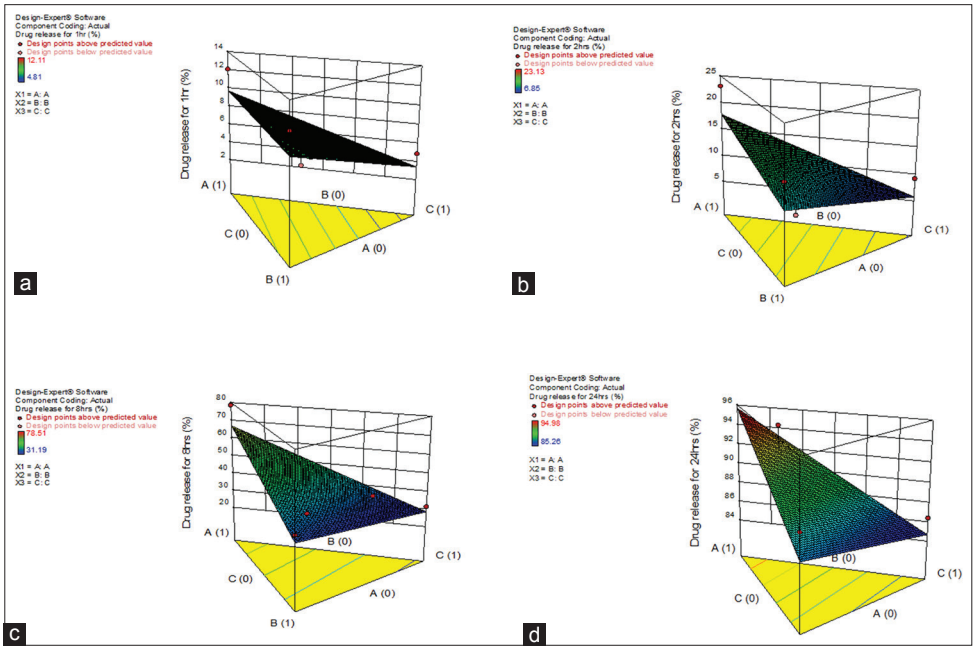

Figure 3: Response surface plots showing the effect of concentration of *Sapindus mukorossi* fruits gum, okra gum, and locust bean gum on % drug release for (a) 1 h, (b) 2 h, (c) 8 h, and (d) 24 h, respectively

Table 3: Summary of ANOVA table for dependent variables from SLD

Source	Sum of squares	Degree of freedom	Mean square	F value	*P* value
Hardness	4.15	2	2.08	5.21	0.0769
f_{lag} time	11556.97	2	5778.48	10.44	0.0258
1 h drug release	29.62	2	14.81	2.34	0.2128
2 h drug release	92.38	2	46.19	1.59	0.3105
8 h drug release	1066.69	2	533.35	5.10	0.0794
24 h drug release	33.93	2	16.96	1.39	0.3745

SLD: Simplex lattice design, ANOVA: Analysis of variance

Table 4: Coded quantities of the check point batch "F8" and their desirability

Constraints						
Name	**Goal**	**Lower limit**	**Upper limit**	**Lower weight**	**Upper weight**	**Importance**
S. mukorossi fruits gum (A)	Is in range	0	1	1	1	3
Okra gum (B)	Is in range	0	1	1	1	3
LBG (C)	Is in range	0	1	1	1	3
Hardness	Is in range	3.14	5.98	1	1	3
f_{lag} time	Minimize	31	140	1	1	3
8 h drug release	Minimize	31.19	78.51	1	1	3
24 h drug release	Maximize	80.5	100	1	1	3
Solutions (desirability 0.693)						
A	B	C	Hardness	Flag time (sec.)	8 h release	24 h release
0.7210	-	0.2789	-	37.62	56.34	98.51

S. mukorossi: Sapindus mukorossi, LBG: Locust bean gum

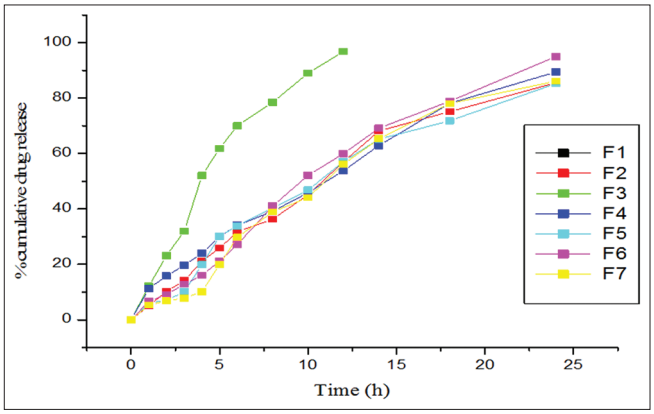

Figure 4: Comparative release profiles of famotidine gastroretentive formulations

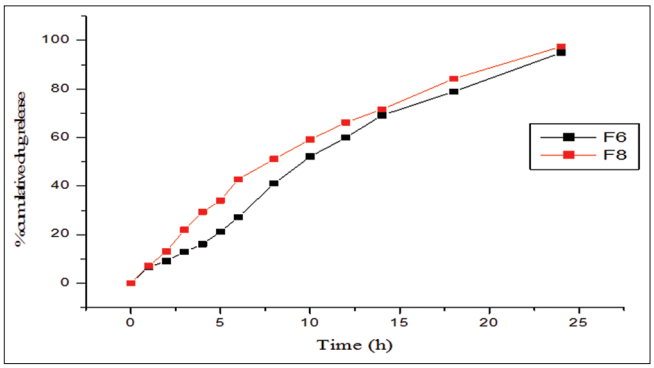

Figure 5: Comparative drug release profiles of F6 and F8 formulations

by comparing results of pharmacokinetics and dissolution profile patterns.[35] Hence, the cumulative drug release results of F6 and F8 formulation were fixed into various mathematical models and the results are shown in Table 6. The *in vitro* drug release pattern of F6 showed the highest regression value ($R^2 = 0.9786$) for Korsmeyer–Peppas as model. The "n" value was found to be between 0.5 and 1, suggesting that the release of drug follows anomalous (non-Fickian) diffusion

Table 5: Comparison of experimented and predicted values of check point batch "F8"

Parameter	Predicted values	Experimented values
Hardness (kg/cm^2)	5.58	5.42
f_{lag} time (sec.)	37.62	37.11
% Drug release at 1 h	7.98	7.03
% Drug release at 2 h	14.50	13.19
% Drug release at 8 h	56.34	51.14
% Drug release at 24 h	98.51	97.47

mechanism. The *in vitro* drug release of checkpoint batch (F8) showed the highest regression coefficient values for Higuchi model (0.997), thus indicating absolute correlation between the two variables for the Higuchi model. Checkpoint batch followed Higuchi's equation proving that the release is by diffusion mechanism. Release kinetics may be following both diffusion and erosion mechanism from these natural gums.[36]

CONCLUSIONS

Famotidine gastroretentive tablet is prepared using plant origin polymers which showed necessary high drug content, ideal hardness, floatability, swelling index, and satisfactory release characteristics. The organized formulation method using SLD in the research helped in understanding the effect of formulation variables. The use of plant origin polymers can be a worthy replacement for synthetic polymers in the progress of controlled release dosage forms because plant-based materials can be altered to encounter the necessities of drug delivery systems. Formulations prepared by eco-friendly polymers can be considered as capable SR polymers substances to bring about sustained release action, supported by other elaborated investigation in this aspect.

Table 6: Kinetic modeling of drug dissolution profiles

Formulation code	Zero order		First order		Higuchi		Korsmeyer–Peppas	
	r^2	K	r^2	K	r^2	K	r^2	n
F6	0.9714	4.1989	0.939	0.0511	0.9762	25.041	0.9786	0.9392
F8	0.9503	3.9576	0.9172	0.0595	0.997	24.11	0.9802	0.8319

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