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Beni-Suef Univ J Basic Appl Sci (2022) 11:5
https://doi.org/10.1186/s43088-021-00186-9

Beni-Suef University Journal of Basic and Applied Sciences

RESEARCH Open Access

Factorial design approach to fabricate and optimize floating tablets based on combination of natural polymer and rice bran wax

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Abstract

Background: The aim of the present research work was to fabricate a novel gastroretentive drug delivery system in the form of tablets using a combination of natural polymer and rice bran wax with an intention to control drug delivery and to enhance the gastric residence time of the model drug Famotidine in the gastrointestinal tract.

Results: The results of the preliminary trial batches prepared by using the hot melt granulation technique resulting in six different formulations showed good physicochemical characteristics and tablets conformed to the Pharmacopoeial specifications. Gastroretentive tablets containing natural polymer showed prolonged drug release comparable to Methocel. The optimized formulation (C3) using 3^2 factorial design showed FLT 27 ± 2.47 s, SI 92.68 ± 1.36% and % CDR 98.89 ± 0.39% at 12 h. The stability studies indicated the stability of the formulation during storage.

Conclusions: It was concluded that the release profile fitted best to zero-order equation with non-Fickian diffusion mechanism of drug release which demonstrates swelling-controlled drug release mechanism. Thus, the formulated tablets have the potential for improved release and gastroretentive properties.

Keywords: Gastroretentive, Natural polymer, Rice bran wax, Factorial design, Drug release, Swelling index

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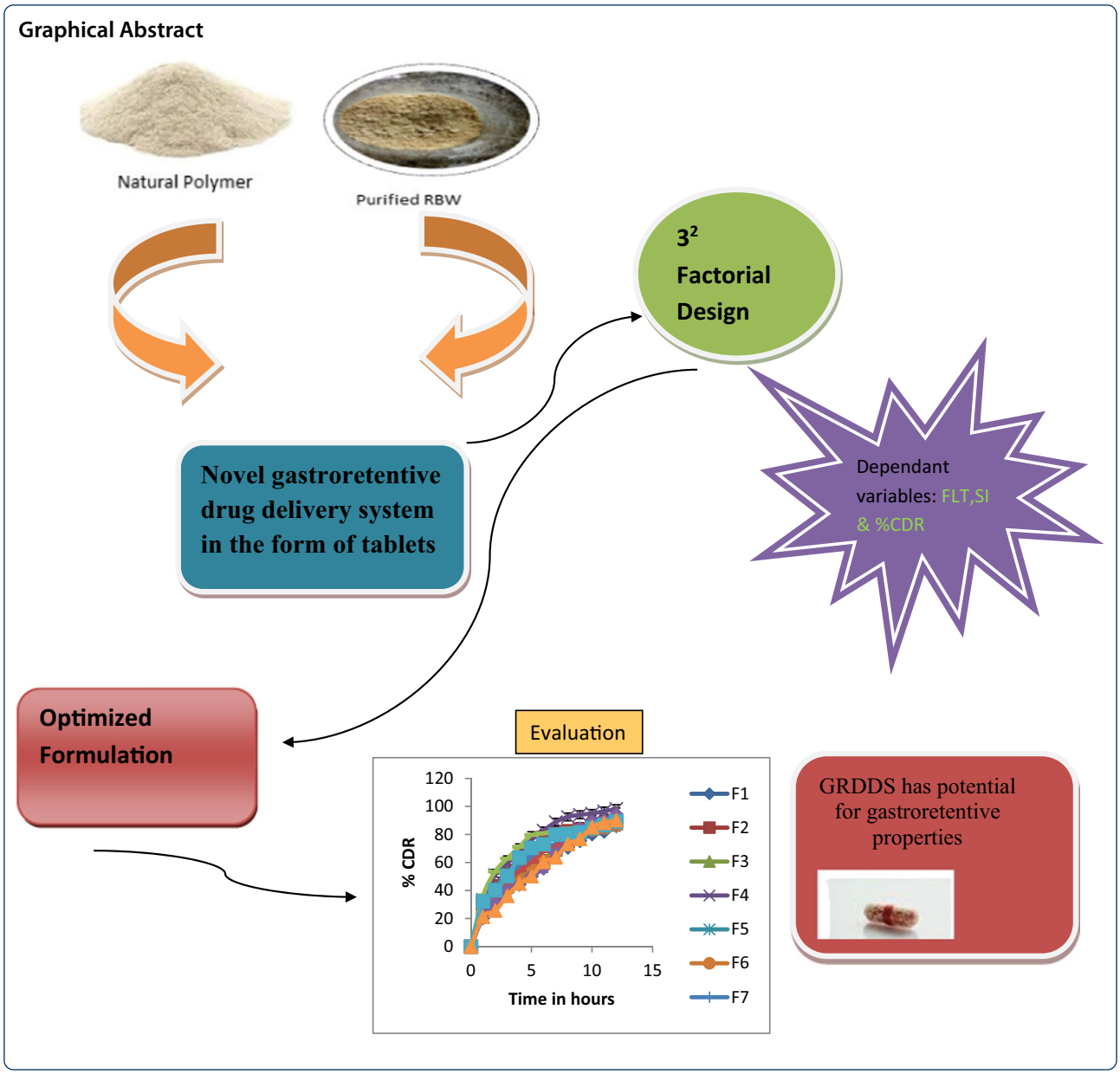

1 Background

The oral route is the most versatile, convenient and normally employed route of drug delivery for systemic action [1]. Controlled release drug delivery by oral route is widely used because of its easy administration, patient suitability and formulation changeability [2]. To achieve the suitable therapeutic activity, frequent dosing of drugs is necessary. Several attempts are being made to reduce dosing frequency of a drug delivery system providing therapeutically effective plasma drug concentration for a longer period of time in a controlled and reproducible manner [2, 3]. In the upper gastrointestinal tract (GIT), for achieving, local or systemic effects, gastroretentive drug delivery system (GRDDS) can be used to prolong the residence time of the drug and also to target the site-specific drug release. Prolonged gastric retention by these systems may improve bioavailability and dissolution for drugs that are less soluble in a high pH environment, provided that the drug is stable in gastric environment [4, 5].

Drug absorption in the GIT depends upon the factors such as gastric emptying process, the gastrointestinal transit time of dosage forms, drug release from the dosage form and site of drug absorption [6]. A drug must be in a solubilized and stable form to successfully cross the biological barrier. As the drug travels through the GIT, its pH ranges from 1 to 8 [7].

Famotidine was used as a model drug which is a potent histamine H2-receptor antagonist. It is widely used in the treatment and prevention of gastric ulcers, duodenal ulcers, Zollinger–Ellison syndrome and gastroesophageal reflux disease. Poor absorption, less bioavailability and short half life of Famotidine after oral administration helped the development of a controlled release formulation [8, 9].

Natural gums are polysaccharides consisting of numerous sugar units such as glucose, galactose, rhamnose, arabinose, xylose, mannose and uronic acids. Due to their availability, safety and biodegradability, they are preferred over synthetic polymers. The majority of the gums are safe enough to be consumed and are hence, widely used in the field of drug delivery and as food additives [10].

Guar gum is obtained from the seeds of the plant Cyamopsis tetragonoloba, family: Leguminosae [11–13]. Guar gum hydrates readily in aqueous media to produce a viscous pseudoplastic solution that has greater low shear viscosity than the other hydrocolloids [14, 15].

The polymer and wax are commonly used as matrix-forming components. The use of wax seems to have a particular advantage due to chemical inertness against other materials, good stability varying at pH and moisture levels and well-established safe application in humans being [16].

The source of rice bran wax (RBW) is *Oryza sativa* belonging to family Graminae which is available plentifully. It is an important by-product of the rice bran oil industry. RBW is used as binding agent, plasticizer, coating and gelling agent. It is also used in cosmetics and in foods as a thickener [16, 17].

The objective of the present work was to formulate floating tablets for increased residence time in the stomach and also for controlling drug delivery using natural polymer (bioadhesive) and RBW (release retardant).

2 Methods

2.1 Materials

Famotidine as a gift sample was supplied by Cipla, Goa. Crude RBWwas obtained from Maheshwari Solvent Extraction Plant, Gondia, Maharashtra, India. Guar gum was purchased from Merck Specialities Pvt. Ltd., Mumbai, and all other excipients used were of analytical grade.

2.2 Purification and characterization of RBW

RBW was purified and characterized for further use in the study [16–19].

2.3 Compatibility study

Mixtures consisting of different ratios of drug/RBW, drug/polymer and either drug or RBW/polymer alone were subjected to FTIR analysis using a model IR Affinity-1S FTIR spectrophotometer (Shimadzu Corporation Kyoto, Japan).

2.4 Formulation of gastroretentive tablets containing natural polymer, methocel K4M and RBW (preliminary trial batches)

For the formulation of gastroretentive tablets, the six different preliminary trial batches were prepared (Table 1) each containing Famotidine as a model drug (40 mg) and by varying the concentration of polymer (20 mg, 25 mg, 30 mg) and RBW (15 mg, 20 mg, 25 mg). Melt granulation technique was used for the preparation of gastroretentive tablets [20]. The tablets (250 mg) were prepared by direct compression method using flat-faced 6-mm punch (Rimek Mini Press-I machine).

Table 1 Preliminary trial batch composition containing HPMC K4 M and RBW, guar gum and RBW

Ingredients	Quantity per mg Tablet (mg)					
	HF1	HF2	HF3	GF1	GF2	GF3
Famotidine	40	40	40	40	40	40
RBW	25	15	20	25	15	20
HPMC K4 M	20	25	30	–	–	–
Guar gum	–	–	–	20	25	30
Ethyl cellulose	10	10	10	10	10	10
Sodium bicarbonate	7.5	7.5	7.5	7.5	7.5	7.5
Magnesium stearate	1	1	1	1	1	1
Talc	2	2	2	2	2	2
Lactose	144.5	149.5	139.5	144.5	149.5	139.5
Total Weight	250					

2.5 Evaluation of gastroretentive tablets containing natural polymer, methocel K4M and RBW (preliminary trial batches)

The prepared tablets were evaluated for precompression and post-compression parameters [21–23].

2.6 In vitro buoyancy

Floating lag time (FLT) and total floating time (TFT) were considered as in vitro buoyancy. The tablets were placed in a 100-ml beaker containing 0.1 N HCl, which was maintained at 37 °C. The time required for the tablet to rise to the surface of the medium was determined as the buoyancy lag time or FLT. The total buoyancy time or total floating time was considered as the time duration for which the dosage form remained floating on the surface of medium [24, 25].

2.7 Swelling index (%)

The tablets were weighed individually and placed separately in Petri dish containing 5 ml of 0.1 N HCl and incubated at 37 °C ± 10 °C. At regular 2-h time intervals until 12 h, the tablets were removed from Petri dish, and the excess surface liquid was removed carefully using the tissue paper. After draining free water by blotting with tissue paper, these were weighed for weight gain on the analytical balance [26, 27]. The following formula was used for calculating swelling index (SI):

Swelling Index = (weight of tablet at time-weight of tablet before immersion)/ (weight of tablet before immersion) × 100.

2.8 In vitro dissolution studies

The in vitro dissolution of all the batches were carried out in 0.1 N hydrochloric acid (HCl) as the dissolution medium using USP Type II Apparatus at 50 rpm and maintaining the temperature at 37 ± 0.5 °C. The dissolution was carried out for 12 h [28, 29].

2.9 Formulation of gastroretentive tablets containing natural polymer and RBW using 3^2 full factorial design

An optimization for the prepared buccoadhesive tablets were carried out using 3^2 (two-factor; three-level) experimental design. The concentrations of Guar gum (X_1) and the concentrations of RBW (X_2) were selected as independent variables (factors), which were varied at three levels (low, intermediate and high). Based on the preliminary trial batches, the levels of the three factors were chosen prior to the application of the factorial design. The FLT (Y1), SI (Y2) and % CDR (Y3) were selected as dependent variables (responses).

2.10 Evaluation of gastroretentive tablets containing natural polymer and RBW using 3^2 full factorial design

The prepared tablets were evaluated for precompression and post-compression parameters [21–23].

2.11 Optimization of formulation using 3^2 factorial design

For optimization, effects of various independent variables upon measured responses and their interactions created by 3^2 factorial design were represented using the following mathematical model equation:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_{12} + b_{22}X_{22} \quad (1)$$

where Y is represented as dependent variable, arithmetic mean response of the nine runs is indicated by b_0, and the estimated coefficient for the factor X_1 is b_1. The main effects ($X1$ and $X2$) are the average result of change of one factor at a time from its low to high value. Change in response with the change in factors simultaneously is given by interaction terms X_1X_2. The polynomial terms (X_{12} and X_{22}) are included to investigate nonlinearity [30]. The significance of the model ($P < 0.05$) and individual response parameters were estimated employing one-way ANOVA.

2.12 Statistical analysis and mathematical model fitting

Statistical optimization was performed using Design-Expert 6.0.8 software (Stat-Ease Inc., USA). Rest of the data were analyzed using simple statistics.

The in vitro dissolution data were fitted to various mathematical models like zero-order, first-order, Higuchi, and Korsmeyer–Peppas models [31–34] for analyzing the mechanism of drug release from the tablets.

2.13 Selection of optimized formulation and validation of mathematical models

To validate the selected experimental design and polynomial equations, three optimum check points (formulation compositions) were chosen by intensive search performed over the entire experimental domain, and final formulation optimization was performed using a graphical optimization. The resultant experimental values were then quantitatively compared with predicted values. Formulation having maximum desirability value of % CDR, SI and FLT was found in the experimental region of the overlay plot which were selected as the optimized formulations.

Table 2 Characterization of RBW

Parameters	Obtained Results
Color	Yellowish white
Odor	Characteristics
Taste	Bland
Melting Point*	78 °C-82°C
Solubility	Hot alcohol, Benzene, Carbon tetrachloride, Ether, Chloroform, Isopropyl ether and insoluble in water
Saponification Value*	80–85
Acid Value*	13–16
Iodine Value*	18–22
Unsaponifiable Matter	45%

*Values are the mean of three readings

2.14 Stability study

The stability studies were carried out following ICH guidelines. The optimized formulation was filled into the container and sealed packed. The studies were performed at 40 ± 2 °C and 75 ± 5% relative humidity (RH) in the desiccators with saturated salt solution for up to 6 months [35].

3 Results

3.1 Characterization of RBW

The wax was characterized for various properties as per Pharmacopoeial guidelines (Table 2).

3.2 Compatibility study

Spectroscopic studies (FTIR) showed that there was no chemical interaction between the Famotidine (model drug) and the polymer as well as RBW (Fig. 1).

3.3 Evaluation of gastroretentive tablets containing natural polymer, methocel K4M and RBW (preliminary trial batches)

All the tablets passed test for weight variation, hardness, content uniformity and showed acceptable results with respect to drug content (99.6 ± 0.7) and % friability (Tables 3, 4).

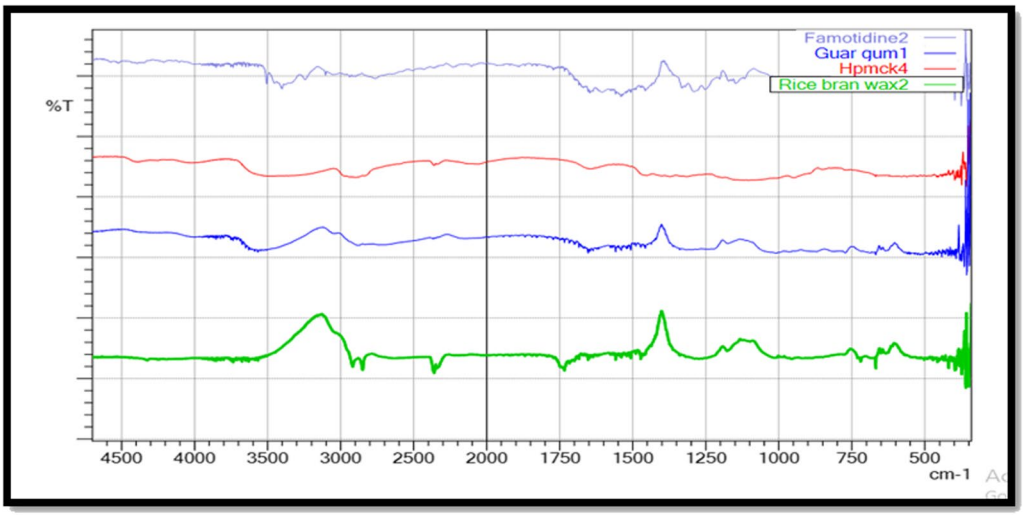

Fig. 1 Overlay spectrum of physical mixture of drug, polymer and gum

Table 3 Evaluation of pre compression parameters (HF1-HF3 and GF1-GF3)

Formulation Code	Loose bulk density (gm/cm^3)*	Tapped bulk density (gm/cm^3)*	Hausner ratio (HR)*	Carr's index (CI)*	Angle of repose (θ°)*
HF1	0.39 ± 0.05	0.55 ± 0.12	1.41 ± 0.19	11.11 ± 0.05	0.58 ± 0.02
HF2	0.44 ± 0.05	0.5 ± 0.1	1.15 ± 0.35	10.93 ± 0.05	0.39 ± 0.02
HF3	0.33 ± 0.01	0.65 ± 0.0	1.9 ± 0.13	11.12 ± 0.06	0.52 ± 0.03
GF1	0.55 ± 0.05	0.63 ± 0.09	1.22 ± 0.19	11.11 ± 0.06	0.51 ± 0.03
GF2	0.52 ± 0.05	0.59 ± 0.0	1.13 ± 0.11	10.86 ± 0.06	0.51 ± 0.05
GF3	0.44 ± 0.06	0.51 ± 0.09	1.17 ± 0.34	10.96 ± 0.07	0.46 ± 0.03

Values are expressed as mean ± S.D., $n = 3$

Table 4 Evaluation of post-compression parameters (HF1-HF3 and GF1-GF3)

Code	Dimension		Hardness (kg/cm^2)*	Friability (%)*	Weight variation (%)*	Drug content (%w/w)*
	Diameter (mm)*	Thickness (mm)*				
HF1	3.03 ± 0.16	6.1 ± 0.21	4.25 ± 0.5	0.310 ± 0.01	90.04 ± 0.023	19.08 ± 0.05
HF2	3.03 ± 0.16	6.0 ± 0.26	4 ± 0.5	0.180 ± 0.01	95.43 ± 0.017	16.60 ± 0.33
HF3	3.03 ± 0.16	6.06 ± 0.24	3.75 ± 0.5	0.624 ± 0.03	87.59 ± 0.629	10.36 ± 0.05
GF1	3.03 ± 0.16	5.96 ± 0.28	4.5 ± 0.5	0.635 ± 0.03	75.51 ± 0.011	15.72 ± 0.017
GF2	3.03 ± 0.16	6.0 ± 0.14	4.5 ± 0.866	0.565 ± 0.03	87.55 ± 0.906	19.23 ± 0.017
GF3	3.03 ± 0.16	6.1 ± 0.25	4 ± 0.28	0.619 ± 0.01	95.43 ± 0.663	27.65 ± 0.011

Values are expressed as mean ± S.D., n = 3

Table 5 In vitro buoyancy study (HF1- HF3 and GF1- GF3) and SI

Formulation code	FLT (s)*	TFT (h)*	SI (%)*
HF1	8 ± 0.60	> 12	65.38 ± 0.003
HF2	12 ± 0.88	> 12	72.6 ± 0.009
HF3	10 ± 0.46	> 12	84.8 ± 0.009
GF1	15 ± 0.43	> 12	73.45 ± 0.004
GF2	10 ± 0.66	> 12	88.85 ± 0.006
GF3	12 ± 0.07	> 12	95.1 ± 0.008

*Values are expressed as mean ± S.D., *n* = 3*

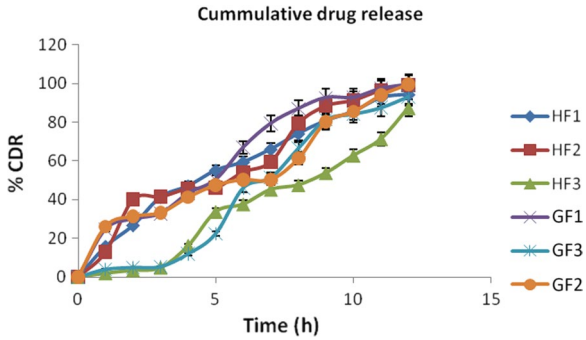

Fig. 2 % CDR of batches (HF1-HF3 and GF1-GF3)

3.4 In vitro buoyancy

The results for in vitro buoyancy, i.e., FLT and TFT are shown in Table 5. FLT for all the tablets was found less than one minute, and for all the tablets, TFT was found more than 12 h.

3.5 Swelling index (SI)

The results of SI are shown in Table 5. A swelling study was performed on all the batches for 12 h. SI was found to be in the range of 65% to 95%.

3.6 In vitro dissolution studies

Cumulative percentage drug release (% CDR) of batches (HF1-HF3 and GF1-GF3) is shown in Fig. 2. Drug release for HF1 to GF3 was found 94.32% to 99.71% for 12 h.

3.7 A 3^2 full factorial design of experiment for gastroretentive tablets containing natural polymer and RBW

In the present investigation, to study the effect of independent variables, i.e., the concentration of guar gum (X1), the concentration of RBW (X2) on dependent variables such as FLT, SI and % CDR, a 3^2 full factorial design was used based on the results of the preliminary trial batches.

Table 6 A 3^2 factorial design experimental layout

Formulation code	Guar Gum (X1)* (mg)	RBW (X2)* (mg)
F1	20 (− 1)	25 (+ 1)
F2	30 (+ 1)	20 (0)
F3	20 (− 1)	20 (0)
F4	20 (− 1)	15 (− 1)
F5	30 (+ 1)	15 (− 1)
F6	25 (0)	15 (− 1)
F7	25 (0)	25 (+ 1)
F8	30 (+ 1)	25 (+ 1)
F9	25 (0)	20 (0)

*X1 and X2 represent the main effects (factors); (+ 1): higher value, (0): intermediate value and (− 1): lower value. Actual values for X1: 30 (+ 1), 25 (0) and 20 (− 1); actual values for X2:25 (+ 1), 20 (0) and 15 (− 1)

All the dependent variables were found dependent on the selected independent variables as the wide variation was observed among the nine batches (F1 to F9). The high values of correlation coefficient (R^2) for the dependent variables indicate a good fit. The experimental runs and their factor combinations are shown in Table 6.

Table 7 Pre-compression parameters of batches (F1 to F9) using factorial design

Formulation Code	Loose bulk density (gm/cm^3)*	Tapped bulk density (gm/cm^3)*	Hausner ratio (HR)*	Carr's index (CI)*	Angle of repose ($\theta°$)*
F1	0.745 ± 0.01	0.838 ± 0.00	1.1248 ± 0.01	11.0978 ± 0.06	21.17 ± 0.21
F2	0.732 ± 0.01	0.822 ± 0.01	1.1229 ± 0.06	10.9489 ± 0.02	21.19 ± 0.58
F3	0.743 ± 0.00	0.836 ± 0.01	1.1251 ± 0.08	11.1244 ± 0.12	20.54 ± 0.49
F4	0.743 ± 0.02	0.836 ± 0.02	1.1251 ± 0.03	11.124 ± 0.18	22.11 ± 0.21
F5	0.732 ± 0.00	0.822 ± 0.01	1.1229 ± 0.09	10.9489 ± 0.20	20.82 ± 0.11
F6	0.733 ± 0.01	0.823 ± 0.02	1.1227 ± 0.04	10.935 ± 0.16	20.29 ± 0.21
F7	0.745 ± 0.01	0.838 ± 0.00	1.1248 ± 0.03	11.0978 ± 0.15	21.39 ± 0.47
F8	0.732 ± 0.01	0.822 ± 0.01	1.1229 ± 0.06	10.9489 ± 0.09	20.59 ± 0.50
F9	0.728 ± 0.03	0.817 ± 0.01	1.1222 ± 0.02	10.8935 ± 0.08	19.58 ± 0.49
C1[a]	0.751 ± 0.02	0.823 ± 0.02	1.0958 ± 0.09	8.74848 ± 0.15	23.24 ± 0.18
C2 [a]	0.746 ± 0.01	0.830 ± 0.01	1.1126 ± 0.10	10.1204 ± 0.21	24.32 ± 0.11
C3 [a]	0.741 ± 0.07	0.825 ± 0.04	1.113 ± 0.60	10.1818 ± 0.26	22.48 ± 0.21

*Mean ± SD; $n = 3$; [a]Extra design check point batches

Table 8 Post-compression parameters of batches (F1 to F9) using factorial design

Code	Diameter (mm)**	Thickness (mm)**	Hardness (kg/cm^2)*	Friability (%)*	Weight variation (%)	Drug content (%w/w)
F1	9.0 ± 0.0	3.18 ± 0.14	5.8 ± 0.25	0.41 ± 0.05	± 2.11	99.81 ± 1.4
F2	9.0 ± 0.0	3.16 ± 0.12	5.7 ± 0.27	0.31 ± 0.08	± 2.16	99.67 ± 1.7
F3	9.0 ± 0.0	3.15 ± 0.12	5.5 ± 0.44	0.36 ± 0.03	± 2.02	98.75 ± 0.5
F4	9.0 ± 0.0	3.28 ± 0.11	5.6 ± 0.41	0.37 ± 0.01	± 2.75	99.47 ± 1.3
F5	9.0 ± 0.0	3.13 ± 0.10	5.7 ± 0.27	0.36 ± 0.08	± 2.46	99.87 ± 0.5
F6	9.0 ± 0.0	3.23 ± 0.16	5.8 ± 0.62	0.28 ± 0.06	± 1.85	98.38 ± 0.8
F7	9.0 ± 0.0	3.18 ± 0.14	5.8 ± 0.37	0.41 ± 0.03	± 1.89	97.01 ± 1.7
F8	9.0 ± 0.0	3.21 ± 0.14	5.7 ± 0.44	0.36 ± 0.12	± 1.86	99.24 ± 0.6
F9	9.0 ± 0.0	3.20 ± 0.16	5.4 ± 0.27	0.22 ± 0.06	± 3.75	99.04 ± 0.1
C1 [a]	9.0 ± 0.0	3.19 ± 0.12	5.9 ± 0.11	0.32 ± 0.14	± 2.30	98.90 ± 0.14
C2 [a]	9.0 ± 0.0	3.24 ± 0.23	5.6 ± 0.23	0.39 ± 0.02	± 2.29	99.07 ± 0.13
C3 [a]	9.0 ± 0.0	3.22 ± 019	5.8 ± 016	0.29 ± 0.11	± 3.12	99.71 ± 0.51

*Mean ± SD; n = 3; [a]Extra design check point batches

3.8 Evaluation of gastroretentive tablets containing natural polymer and RBW using 3^2 full factorial design

Gastroretentive tablets were evaluated for pre- and post-compression parameters and results are shown in Tables 7 and 8. All the tablets passed test for weight variation, hardness, content uniformity and showed acceptable results with respect to drug content (99.87 ± 0.5) and % friability.

3.9 Evaluation of gastroretentive tablets containing natural polymer and RBW using 3^2 full factorial design for FLT, SI and %CDR

The FLT, SI and % CDR of F1 to F9 along with the three extra check point formulations are shown in Table 9 and Figs. 3, 4 and 5.

The total FLT of all the formulations was within the limits (less than three minutes). The SI of the formulations F1 to F9 and extra check point formulations C1–C3 was evaluated where the highest and lowest swelling was observed with the formulation F7 and F1 after 12 h. The drug release was found to be retarded for 12 h.

Formulations containing low level of polymer showed higher drug release (94.21 ± 0.57 to 98.28 ± 0.48%) than the formulations containing high level of polymer that showed drug release 87.59 ± 0.39 to 89.68 ± 0.26% at 12 h which may be due to increased viscosity offered by gelling of hydrophilic polymer.

Table 9 Factorial design and their observed response values in gastroretentive tablets

Formulation code	Guar Gum (mg) (X1 = A)	RBW (mg) (X2 = B)	Responses*		
			FLT (s)	SI	%CDR
F1	20 (− 1)	25 (+ 1)	10 ± 1.154	79.63 ± 0.22	94.21 ± 0.57
F2	30 (+ 1)	20 (0)	10 ± 3.60	80.48 ± 0.55	89.68 ± 0.26
F3	20 (− 1)	20 (0)	15 ± 2.51	82.31 ± 1.21	96.24 ± 0.85
F4	20 (− 1)	15 (− 1)	15 ± 1.73	86.62 ± 0.20	98.28 ± 0.48
F5	30 (+ 1)	15 (− 1)	20 ± 2.88	88.01 ± 0.28	87.59 ± 0.39
F6	25 (0)	15 (− 1)	20 ± 2.88	88.63 ± 0.375	86.89 ± 0.37
F7	25 (0)	25 (+ 1)	22 ± 2.51	90.31 ± 0.739	85.53 ± 0.41
F8	30 (+ 1)	25 (+ 1)	25 ± 10.40	85.02 ± 0.49	88.86 ± 0.43
F9	25 (0)	20 (0)	27 ± 2.47	89.68 ± 1.36	88.98 ± 0.51
C1 [a]	19.75	14.92	28 ± 1.23	82 ± 1.21	94.20 ± 0.32
C2 [a]	24.85	19.64	27 ± 2.30	80.89 ± 1.34	89.30 ± 0.63
C3 [a]	29.80	24.78	28 ± 2.0	88.96 ± 1.82	92.24 ± 0.75

Values are expressed as mean ± S.D., $n = 3$; [a]Extra design check point batches

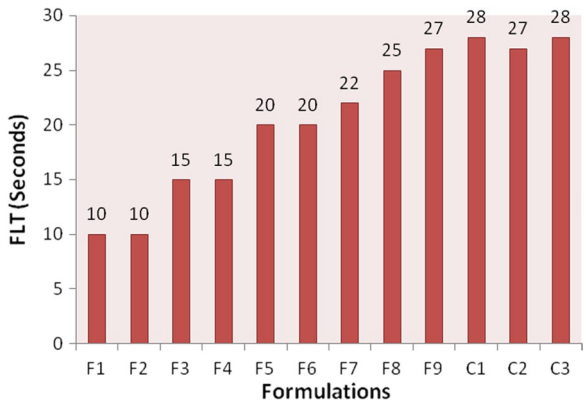

Fig. 3 FLT of gastroretentive formulations

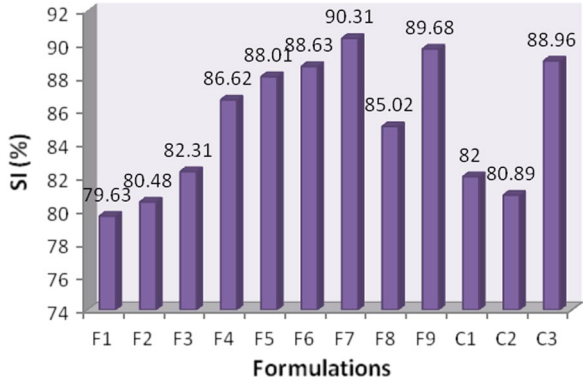

Fig. 4 SI of gastroretentive formulations

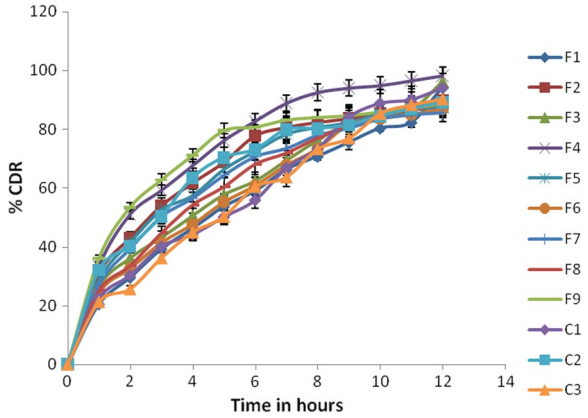

Fig. 5 In vitro drug release profile of gastroretentive formulations along with extra check point formulations

3.10 Kinetic analysis of the drug release data

To analyze the mechanism of drug release from the tablets, the in vitro dissolution data (Fig. 5) were fitted to various mathematical models like zero-order, first-order, Higuchi, and Korsmeyer–Peppas models (Table 10).

3.11 Statistical analysis and mathematical model fitting

As per the 3^2 factorial design, different trial formulations of gastroretentive tablets were prepared by melt granulation method. Overview of the experimental trial and observed responses is shown in Table 8. The models were

Table 10 Model fitting of gastroretentive tablets (F1–F9)

Batch No	Regression coefficient			
	Zero-order kinetics	First-order kinetics	Higuchi kinetics	Krosmeyer–Peppas
F1	0.9787	0.8691	0.8398	0.4928
F2	0.9666	0.5806	0.9511	0.4859
F3	0.9885	0.6454	0.8443	0.5018
F4	0.9757	0.5620	0.9103	0.4268
F5	0.9707	0.8963	0.8126	0.4153
F6	0.9683	0.5858	0.8821	0.4858
F7	0.9906	0.9693	0.9988	0.5988
F8	0.9766	0.7970	0.8979	0.4979
F9	0.9649	0.8978	0.7949	0.6949
C1[a]	0.9769	0.9021	0.9139	0.5428
C2[a]	0.9843	0.7989	0.8946	0.6231
C3[a]	0.9898	0.8648	0.9010	0.5963

[a] Extra design check point batches

Table 11 Statistical analysis of generated models

Response	*F* value	*P* value	R^2 value	Adequate precision
FLT (Y1)	5.44	0.0365	0.8657	3.849
SI (Y2)	6.53	0.0429	0.903	0.114
% CDR (Y3)	8.26	0.021	0.892	0.840

found significant for all response parameters as indicated by ANOVA. Table 11 shows the F and P value for the responses using factorial design along with the percentage predicted errors for the trial formulations.

The effects of the independent variables (factors) on each investigated response are shown in Fig. 6 (a-f) as three-dimensional response surface plots and contour plots. The three-dimensional response surface plots relating FLT, SI and % CDR indicated the lessen values of FLT and % CDR and increased values of SI with the rise of guar gum and RBW.

From the predicted and experimental values (Table 12), it was observed that the lower magnitude of error as well as the significant value of R^2 (0.9977) in the current study indicated a high prognostic ability of formulation with the use of response surface methodology.

3.12 Stability studies

From the stability studies of the optimized gastroretentive tablet formulation (C3), it was observed that there was no considerable change in FLT, SI and % CDR which proved the stability of the formulation.

4 Discussion

It was concluded from the study that swelling increased with time as the polymer gradually absorbs water due to its hydrophilicity. The hydrophilic polymer in the outermost layer hydrates and swells to form a gel barrier.

FLT was found to increase with the increase in the concentration of polymer and RBW. The SI was found to increase with the increase in the concentration of polymer and also due to hydrophilic nature of the polymer. In all the formulations, good matrix integrity was observed.

It was observed that formulations containing high level of polymer and RBW exhibited delayed drug release indicating better matrix characteristics.

It was observed that the release profile fitted best to zero-order equation with non-Fickian diffusion mechanism of drug release which demonstrates swelling-controlled drug release mechanism.

Design Expert software gave suitable polynomial model equations involving individual main factors and interaction factors after fitting these data. The model equations relating FLT, SI and % CDR as responses by eliminating nonsignificant terms ($P > 0.05$) are

$$\mathrm{FLT} = +8.75 - 0.25 * A + 1.25 * B + 2.25 * A * B \quad [R^2 = 0.8657;\ F\text{-value} = 5.44;\ P < 0.05] \tag{2}$$

$$\mathrm{SI} = +86.25 + 0.25 * A - 2.25 * B + 3.75 * A * B \quad [R^2 = 0.903;\ F\text{-value} = 6.53;\ P < 0.05] \tag{3}$$

$$\%\mathrm{CDR} = 83.00 + 0.50 * A - 3.00 * B + 4.50 * A * B \quad [R^2 = 0.892;\ F\text{-value} = 8.26;\ P < 0.05] \tag{4}$$

Each response coefficient was studied for its statistical significance and the relationship between the variables was further elucidated by using the response surface plot and contour plot. Ratio of 3.849 (FLT), 0.114 (SI) and 0.840 (% CDR) indicated an adequate signal. All the variables had P value less than 0.05 ($P < 0.05$) which is considered as significant.

Three formulations having maximum desirability value of FLT, % SI and % CDR were found in the experimental region of the overlay plot which were selected for the optimization of formulations. Based on maximum desirability values of FLT, SI and % CDR, formulation C3 was selected as final optimized formulation from the three formulations.

5 Conclusions

The present investigation aimed at formulation and evaluation of gastroretentive tablets based on combination of natural polymer and RBW containing Famotidine as a

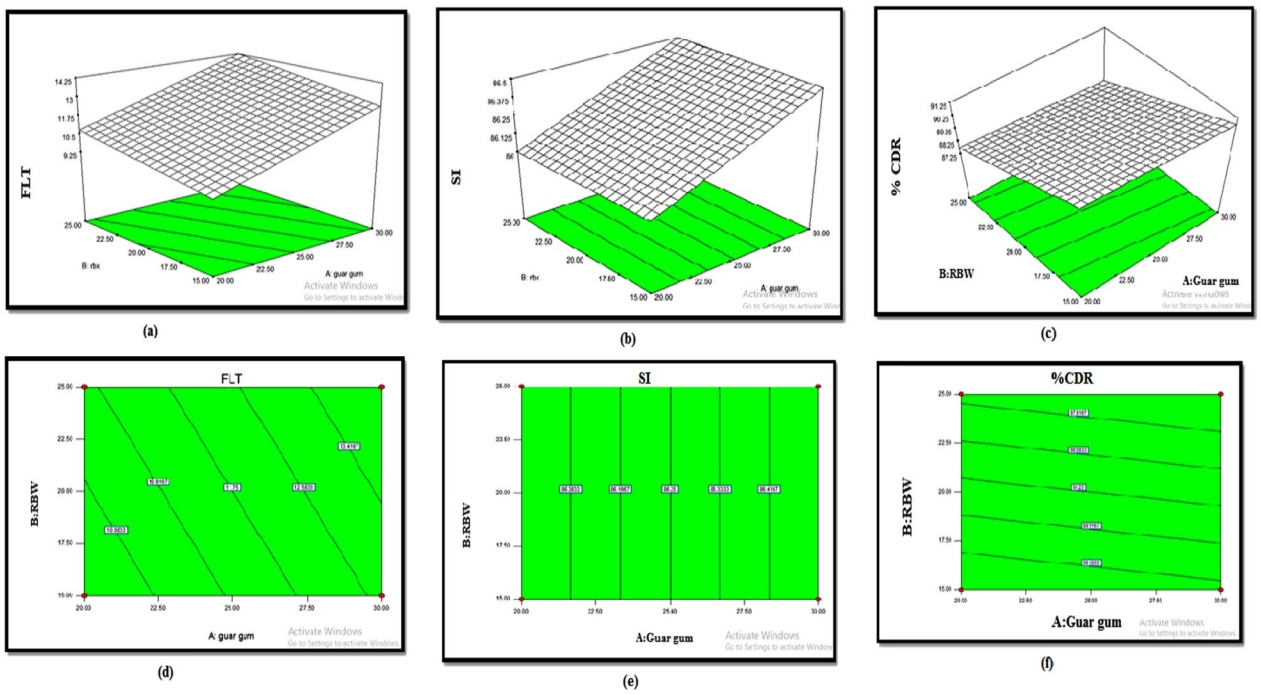

Fig. 6 Three-dimensional response surface plots (**a**–**c**) and contour plots (**d**–**f**) relating FLT, SI and % CDR

Table 12 Check point formulations and % Error

Batch Code	Composition		Responses*	Predicted Value	Experimental Value	% Error
	X1*	X2*				
C1	30	25	Y1	15.00	11.44	3.56
			Y2	82.65	82.31	0.34
			Y3	70.19	70.14	0.05
C2	20	20	Y1	12.00	11.44	0.56
			Y2	88.16	88.63	0.47
			Y3	70.14	70.09	0.05
C3	25	20	Y1	10.00	11.44	1.44
			Y2	78.74	79.63	0.89
			Y3	92.93	90.03	2.9

*X1-Guar Gum; X2-RBW; Y1-FLT; Y2-SI; Y3-% *CDR*

model drug. The results of compatibility study indicated the compatibility of selected excipients with the drug. All the tablets passed test for weight variation, hardness, content uniformity and showed acceptable results with respect to drug content (99.6 ± 0.7) and % friability in the preliminary trial batches using various polymers like hydroxypropyl methyl cellulose (HPMC), ethyl cellulose, guar gum and RBW. FLT for all the tablets was found less than one minute and for all the tablets TFT was found more than 12 h. It was concluded from the SI study that, swelling increased with time as the polymer gradually absorbs water due to its hydrophilicity. Drug release for HF1 to GF3 was found 94.32% to 99.71% for 12 h. In the present investigation, to study the effect of independent variables, i.e., the concentrations of guar gum (X1), the concentrations of RBW (X2) on dependent variables such as FLT, SI and % CDR, a 3^2 full factorial design was used based on the results of the preliminary trial batches.

The high values of correlation coefficient (R^2) for the dependent variables indicate a good fit. All the tablets

passed test for weight variation, hardness, content uniformity and showed acceptable results with respect to drug content (99.87 ± 0.5) and % friability. The total FLT of all the formulations was within the limits (less than three minutes). FLT was found to increase with the increase in the concentration of polymer and RBW. In all the formulations, good matrix integrity was observed and drug release was found retarded for 12 h. Formulations containing low level of polymer showed higher drug release (94.21 ± 0.57 to $98.28 \pm 0.48\%$) than the formulations containing high level of polymer that showed drug release 87.59 ± 0.39 to $89.68 \pm 0.26\%$ at 12 h which may be due to increased viscosity offered by gelling of hydrophilic polymer. It was concluded that the release profile fitted best to zero-order equation with non-Fickian diffusion mechanism of drug release which demonstrates swelling-controlled drug release mechanism. The models were found significant for all response parameters as indicated by ANOVA. The three-dimensional response surface plots relating FLT, SI and % CDR indicated the decreased values of FLT and % CDR and increased values of SI with the increment in guar gum and RBW. Out of the three check point formulations, C3 was selected as final optimized formulation based on maximum desirability values of FLT, SI and % CDR. Stability studies proved the stability of the formulation. Thus, gastroretentive tablets were formulated successfully to control the drug delivery with the help of natural polymer and RBW.

Abbreviations

GIT: Gastrointestinal tract; GRDDS: Gastroretentive drug delivery system; RBW: Rice bran wax; FLT: Floating lag time; TFT: Total floating time; SI: Swelling index; %CDR: Cumulative percentage drug release; h: Hour; R^2: Correlation coefficient; ANOVA: Analysis of variance; HPMC: Hydroxypropyl methyl cellulose.

Acknowledgements

The authors express their gratitude to the Principal and President of Dadasaheb Balpande College of Pharmacy, Besa for providing the facilities to carry out the research work.

Authors' contributions

VPS involved in conceptualization, supervision and writing–original draft preparation. GGG involved in methodology, investigation and analysis. All authors read and approved final manuscript.

Funding

None.

Availability of data and materials

All data generated or analyzed during this study are included in the article.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

Authors declare no competing interests.

Received: 29 October 2021 Accepted: 20 December 2021
Published online: 06 January 2022

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