Research Article

Prospective of Grewia Fruit Mucilage as Gastro Retentive Drug Delivery System: Statistical Optimization of Formulation Variables

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ABSTRACT

In this study we demonstrate the preparation and characterisation of Grewia fruit mucilage individually and in combination with HPMC K100M and xanthan gum, for gastro retentive tablet formulation. Simplex lattice design was used to evaluate the formulation characteristics such as hardness, f_{lag} time, floating time and cumulative drug release (%) at the end of 1 h, 2 h, 8 h and 24 h. A checkpoint batch was also prepared by considering the constraints and desirability of optimized formulation to improve *in vitro* performance. Significance of results was analyzed using ANOVA and $p < 0.05$ was considered statistically significant. Observed experimental values were very close to the predicted results indicating the applicability of the model. The combination of Grewia fruit mucilage was found to be useful in floatability of dosage form and sustaining the drug release. The pattern of drug release from the optimized formulation was found follow first order kinetics. The mechanism of drug release through the polymer network was said to follow non-Fickian transport with the exponent (n) value being 0.498 to 0.524 for Korsmeyer-Peppas model. This result confirms that the drug release through GFM is mostly combined diffusive-erosion mechanism. In conclusion, Grewia fruit mucilage is currently seen as a promising biomaterial for oral drug delivery.

Keywords: Grewia fruit mucilage; HPMC K100M; Xanthan gum; Ranitidine HCl; Gastro retentive formulation; Simplex lattice design.

INTRODUCTION

Objective of this study is to show the potential use of natural gums in the development of drug delivery systems. Grewia fruit mucilage (GFM), a hydrophilic polymer is evaluated for gastro retentive controlled release tablet formulation.[1] The large flowering plant *G. subinaequalis* Dc (Syn. *G. asiatica* Mast), of the genus Grewia of the family Malvaceae, yields edible fruit: Phalsa is the most used vernacular name in India where there are a number of dialectal names.[2,3] The Phalsa is distributed throughout much of India and Southeast Asia.[4] It is cultivated commercially in Punjab and around Mumbai for Grewia fruits. These fruits are eaten fresh as dessert, are made into syrup, and extensively employed in the manufacture of soft drinks. The fruit is astringent and stomachic and when unripe, it alleviates inflammation.[5]

The Grewia fruit yields mucilaginous ex-tract which has not been much studied for pharmaceutical applications. This mucilaginous extract consists of pelargonidin-3, 5-diglucoside, quercetin, quercetin-3-0-P-D- glucoside, naringenin 7-0-PD-glucoside, delphinidin 3-glucoside and cyanidin-3-glucoside, lysin, proline, glutaric acid, phenylalanine, glucose, xylose, arabinose, tannins- catechin and leucoanthocyanins.[6–8] This chemical composition infers that the GFM can form a hydrogel and that would be of particular interest for the gastro retentive drug delivery system.[9,10] Furthermore, the polysaccharide hydrogels in the last decades aroused increasing

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interest in the biopharmaceutical field for the design of modified drug release formulations. It is even more important to study the behaviour of these systems as it is well known that the bioavailability of many drugs is deeply dependent on the performance of the carrier system. Hence, in the present study the goal has been set to evaluate the potential of GFM as a drug carrier individually and in combination with HPMC K100M and xanthan gum. The experiment was conducted using Ranitidine HCl as model drug candidate and the study was executed using simplex lattice design (SLD). The formulation variables were optimized, the significance of the results, and the relationship between influential factors and output response were assessed.

MATERIALS AND METHODS

Ranitidine HCl (IP*)* and HPMC K100M were received as a gift sample from Micro labs Ltd, Bangalore, India. Xanthan gum (Loba Chemie Pvt. Ltd) and polyvinyl pyrollidone (Sisco research laboratories Pvt. Ltd) were purchased. All other chemicals used in the study were of analytical grade. Stat-ease Design-Expert® software is used to design the formulation.

Extraction and purification of GFM–Preparation of GFM

Phalsa fruits authenticated, air dried in shade were received from College of Horticulture, Sirsi, University of Horticultural Sciences, Bagalkot, India. They were certified (Vocher No:KLES/Phalsa/101) for the pharmaceutical use by Prof. Chandan K, Botanist of the same university. The dried fruits were crushed and mixed with sodium metabisulphite (0.1% w/v) solution in the ratio of 1:2. The temperature of mixture was kept to 30°C and blended for 24 h. The dispersion was filtered using muslin cloth to remove debris. The filtrate was blended with 0.1 N NaOH and centrifuged at 3,000 rpm for 10 min. The supernatant mucilage solution (1 part) was added to 3 parts of double distilled ethanol (95%) and the precipitate obtained was centrifuged as described previously.[10] The derived sediment was dried in an oven at 40°C, crushed and passed through a sieve #80 to obtain discrete powder called GFM.

Scanning electron microscopy (SEM)

The shape and surface morphology of GFM were investigated using scanning electron microscope (Jeol JSM-1600, Tokyo, Japan). The samples for SEM study were prepared by keeping the formulation on a double-adhesive tape stuck to an aluminium stub. The stubs were then coated with gold. The coated samples were then randomly scanned and photomicrographs were taken.

Characterization by Infra-red spectroscopy

Physico-chemical compatibility between the drug and polymers were studied using infra-red spectrophotometer, model- 8400S, Shimadzu Corporation, Kyoto, Japan, in the range of 4600–400 cm^{-1} with resolution of 4.0 cm^{-1}. KBr pellets were prepared by gently mixing the sample with KBr (1:100) and pressing the pellets at the pressure of 150 kg/cm^2 using pelletizer.

Simplex lattice design (SLD)

A simplex lattice design was adapted to assess the suitability of GFM for gastro retentive formulation of ranitidine HCl. The SLD is represented by an equilateral triangle in 2-dimensional space for a 3-component system (Fig. 1). Concentrations of GFM (A), HPMC K100M (B) and xanthan gum (C) were selected as independent variables. In this design, 3 components were evaluated by changing their concentrations simultaneously and keeping their total concentration constant. Seven formulations (F1–F7) were prepared using the three components; three at vertex of triangle (A, B and C), three at the halfway point between vertices (AB, BC, AC), and one at the centre point (ABC). Each vertex represents a single component of the 3 component formulation e.g. A= GFM 100%; B=HPMC K100M 100% and C= Xanthan gum 100%. The halfway point between the 2 vertices represents a formulation containing minimum of the 2 ingredients and the average of the one ingredient E.g. AB= 25%, GFM + 25%, HPMCK100M and 50%, Xanthan gum. The centre point of the triangle represents a formulation containing one third of each ingredient (*vide* Table 1 for details).

Hardness (kg/cm^2), floating lag time (f_{lag} time, sec), cumulative drug release (%) at the end of 1 h, 2 h, 8 h and for 24 h were taken as response values (Dependent variables). The response values were analyzed using multiple regression analysis to find the relationship with the independent variables.

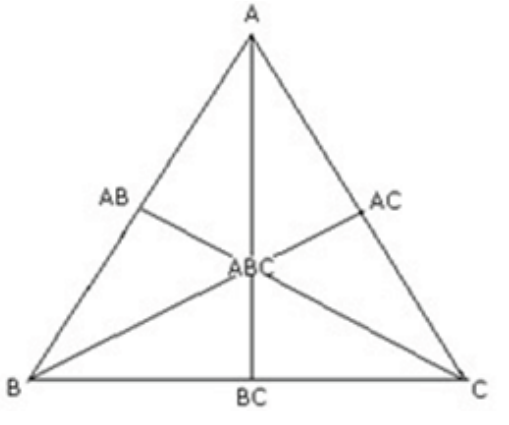

Figure 1: Equilateral triangle representing simplex lattice design for 3 components (A, B and C).

Table 1: Formulations of Ranitidine HCl IP according simplex lattice design

Ingredients	Formulation code*							
	F1	F2	F3	F4	F5	F6	F7	F8
Ranitidine HCl *IP*	150	150	150	150	150	150	150	150
GFM (A)	30	30	120	180	–	–	60	160.72
HPMC K100M (B)	120	30	30	–	180	–	60	19.28
Xanthan gum (C)	30	120	30	–	–	180	60	–
Sodium bicarbonate	90	90	90	90	90	90	90	90
Tartaric acid	10	10	10	10	10	10	10	10
Poly vinyl pyrrolidone	10	10	10	10	10	10	10	10
Magnesium stearate	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5

*All values are in mg

Formulation of gastro retentive tablets

A batch size of 50 tablets for each formulation was prepared using weighed quantity of Ranitidine HCl, polymers, effervescent combination as shown in the Table No.1. GFM and HPMC K100M are highly swellable hydrophilic matrixing agents. Xanthan gum is relatively hydrophobic in nature and is release retarding agent in the formulation. Sodium bicarbonate generates CO_2 gas in the presence of tartaric acid upon contact with dissolution medium. The gas generated is trapped and protected within the gel (formed by hydration of GFM, HPMC K100M), thus decreasing the density of the tablet. As the density of the tablet falls below 1 (density of gastric juice), the tablet becomes buoyant.

Ingredients were passed through sieve #80 and the under pass was mixed and triturated in a mortar for a period of 10 min to obtain uniform mixture. Powder was further mixed with lubricant; the lubricated powder was compressed with 10-station Rimek Minipress-I Karnavati, tablet punching machine using 10 mm concave punches. The dimensional specifications were measured using thickness gauge (Okimoto) and hardness of the tablet was measured using Pfizer hardness tester. Weight variation test was conducted as per pharmacopoeia of India specifications.[11]

Drug content estimation

Standard calibration curve[12] of Ranitidine HCl was constructed using UV-Visible spectrophotometer (Shimadzu-1700, Kyoto, Japan). Drug solution was prepared by taking 5 µg/mL to 25 µg/mL of Ranitidine in 0.1 N HCl (pH 1.2), sonicating for 5 min and filtered using 0.45 µ (Millipore) membrane. Drug content of each tablet formulation was measured at 313 nm using the standard curve. This method was found to have good repeatability, reproducibility and the relative standard deviation (RSD) was not more than 2%. The working curve equation for Ranitidine HCl was y = 0.038x with correlation coefficient value, $r^2 = 0.999$.

In vitro floatability

An *in vitro* floatability of the tablet formulation was carried out in USP, Type-II (paddle) dissolution testing apparatus.[13] Formulation was placed in 900 ml of enzyme free, simulated gastric fluid (0.1 N HCl, 0.2% NaCl) at 37 ± 0.5°C and rotated at 50 rpm. The time required for the tablet to rise to the surface was determined as f_{lag} time. Floating time was the time the tablet floats (excluding f_{lag} time) in simulated gastric fluid.

Swelling index

The extent of swelling was measured in terms of percent weight gain by the tablet.[14] Each tablet formulation was kept in a beaker containing 100 ml of simulated gastric fluid as described earlier. The tablet was withdrawn after every 1 h, blotted with tissue paper and reweighed. Weights of the tablets were noted and the process was continuous till the end of 24 h. Average of three such swelling experiments was taken to calculate the percentage weight gain by the tablet using the formula

$$SI = \{(Mt - Mo)/Mo\} \times 100,$$

Where, SI is swelling index, *M*t is the weight of tablet at time "*t*", and *M*o is the weight of tablet when "*t*"=0.

Dissolution studies

The Dissolution rate of Ranitidine HCl from floating matrix tablet was determined using dissolution apparatus (TDT-08L, Electrolab) USP Type-II (paddle).[15] Study was conducted using 900 mL of simulated enzyme free gastric fluid (0.1 N HCl, 0.2% NaCl), at 37 ± 0.5°C at 50 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 simulated gastric fluid, filtered and drug content was determined using the standard UV-curve.

Kinetics of drug release

The mechanism of drug release of the formulation is predicted by various models, e.g., zero-order, first-order, Higuchi and Korsmeyer-Peppas models. The models were transformed into straight-line equations and the best fitness of the model was chosen on the basis of r^2 values.[17]

Statistical analysis

The means of three responses were assessed using One-Way ANOVA to know whether they differ significantly from one another. F- test is used to estimate the differences between the formulation groups. Model terms are significant if the measured value is less than the critical value of '*p*' (0.05).

RESULTS AND DISCUSSION

Scanning electron microscopy (SEM)

Surface morphology and structure of the GFM granules were revealed by SEM photographs (Fig. 2). The granules were rough, irregular and discrete particles. Granules were found to be hard and tough.

Characterization by Infra-red spectroscopy

The FT-IR spectra of drug and its physical mixture (1:1) with polymers showed (Fig. 3) no significance shift or reduction in intensity of peaks of drug. These results infer there is no interaction with the drug and the polymers selected for the study.

Simplex lattice design (SLD)

The general equation for the response based SLD for three components system consisting terms for pure component and mixtures of component is,

$$R = b0 + b1\,A + b2\,B + b3\,C \quad (1)$$

Where, 'R' is the Response Variable and A, B and C are the proportions of formulation components. b0 is the arithmetic mean response of the 7 runs and b1, b2 and b3 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 reflect the hardness, f_{lag} time, and cumulative drug release (%) at the end of 1 h, 2 h, 8 h and 24 h period. The transformed factor was 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

The linear equation obtained (eqn.2) from the design infers, the selected independent variables are not significant {'*F*' value of 4.04 and '*P*' value of 0.0903 (<0.05)} for hardness.

$$R1\ (\text{Hardness}) = 3.10*A + 3.55*B + 3.19*C \quad (2)$$

However, the 3D response surface plot shows that all the three variables have equal contribution to hardness (Fig. 3a).

Effect of independent variables on f_{lag} time

The effect of concentration of independent variables on f_{lag} time is found to be insignificant, shown in the below equation.

$$R2\ (f_{lag}\ \text{time}) = 49.02*A + 46.17*B + 68.90*C \quad (3)$$

Although the statistical results infers {'*F*' value of 1.20 and '*P*' value of 0.3741 (<0.05)} the linear model equation is not significant for f_{lag} time, the values of regression coefficient infers, the concentration of GFM (A) and HPMC K100M (B) may be equally contributed for the f_{lag} time (Fig. 3b). The reason behind this is their molecular gelation and high swelling property of both

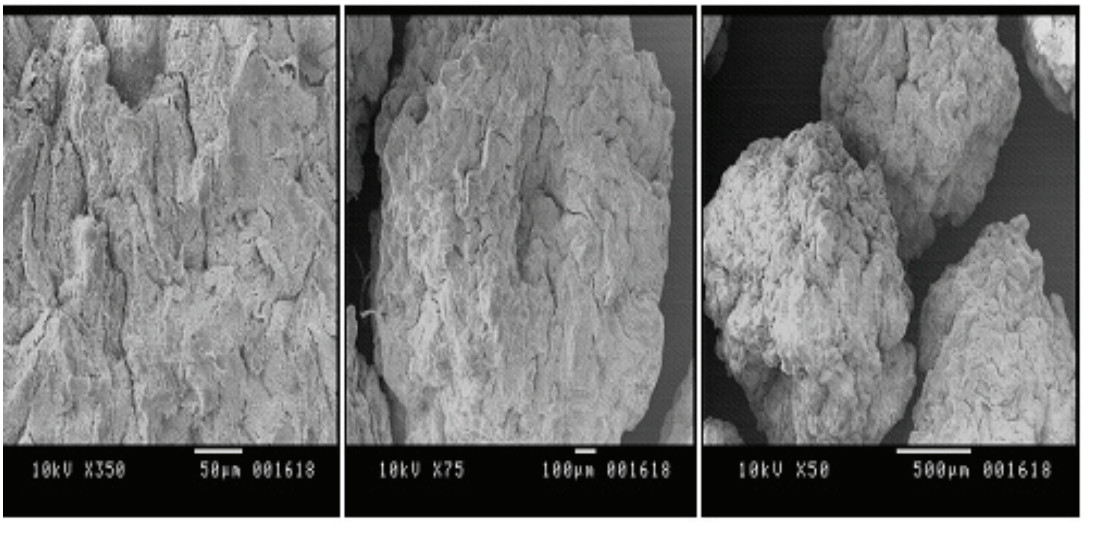

Figure 2: Scanning electron mircrograph of GFM granules.

the polymers.[18] The polarity and polymer solubility of GFM and HPMC K100M at physiological pH allows for rapid hydrogel formation. This study does not provide sufficient data to allow a complete molecular description of the mechanism of gelation. However, evidence can be found in the literature to support the occurrence of pH-induced alterations of molecular interactions in the hydrophilic polymers, consequently formation of hydrated gel. This is evident from the results of swelling index study conducted for 12 h (239.23 to 287.18(%) for F1 to F7 at the end of 12 h). Swelling index increases with increase in concentration of GFM in the formulation signifying role of GFM in hydrogel formation. Further f_{lag} time of the formulation decreases as swelling index increases confirming the relationship between hydrogel formation and f_{lag} time. All formulations were found to be buoyant for more than 24 h.

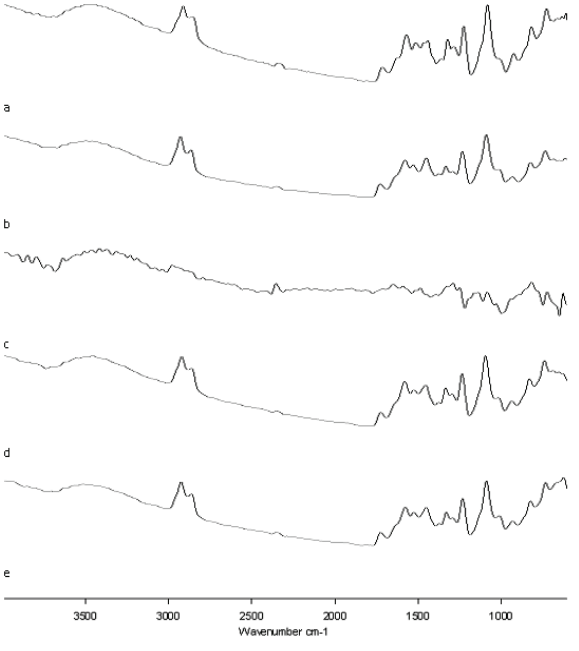

Figure 3: FTIR spectra of (a) Ranitidine HCl, and its 1:1 physical mixture with (b) GFM, (c) HPMC K100M (d) Xanthan gum, and (4) Physical mixture of Ranitidine HCl, GFM, HPMC K100M and Xanthan gum.

Effect of independent variables on drug release

The magnitude of coefficients obtained from multiple linear regression analysis for 1, 2, 8 and 24 h cumulative drug release (%) are expressed in equations 4, 5, 6 and 7 respectively. The release rate and the percentage drug release for the 7 batches (F1 to F7) showed a wide variation (i.e., 80 to 95%) as shown in Table No.2. Formulation F4 prepared using only HPMC K100M, exhausted before 20 h and fails to sustain the drug release till 24 h. This highest drug release observed in initial hours is due to low concentration of both the independent variables (B and C), thus weakening the gel strength. The fast release of drug is due to enormous swelling process and the rupture of the polymer network.[19] Formulation F6, made only with xanthan gum could release only 43.31 ± 1.25 (%) of the drug at the end of 24 h, indicating its drug retarding action.[20] The main reason for promoting or retarding of drug release from the polymer network is the molecular alterations of polymers in aqueous solutions. The main molecular forces and effective interactions responsible for the drug release from polymer matrix are multiple: 1) the increase of polymer inter-chain hydrogen bonding as a consequence of the reduction of electrostatic repulsions in aqueous solution. 2) The electrostatic attractions between hydrophilic and hydrophobic polymers in aqueous solutions. 3) Hydrogen bonding between polymer chains.[21]

Drug release for 1h and 2h

$$R3 \text{ (Drug release for 1 h)} = 28.89*A + 19.44*B + 15.05*C \quad (4)$$

$$R4 \text{ (Drug release for 2 h)} = 45.51*A + 30.75*B + 24.10*C \quad (5)$$

Table 2: Characterization of Ranitidine HCl IP gastro retentive formulation

Formulation code	Responses (Dependent variables)					
	Hardness (kg/cm²)	f_{lag} time (sec)	Drug release at the end of 1 h (%)	Drug release at the end of 2 h (%)	Drug release at the end of 8 h (%)	Drug release at the end of 24 h (%)
F1	3.13 ± 0.32	61.66 ± 2.88	16.28 ± 0.65	24.04 ± 1.50	51.62 ± 1.60	87.32 ± 0.89
F2	3.0 ± 0.05	45 ± 3	18.14 ± 1.37	27.56 ± 0.97	54.06 ± 1.38	82.70 ± 0.71
F3	3.56 ± 0.01	38.33 ± 2.08	17.13 ± 1.20	36.38 ± 1.69	71.52 ± 1.78	94.46 ± 1.67
F4	3.13 ± 0.15	45.33 ± 1.52	32.43 ± 1.03	48.45 ± 0.91	75.11 ± 0.55	-
F5	3.5 ± 0.03	50.28 ± 0.03	18.81 ± 0.09	24.52 ± 0.94	54.30 ± 0.56	90.65 ± 0.55
F6	3.30 ± 0.30	75.33 ± 2	07.17 ± 1.60	09.20 ± 1.13	30.65 ± 1.25	67.31 ± 1.25
F7	3.33 ± 0.30	69.66 ± 2.51	07.64 ± 1.82	06.64 ± 0.80	27.82 ± 1.14	65.09 ± 0.55
F8	3.13 ± 0.32	50.33 ± 2.51	18.49 ± 0.71	24.20 ± 0.96	54.14 ± 3.18	96.34 ± 3.71

*All values are mean of 3 readings ± SD

The equations 4 and 5 infer that the component 'A' has more favourable effect on promoting drug release and the component 'B' and 'C' has effect on retarding the drug release in the first two hours. Although, the model terms are not significant {'*P*' value of 0.1438 and 0.0803 (<0.05) for 1 h and 2 h drug release}, it is understood that the hydrophilicity of GFM is responsible for increase in drug release and the hydrophobicity of xanthan gum responsible for retarding the drug release. So it is understood that the optimum concentration of GFM must be there in the formulation to release effective concentration of drug at the initial hours.

Drug release for 8h and 24h

Concentration of GFM and HPMC K100M together play an important role in increased drug release at the end of 8 and 24 h, and reverse is true with increase in concentration of xanthan gum. Because, increase in concentration of xanthan gum in the formulation causes an increase in viscosity of the gel matrix, which decreases the diffusion of water in to the core of the matrix. Decrease in hydration of matrix causes more hindrance for drug diffusion and consequently decrease in drug release rate.[21] This can be further elucidated with the help of response surface plot (Fig. 4).

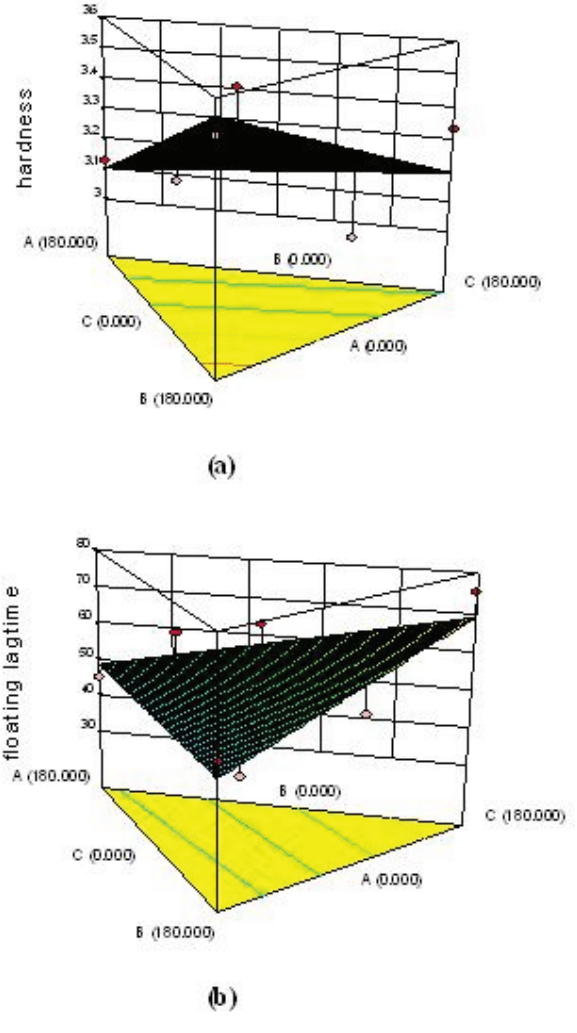

Figure 4: Response surface plot showing the effect of concentration of GFM, HPMC K100m and xanthan gum on (a) hardness (kg/cm^2) and (b) f_{lag} time (sec).

$$R5 \text{ (Drug release for 8 h)} = 74.32*A + 56.41*B + 47.14*C \quad (6)$$

$$R6 \text{ (Drug release for 24 h)} = 99.72*A + 83.84*B + 80.42*C \quad (7)$$

The model terms for *R5* (8 h release) and *R6* (24 h release) were found to be significant with an '*F*' value of 6.58 and 11.05, and '*P*' value of 0.0398 and 0.0146 (<0.05) respectively. These results clearly indicate that the percentage drug release is deeply dependent on stochiometry, chain length and concentration of all the selected independent variables. Furthermore, result infers judicious combination of GFM, HPMC K100M and xanthan gum are necessary to control and sustain the drug release for 24 h. Table No. 3 shows the results of the analysis of variance (ANOVA), which was performed to identify insignificant factors.

Based on this analysis, formulation F3 was arbitrarily selected as an optimized batch which releases the drug satisfactorily till the end of 24 h. Further, to improve the characteristics of F3 formulation a checkpoint batch F8 was prepared and analysed by considering the constraints and desirability to (Table No.4) improve the *in vitro* performance. The f_{lag} time and total floating time for formulation F8 were found to be 50.33 ± 2.51 sec and >24 h respectively. The *in vitro* drug release data was found to be sustained well compared to the most satisfactory formulation (F3) of 7 runs (Fig. 5 and Fig. 6). Predicted results were almost similar to the observed experimental values indicating the accuracy of the design (Table No. 5).

Table 3: Summary of ANOVA table for dependent variables from simplex lattice design

Source (Linear mixture)	Sum of squares	Degree of freedom	Mean square	'*F*' value	Probability '*P*' value
Hardness	0.17	2	0.084	4.04	0.0903
f_{lag} time	411.67	2	205.84	1.20	0.3741
1 h drug release	177.73	2	88.86	2.93	0.1438
2 h drug release	427.08	2	213.54	4.36	0.0803
8 h drug release	675.07	2	337.54	6.58	0.0398*
2 4h drug release	385.53	2	192.76	11.05	0.0146*

P < 0.05 indicates model terms are significant

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**
GFM	Is in range	0	1	1	1	3
HPMC K100M	Is in range	0	1	1	1	3
Xanthan gum	Is in range	0	1	1	1	3
Floating lag time	Minimize	38.33	75.33	1	1	3
8h release	Minimize	47.82	75.11	1	1	3
24h release	Maximize	80.09	100	1	1	3

Solutions (Desirability)						
Number	**A**	**B**	**C**	**f_{lag} time (sec)**	**8 h release**	**24 h release**
1	160.72	19.28	-	46.47	58.32	97.02

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

Parameter	Predicted values	Experimented values
Hardness (kg/cm^2)	3.56	3.53 ± 0.03
F_{lag} time (sec)	46.47	48.33 ± 2.51
% Drug release at the end of 8 h	58.32	54.14 ± 3.18
% Drug release at the end of 24h	97.02	96.34 ± 3.71

*All values are mean of 3 readings ± SD

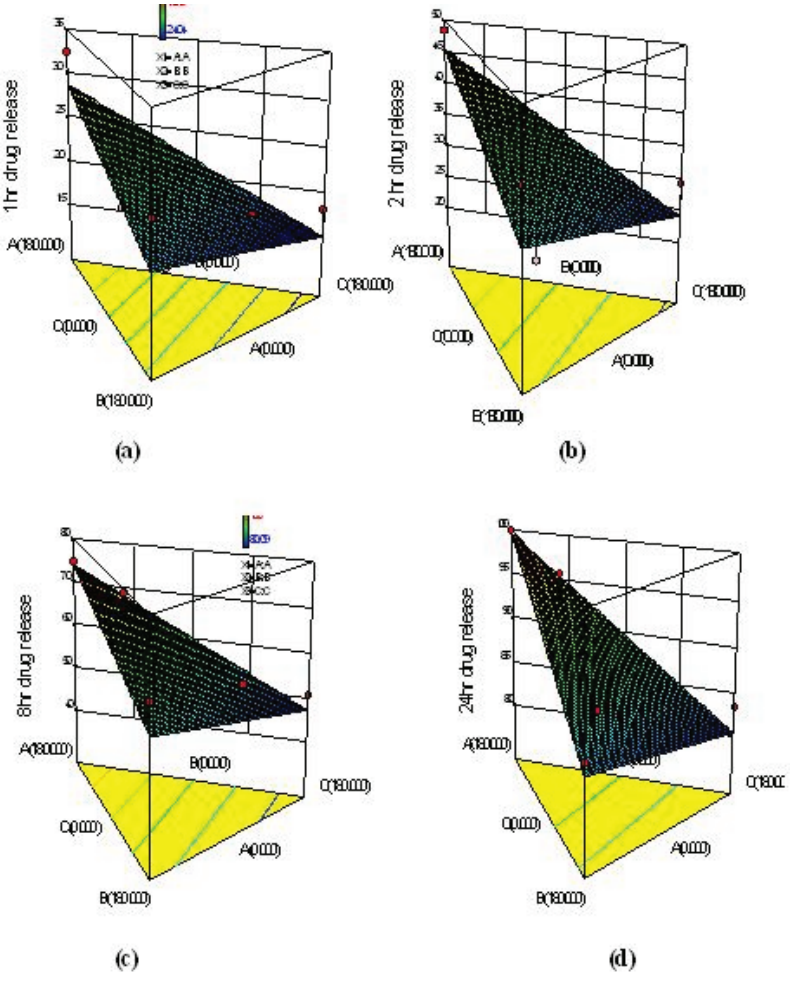

Figure 5: Response surface plot showing the effect of concentration of GFM, HPMC K100M and xanthan gum on drug release at the end of (a) 1 h, (b) 2 h, (c) 8 h and (d) 24 h respectively.

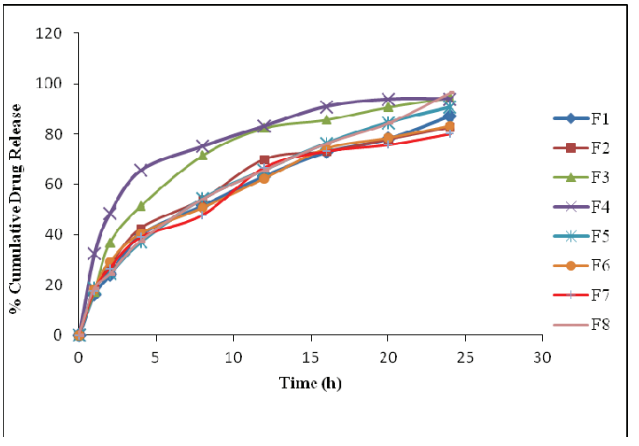

Figure 6: Comparative release profiles of Ranitidine HCl *IP* gastro retentive formulations.

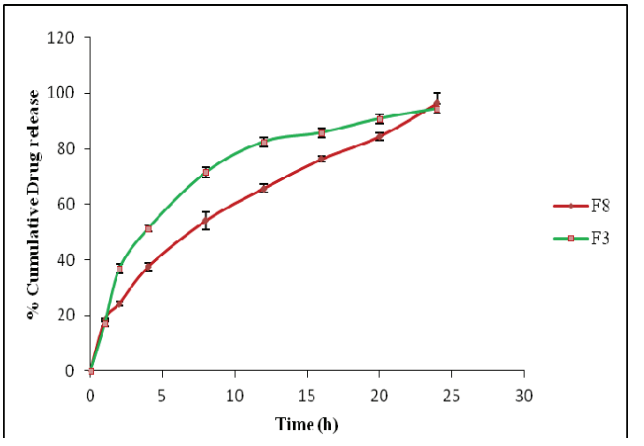

Figure 7: Comparative drug release profile of F8 and F3 formulations.

Table 6: Kinetic modelling 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
F3	0.814	3.530	0.985	0.049	0.959	20.072	0.934	0.498
F8	0.942	3.614	0.989	0.052	0.998	19.492	0.997	0.524

Kinetics of drug release

The release profile and kinetics of drug release are important because they correlate the *in vitro* drug dissolution profile with the pharmacokinetics. Hence the cumulative drug release of F3 and F8 formulation were fitted into various mathematical models.

The pattern of drug release from formulation F3 and F8 were found to be highly linear and close to unity. Further, the regression coefficient value obtained from first order kinetics is found to be higher than r^2 value of zero order kinetics (Table No. 6), ascertaining drug release follow first order kinetics.

The mechanism of drug release through the polymer network depends on several parameters, such as polymer concentration, molecular weight and hydrophilic nature of the polymer. Accordingly, the mechanism of drug release through the polymer network was said to follow non-Fickian transport with the exponent (n) value being 0.498 to 0.524 for Korsmeyer-Peppas model.[22] This result confirms that the drug release through GFM is mostly combined diffusive-erosion mechanism.

CONCLUSION

The gastro retentive tablet of Ranitidine HCl using newer polymer GFM was developed by simplex lattice design. Optimization process was proven to be accurate and optimized formula was prepared from the derived equation for the desirable and observed response. The optimized formula showed that the predicted value is nearer to the experimental value. The optimized formulation was found to have sufficient hardness, f_{lag} time and sustained release of drug up to 24 h. It showed no significant change in physicochemical properties, drug content, floating properties and *in vitro* dissolution pattern after storage at 30 ± 2°C/65 ± 5 % RH for six months. In conclusion, GFM is currently seen as a promising matrix forming biomaterial combined with a controllable residence time. The delivery of biological therapeutics with hydrogel presented in this paper represents a significant achievement in the field of drug delivery.

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