



FORMULATION AND EVALUATION OF FAMOTIDINE ION ACTIVATED INSITU GELLING SYSTEM

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ABSTRACT:

Famotidine, an anti-ulcer agent was chosen as a drug which is a more potent H₂ receptor antagonist than ranitidine and cimetidine. The purpose of this research work was to formulate and evaluate Famotidine oral *in-situ* gelling system for sustained oral drug delivery to overcome its shorter elimination half-life and less protein binding nature. Formulation chart was prepared by applying 3² full factorial design using two independent variables, i.e. concentration of gelrite and HPMC K100M. The solution form of prepared formulations was changed into gel by the addition of 0.1N HCl. The formulations prepared were evaluated for several physico-chemical parameters like drug-polymer interaction, pH, gelling capacity, drug content uniformity, *in vitro* drug release, viscosity and anti-ulcer activity (*In-vivo* study). The stability studies were carried out on the optimized formulation and no significant change was found in physico-chemical properties and *in vitro* dissolution studies. The best-fit release kinetic was achieved with zero order. The results of a 3² full factorial design revealed that the concentrations of gelrite and HPMC K100M significantly affected the dependent variables like viscosity, drug content (%) and drug release (Q₁₂). The results of the *in-vivo* study showed that sustained release of drug from the prepared formulation shows better % protective effect on alcohol induced stomach ulcer compared to that of the marketed conventional tablet. It was concluded that prepared Famotidine *in situ* gel is a good candidate for controlled oral drug delivery system.

Key words: Famotidine; Anti-ulcer; *In situ* gel; Sustained oral drug delivery; Gelrite; *In-vivo* study.

1. INTRODUCTION:

Objective: *In-situ* gel forming drug delivery systems are controlled drug delivery system, sol-gel systems. These *in situ* gels are liquid at room temperature but will undergo gelation when in contact with biological conditions like, pH, ions and temperature of body system. [1]

Gastric emptying is a complex process that is highly variable and makes the *in vivo* performance of drug delivery systems

uncertain. To reduce the dosing frequency, minimize fluctuations in plasma drug concentration and to prolong gastric emptying several attempts were made to develop controlled drug delivery systems. [2-4]

Famotidine is a more potent H₂ receptor having drawbacks such as low oral bioavailability (40 to 45 %), less plasma level after multiple doses (15 to 20 %), first-pass metabolism. The drug has an elimination potential of 65 to 70 % by renal route and 30

to 35 % of metabolic routes [5, 6]. These facts led to the focus of this research on stomach-specific oral *in-situ* gel of Famotidine to reduce its unwanted side effects at other sites by localized and systemic prolonged delivery to stomach ulcers.

2. MATERIALS AND METHODS

2.1 Drug-excipient compatibility studies

Compatibility studies were carried out to know the possible interactions between Famotidine and excipients used in the formulation. Physical mixtures of drug and excipients were prepared and the compatibility studies were carried out at 600-4000 cm^{-1} by using *FT-IR* spectroscopy.

2.2 Preparation of ion activated *in situ* gelling system for Famotidine

Gelrite and HPMC K100M were used as polymers in the formulation of Famotidine. Calcium chloride was used for cation induced gelation in the stomach. Sodium citrate was added to delay the gelation of preparation until the preparation reaches the acid environment of stomach where cation induced gelation occurs.

A Gelrite solution was prepared in 30 ml of deionized water containing sodium citrate; the gelrite was added and heated to 90 °C. It was cooled to 40 °C (step 1). In 35 ml water, HPMC K100M was dissolved. Calcium chloride and Famotidine were added to it while stirring so that there was proper and homogenous dispersion of the drug (step 2). The solutions from step 1 to step 2 were mixed well. A solution of sodium propyl
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paraben and sweetener in 5 ml of water was added to above mixture and stirred well. Coloring agent (Amaranth) was added to the above mixture. The volume was made up to 100 ml with de-ionized water and stirred well (Table-2) [2].

In the preliminary batches P1 to P5 (Table-1), the concentrations of the gelrite were 0.25-1.25 % and the concentration of HPMC K100M, calcium chloride and sodium citrate were constant at 0.4 %, 0.016 % and 0.17 % respectively. While in F1 to F9 (Table-2), concentrations of Gelrite (0.25 %, 0.50 % and 0.75 %) were taken as the variable X_1 and concentrations of HPMC K100M (0.30 %, 0.40 % and 0.50 %) were taken as the variable X_2 , while concentration of calcium chloride and sodium citrate were kept constant.

In the present study a 3^2 full factorial design was employed to study the effect of independent variables, i.e. concentration of Gelrite (X_1) and the concentration of HPMC K100M (X_2) on dependent variables like % cumulative drug release (Q_{12}), % drug content uniformity and viscosity. The high values of correlation coefficient for the dependent variables indicate a good fit. The equation may be used to estimate the response; a small error of variance was noticed in the replicates. [11]

2.3 Evaluation of formulation

2.3a pH measurement

All the prepared gelrite based *in-situ* solutions of Famotidine were checked for their pH. The pH was measured using a

calibrated pH meter at 25°C. The measurements of pH of each data were in triplicate and the average values of preliminary trial batches (P1-P5) and factorial design batches (F1-F9) are shown in Table 1 and Table 3.^[11]

2.3b Gelling capacity

Gelling capacity was determined by mixing the formulation with 0.1 N HCl in the proportion of 3:15 and the gelation was assessed by visual examination. The time taken to form a gel and the integrity of the gel was noted.

A series of symbols were used to indicate the gelling time and gel retention capacity:

- + - Gelation after few min, weak gel formed.
- ++ - Gelation immediate, good gel formed.
- +++ - Gelation immediate, stiff gel.

O.V. - Outside viscous^[2, 3].

2.3c Drug content uniformity

Drug content estimation of the formulation was done by single point standardization method with spectrophotometer.

5 ml of formulation was transferred into a 250 ml conical flask and 100 ml of 0.1 N HCl was added. The mixture was kept aside for 24 h with occasional shaking in a bottle shaker. After 24 h, 5 ml of this mixture was taken and diluted up to 100 ml with 0.1 N HCl (Dilution factor=2000 times). A blank estimation was performed without the drug. The solutions were filtered and the absorbance was measured at 265 nm^[11].

2.3d Viscosity study

The viscosity measurements were done by using Brooke a field DV-II+ viscometer using LV-3 spindle. The formulation was taken in a 100 ml beaker and the angular velocity increased gradually from 10 to 100 rpm, with a wait period of 30 sec at each speed. Viscosity was measured at room temperature and 100 ml of the formulation was used to measure the viscosity. Upper surface of the formulation was adjusted to the mark given in the spindle to measure accurate viscosity. Although these formulations contain sodium citrate and calcium chloride, the hydrogen ion concentration is not sufficiently high to release calcium ions from the complex and gelation does not occur. Increasing the concentration of a dissolved or dispersed substance generally gives rise to increasing viscosity^[7].

2.3e In-vitro dissolution study

The drug release study was carried out using USP type-II apparatus (Rotating Paddle type) at 37 ± 0.5 °C and at 50 rpm using 900 ml of 0.1 N HCl as a dissolution medium (rationale to study n=3). *In-situ* gel equivalent to 40 mg of Famotidine (5 ml of formulation) was placed into a petri dish (5.5 cm i.d.) which was kept in the dissolution vessel and simulated gastric fluid was carefully added to the vessel avoiding any disturbance to the Petri dish. A sample solution of 10 ml was withdrawn at predetermined time intervals, diluted and analyzed spectrophotometrically at 265 nm. An equal amount of fresh

dissolution medium was replaced immediately after withdrawal of the sample solution [11, 13].

2.3f Stability studies

The formulation was subjected to accelerated stability studies as per ICH (The International Conference on Harmonization) guidelines. The most satisfactory formulation was sealed in an aluminum foil and stored at 30 ± 2 °C, $65 \pm 5\%$ RH and at 40 ± 2 °C, $75 \pm 5\%$ RH for 2 months. Formulation was periodically removed and evaluated for physicochemical parameters and *in-vitro* drug dissolution [6].

2.3g In-vivo study (Anti-ulcer activity)

The formulation F4 was selected for investigation of anti-ulcer activity in rats by 'Ethanol induced method'. Ethanol induced method in rats: Randomly divided into three groups of five rats each.

Group-1: Control

Group-2: Standard (Standard marketed formulation, Famtac-40)

Group-3: Test (*In-situ* Famotidine gel, Formulation-F4).

Animals were fasted for 24 h and allowed free access to water. The animals of group I received control vehicle (Water). The animals of groups II and III received standard

marketed tablet (Famtac 40 mg, Dose: 12 mg/kg) and optimized formulation F4 (12 mg/kg) orally, respectively. Thirty minutes later, 1 ml of absolute ethanol was given orally. Animals of group-1 were sacrificed after 1 h and the stomachs were removed, cut along the greater curvature and subjected to measurement of ulcer index. Animals belonging to group-2 and group-3 were sacrificed after 4h and 12h, respectively. Stomachs were subjected to measurement of ulcer index. Animals of group-3 were checked whether the gel was formed in the stomach of rats [8, 12].

Ulcer Severity is graded as:

- 0- No ulcer
- 1- Superficial Ulcer
- 2- Deep ulcer
- 3- Perforation.

The Ulcer Index (U_i) is calculated by the following equation:

$$U_i = U_N + U_S + U_P * 10^{-1}$$

Where, U_N = Average of number of ulcers/animal;

U_S = Average of Severity Scores;

U_P = Percentage of animals with ulcers.

The percentage of ulcer protection was determined as follows:

$$\% \text{ Protective} = \frac{(\text{Control mean ulcer index} - \text{Test mean ulcer index})}{(\text{Control mean ulcer index})} \times 100$$

3. RESULTS AND DISCUSSION

3.1 Drug-excipients compatibility studies

FT-IR study showed that there was no interaction between the drug and the

polymers. Therefore, the drug and polymers are compatible. FT-IR Spectra of Famotidine (Pure drug) and drug-polymer mixture are shown in Fig. 1 and 2.

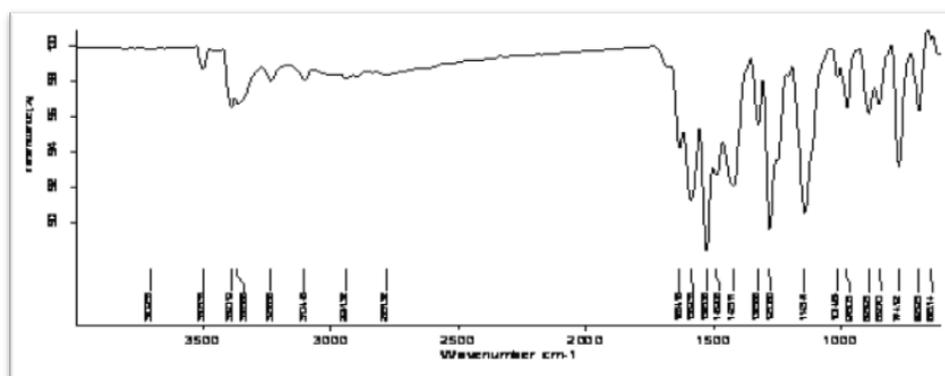


Fig. 1: FT-IR spectrum of pure drug (Famotidine)

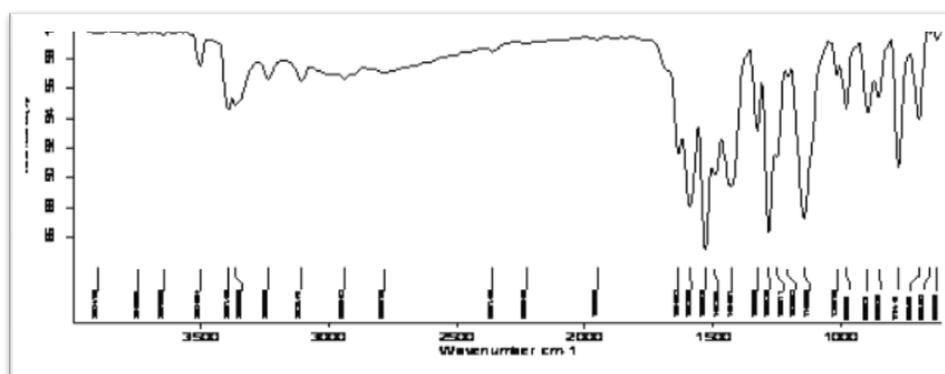


Fig. 2: FT-IR spectrum of physical mixture of drug + polymer + excipients

3.2 Preliminary optimization trials

Preliminary studies were carried out to optimize the gelrite concentration necessary for drug delivery. Batches P1 to P5 (Table-1) were prepared to study the effect of polymer concentration on the viscosity of the solutions, drug content, pH. The concentration of gelrite was varied from 0.25, 0.50, 0.75, 1.00 and 1.25 %. Gelrite based formulations P1-P5 were clear and pH of the formulations was varied from 5.98 to 6.10.

Content uniformity of the developed formulations P1-P5 varied from 98.39 to 99.99, which are within acceptable range as specified in the Indian Pharmacopoeia (95%-105%). The viscosity of formulations P4 and P5 were very high because of the higher concentration of gelrite which decreased the pourability of the solution. Thus gelrite concentration range of 0.25 to 0.75 was selected for 3² factorial design studies. All the batches were prepared by using a constant

amount of Famotidine (0.8%), HPMC K100M (0.4%), Sodium citrate (0.17%), Calcium chloride (0.016%) and Sodium propyl paraben (0.02%).

3² factorial design batches

pH measurement

Gelrite based formulations F1 to F9 were checked for their pH using calibrated pH meter. pH of the formulations was varied from 5.96 to 6.12. The measurements of pH of each formulation were in triplicate and the average values are depicted in Table-2.

Gelling capacity

Gelling capacity of Gelrite based formulations F1 to F9 was determined by mixing the formulation with 0.1 N HCl. Due to the ion cross linking of the gelrite chains by the divalent cations, gelation occurs.

Formulations F1-F3 shows weak gel formation because of the comparatively less concentration of gelrite (0.25%) to that of the

other batches. Formulation F4 and F5 shows good gel formation having gelrite concentration 0.50%. Stiff gel formation was observed in formulation F6 and F7 due to the higher concentration of gelrite and HPMC K100M. The viscosity of F8 and F9 was very high which was difficult to pour the solution. Observations of gelling capacity of prepared gel for gelrite based formulations are depicted in Table-2.

Drug content uniformity

The drug content was determined using single point standardization method. Content uniformity of the developed formulations F1 to F9 varied from 95.79 to 99.72, which are within acceptable range as specified in Indian Pharmacopoeia for Famotidine (95%-105%). The drug content of the of P₁ to P₅ are depicted in Table-1 while the data of drug content for batches F1 to F9 are depicted in Table-2.

Table 1: Results of preliminary trial batches for gelrite based *in-situ* gel

Batch No.	Conc. of Gelrite (%w/v)	Conc. of HPMC K100M (%w/v)	pH* (Average±S.D.)	Viscosity** (cps)	Drug content* (%) (Average±S.D.)
P ₁	0.25	0.4	6.10±0.011	965.79	99.65±1.193
P ₂	0.50	0.4	6.07±0.020	2735.42	99.66±1.160
P ₃	0.75	0.4	6.02±0.025	4553.03	98.39±1.017
P ₄	1.00	0.4	5.99±0.015	----	99.99±2.245
P ₅	1.25	0.4	5.98±0.005	----	99.28±1.081

* Average of three trials ** Viscosity measured at 20 rpm

Table 2: Formulation chart for gelrite based *in-situ* gel by using 3² full factorial designs

Batch No.	Amount of drug (mg)	Conc. of Gelrite (mg)	Conc. of HPMC K100M (mg)	Conc. of sodium citrate (mg)	Conc. of calcium chloride (mg)	De-ionized water
F1	800	250	300	170	160	
F2	800	250	400	170	160	
F3	800	250	500	170	160	
F4	800	500	300	170	160	
F5	800	500	400	170	160	q.s. up to 100
F6	800	500	500	170	160	ml
F7	800	750	300	170	160	
F8	800	750	400	170	160	
F9	800	750	500	170	160	

➤ All the batches were prepared using constant amount of

- Famotidine: 0.8% w/v,
- Sodium citrate: 0.17% w/v,
- Calcium chloride: 0.016% w/v,
- Sodium propyl paraben: 0.02% w/v

Viscosity study

Formulations F1-F9 were evaluated for their rheological property using Brookfield viscometer. All the formulations exhibited pseudo-plastic rheology, as shown by shear thinning and a decrease in the viscosity with increase in angular velocity. Results of the

rheological studies show that as the concentration of polymers increases from F1 to F9 formulation, viscosity also increases.

The viscosity of the gelrite based *in-situ* formulations of P1 to P5 and batches F1 to F9 are depicted in Table-1 and Figure-3, respectively.

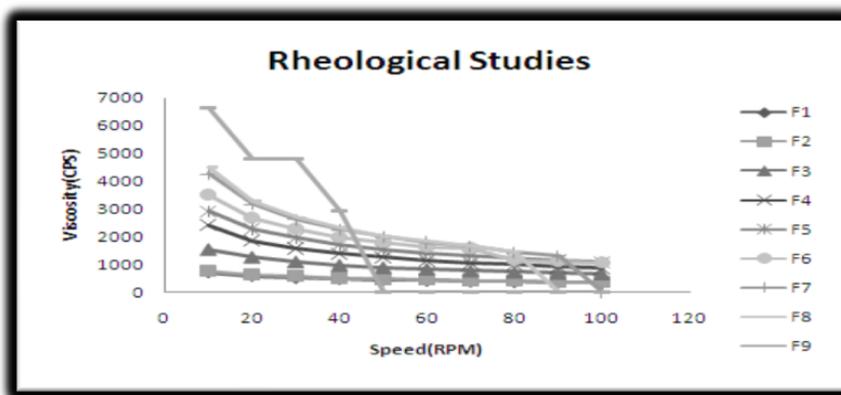


Fig. 3: Rheological studies on formulation F1-F9

***In-vitro* dissolution study**

In-vitro dissolution study was carried out for 12 h. The amount of cumulative drug release from the gel at the end of 12 h was found to be highest in formulation F1 and lowest in F9

which could be due to increase in the concentration of polymers. The dissolution profiles for gelrite based *in-situ* gels from batches F1 to F9 are shown in Figure-4.

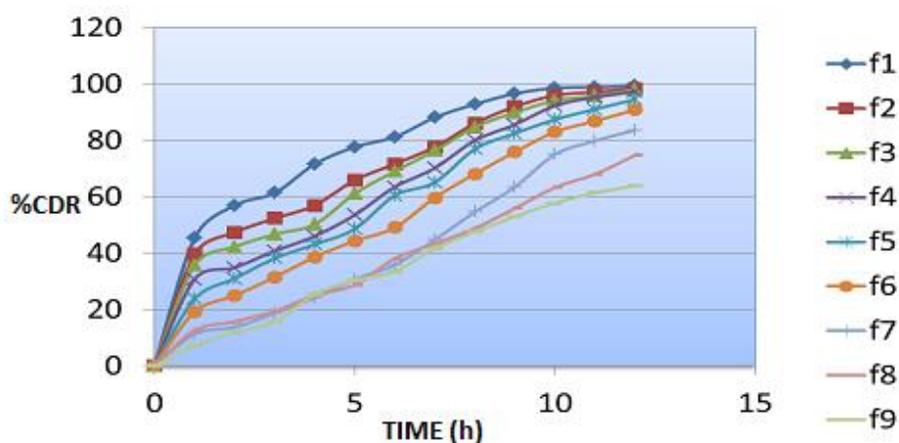


Fig. 4: *In-vitro* dissolution studies of gelrite based formulations batch F1-F9.

Selection of the best batch

The selection of the best batch depends on gelling capacity, viscosity and drug content of formulation. Formulation F4 was selected the best formulation because of its good gelling capacity and optimum viscosity compared to other formulations. F4 shows the drug content 98.84 which is within the acceptable range as specified in the Indian Pharmacopoeia. The viscosity of batch F4 is 1857.60 cps (at 20 rpm) which is easy for swallowing and good ability for gelation immediately after oral administration. In the batches F1 to F3 the rate of drug release are very high because of the low concentration of polymers and weak gel formation. Formulations F5 to F9 showed less cumulative drug release compared to F4. The

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amount of drug released for the batch F4 after 12 hours was 97.23%. So, the batch F4 was selected for further study.

***In-vivo* study (Anti-ulcer activity)**

The anti-ulcer activity was evaluated by ethanol induced ulcer in rats to check the effect of drug release in a sustained manner from the gel by assessing the ulcer index. In group 3 which served as a test, ulcers were reduced compared to group 1 (control) and 2 (standard). The gel formation takes place inside the stomach of the test group rats and was found after 12 h. The ulcer index for group 1, 2 and 3 are 35.4, 14 and 7.2 respectively. The formulation F4 has decreased the intensity of gastric mucosal damage induced by ethanol and showed a protection index of 79.66% when compared

to control, whereas standard marketed tablet of Famotidine has shown 60.45% of protection induced by ethanol when compared to control. Graph of % protective v/s groups shows that sustained release of

the drug from *in-situ* formulation has better % protective effect on alcohol induced ulcer compared to that of conventional Famotidine tablet. Results of ulcer index for ethanol induced model are shown in Figure-7.

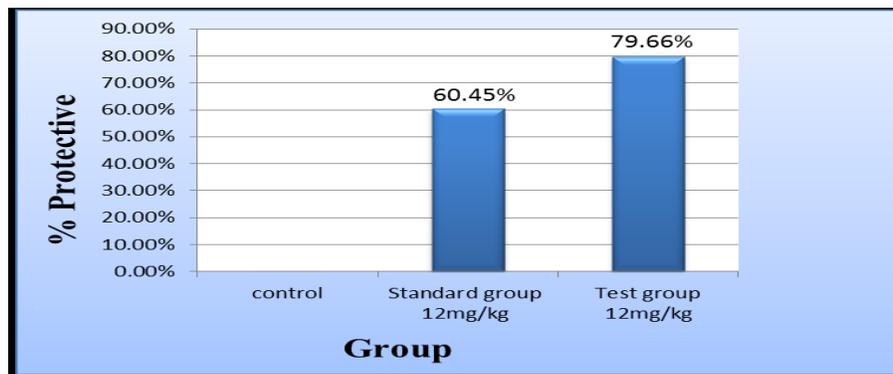


Fig.7: Percentage protection of drug in ethanol induced ulcer.

Release mechanism

The results of regression analysis from Zero order, First order, Higuchi model and Korsmeyer-Peppas model (Table-4) of best formulation F4 show that zero order gave the highest value of R^2 with significant difference to that of other models. From these results it was concluded that F4 follows Zero order kinetic because of the good linearity obtained by this model.

Stability study

Stability studies were carried out on the most satisfactory formulation as per ICH Guidelines Q1C. The most satisfactory formulations were stored in sealed aluminum foil at $30 \pm 2^\circ\text{C}$, $65 \pm 5\%$ RH and at $40 \pm 2^\circ\text{C}$, $75 \pm 5\%$ RH for 2 months. The formulation was periodically evaluated for physicochemical parameters and *in-vitro* drug release. Figure-5 and Figure-6 showed that there were no significant changes found after 2 month stability study.

Table3: Evaluation of physicochemical parameters of formulation F4 (After stability).

Physicochemical Parameters		Time (Days)		
		0	30	60
pH	A*	6.07	6.04	6.12
	B**		6.08	6.07
Drug Content (%)	A*	98.84	97.34	98.17
	B**		96.51	95.68
Viscosity(cps)***	A*	1857.60	1679.64	1589.37
	B**		1704.89	1649.65

*A: $30 \pm 2^\circ\text{C}$ and $65 \pm 5\%$ RH ** B: $40 \pm 2^\circ\text{C}$ and $75 \pm 5\%$ RH *** Viscosity measured at 20 rpm

Table 4: Release kinetic for gelrite based formulation F4

Batch No.	Regression			
	Zero order kinetic	First order kinetic	Higuchi kinetic	Korsmeyer-Peppas
F4	0.9886	0.910	0.9667	0.9478

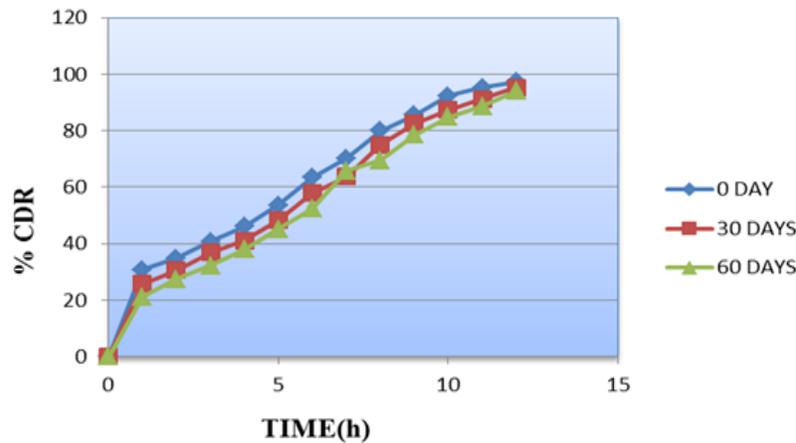


Fig. 5: *In-vitro* dissolution studies of F4 (A) (After stability). [A: 30±2°C and 65±5% RH]

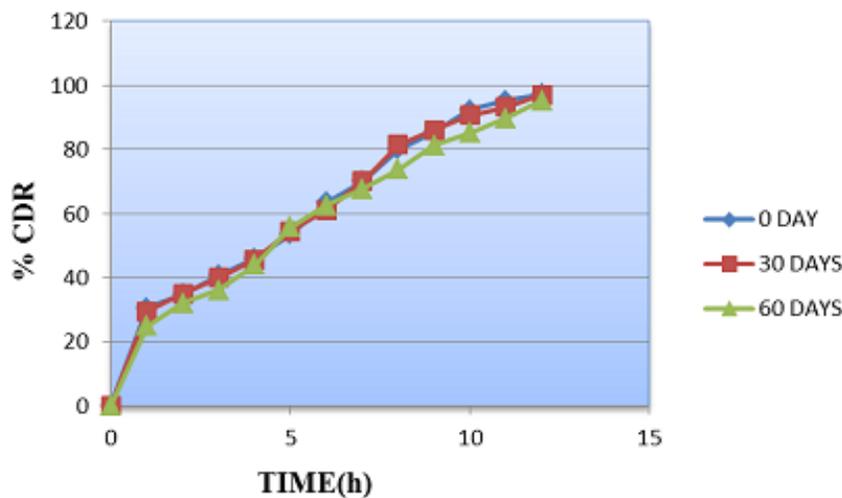


Fig. 6: *In-vitro* dissolution study of F4 (B) (After stability). [B: 40±2°C and 75±5% RH]

OPTIMIZATION BY USING 3² FULL FACTORIAL DESIGNS

Factorial equation for viscosity

$$\text{Viscosity} = 2046.45 + 1458.023X_1 + 518.55X_2 + 238.44 X_1^2 + 5.66 X_2^2 + 336.59 X_1 X_2$$

The viscosity is an important variable because it affects the gelation of the solutions, the flow of the formulation and time required for the gelation. The viscosity is dependent on the concentration of the polymer and concentration of the HPMC K100M. The

viscosity of the gelrite solutions varied from 583.87 cps to 4782.98 cps which was measured at 20 rpm and showed good correlation coefficient as 0.9931. Results of the equation indicate that the effect of X_1 (concentration of gelrite) is more significant than X_2 (concentration of HPMC K100M). The b_0 equals to 2046.45 was the arithmetic mean of all nine trials. The positive X_1 and X_2 coefficient indicates there is increase in the viscosity with increased concentration of both gelrite and as well as HPMC K100M.

Factorial equation for drug content

$$\text{Drug content} = 98.92 - 0.092X_1 + 0.544X_2 - 1.32X_1^2 - 1.437X_2^2 + 0.359X_1X_2$$

The drug content varied from 95.79% to 99.72% in batches F1 to F9 gelrite based *in-situ* formulations of Famotidine and showed good correlation coefficient as 0.9706. Results of the equation indicate that the effect of X_2 (concentration of HPMC K100M) is more significant than X_1 (concentration of gelrite). So, the effect of the concentration of the HPMC K100M was more responsible for the drug content of the *in-situ* formulations than the concentration of gelrite.

Factorial equation for %CDR

$$\%CDR = 94.45 - 12.26X_1 - 4.596X_2 - 4.649X_1^2 - 7.857X_2^2 - 0.412X_1X_2$$

The amount of drug released is an important parameter for sustained release action of the *in-situ* gel of Famotidine. The amount of drug released after 12 hours from the *in-situ* gel of Famotidine varied from 63.78% to 99.30% in formulations F1-F9 and showed good

linearity. Results of the equation indicated that both the effect of the concentration of gelrite (X_1) and the effect of the concentration of HPMC K100M (X_2) were in negative values, but X_1 was more significant than the X_2 . So, the concentration of X_1 was more effective as for controlled release action of the gels than the concentration of X_2 . The negative X_1 and X_2 coefficients indicate there is decrease in cumulative drug release with increase in the concentration of both gelrite and as well as HPMC K100M.

4. CONCLUSION

In the present study, an attempt was made to formulate and evaluate oral *in-situ* gel of Famotidine for the treatment of stomach ulcer. The main interest in such a dosage form was to target the drug to its absorption site by preparing gastro retentive drug delivery system as the absorption window of Famotidine is stomach. The possible interaction between the drug and excipient was studied by FT-IR spectroscopy which showed that there was no interaction between the selected drug and polymers under study.

Oral *in-situ* gel of Famotidine was prepared by using Famotidine and other additives as shown in formulation chart. In this study, various formulations were developed using gelrite and HPMC K100M as polymers, calcium chloride as a cross linking agent. F4 was selected as best formulation because of its good gelling capacity and showed 97.23% cumulative drug release after 12 h. The

formulation F4 followed zero order kinetic which describes that the rate of drug release is independent of its concentration. Results of the stability study showed that there were no significant changes found after 2 months.

The results of optimization by 3² full factorial design revealed that the concentration of gelrite and concentration of HPMC K100M significantly affect the dependent variables viscosity, drug content and %CDR (Q₁₂). The *in-vivo* study shows significant anti-ulcer effect of the sustained release gelrite based

in-situ gel of Famotidine compared to conventional marketed tablet over long period of time. These *in-situ* gels are, thus, suitable for oral sustained release of Famotidine.

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