In vitro and In vivo Characterization of Pectin Based In situ Gelling System of Famotidine

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Received June 29, 2011; accepted July 5, 2012

ABSTRACT

In this study famotidine was used as a model drug to formulate and evaluate pH-induced in situ gelling system for oral sustained release drug delivery in stomach which has shorter biological half-life. To study the effect of independent variables full factorial design was employed, concentration of pectin as pH dependant polymer and concentration of calcium chloride on dependent variables like viscosity, drug content, 50% and 80% drug release and similarity factor. It was found that both the concentration of pectin and concentration of calcium chloride had significant effect on viscosity, drug content, 50% and 80% drug release and similarity factor of the system. In vitro drug release study showed that drug released from the in situ gel followed non-Fickian diffusion. Mathematical modeling was employed for quantitative evaluation of the effect of formulation variables. Rat pylorus ligation model was used for in vivo study of the selected formulation. Results shows gel formation in gastric juice and reduction in ulcer index. There were few or no major changes in the formulation during three months stability testing. The in situ gelling systems are useful for delivery of famotidine.

KEYWORDS: Famotidine; pectin; in situ gel; Mucoadhesion; pylorus ligation; antiulcer agent.

Introduction

In situ gelling systems (IGSs) are in principle capable of releasing drug molecule in a sustained manner affording relatively constant plasma profiles. These hydrogels are liquid at room temperature but undergo gellation when in contact with body fluids or change in pH. These have a characteristic property of temperature dependent, pH dependent and cation induced gellation. Compared to conventional controlled release formulations, IGSs possess potential advantages like simple manufacturing processes and ease of administration (Miyazaki et al., 1999; 2003).

Intimate contact of a delivery system at the absorbing site maximizes not only drug absorption, but also influences the rate of drug absorption. These IGSs can be easily formulated in bulk and these formulations give homogeneity of drug distribution when compared to other conventional suspensions. These IGSs also have good mucoadhesion property, which helps in coating of the ulcer lining once the solution comes in contact with the gastric pH (Ganguly et al., 2004).

Famotidine, an antiulcer agent was chosen as a drug which is an H₂ receptor antagonist, which is 8 times more potent than ranitidine, and 20 times more potent than cimetidine. Famotidine is rapidly and incompletely absorbed from gastrointestinal tract with the bioavailability of about 43% having an elimination half life (t₁/₂) of 3 hours. Some patients with reflux oesophagitis who are being treated with proton pump inhibitor may continue to produce acid in the night (nocturnal acid breakthrough) and could be benefited by taking a sustained release formulation of H₂ receptor antagonist (Hardman et al., 2006).

It is also reported that oral treatment of gastric disorders with an H₂ antagonist like ranitidine or famotidine used in combination with antacids promotes local delivery of these drugs, also increases stomach wall receptor site bioavailability and increases the efficacy of drugs to reduced acid secretion (Dave et al., 2004). Several approaches are currently used to prolong gastric retention time. Among them the principle of bioadhesive preparations offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release (Coffin et al., 1995).

In the present study we prepared and evaluated a formulation of famotidine as IGS for oral delivery by using mucoadhesive polymer of pectin (Sing et al., 2000).

Materials and Methods

Materials

Famotidine was a gift sample from Shehat Pharma Ltd. Himmatnagar, Gujarat, India. Pectin, sodium citrate, calcium chloride, sodium hydroxide were
obtained from commercial sources (S. D. Fine Chemicals, Mumbai, India). All other reagents and chemicals used were of analytical grade.

**Methods**

**Preparation and preliminary studies**

The different concentrations of pectin solutions were prepared in ultra pure water containing sodium citrate at 60°C in beaker. Calcium chloride was added to the solution after cooling at below 40°C with stirring using magnetic stirrer (Remi Equipments Pvt. Ltd., Mumbai). Famotidine (40 mg) was dissolved separately in 0.1 N HCl solution and then added slowly to the above pectin solution while stirring to get the homogeneous dispersion of the drug. 0.1 N NaOH was added to the above solution to neutralize the hydrochloric acid while stirring (Figure 1). The above formulations were sonicated in a bath sonicator (Enertech Electronics Pvt. Ltd., Mumbai) for 15 minutes and then checked the viscosity of the solutions by a Brookfield viscometer (Model no LVDV 2P230) with spindle number 1 and then add the prepared solutions in pH 1.2 buffer, to see the gel formation (Figure 2) and checked its physical appearance and dissolutions using USP XXVI basket apparatus (TDT-06T, Electrolab, Mumbai, India) at 37°C ± 0.5°C and at 100 rpm using 900 mL of pH 1.2 buffer as a dissolution medium (n = 3) as per USP XXVI dissolution test prescribed IP of the prepared gels (Kubo et al., 2003).

In batches R1 to R12 shown in Table 1, the concentration of the pectin was 0.5 to 2% w/v and the concentration of calcium chloride and sodium citrate were constant at 0.1% w/v and 0.25% w/v respectively. While in S1 to S9 (Table 2) takes 1, 1.5 and 2% w/v of pectin as X1 variable and takes 0.075, 0.1 and 0.125% w/v of CaCl2 as X2 variable while concentration sodium citrates keep constant (0.25% w/v). All the formulation from S1 to S9 was checked their viscosity, pH, drug content and after formation of gel studied on percentage drug released. The effect of formulation variables on characteristics of the IGS is summarized in Table 1 and Table 2.

**Fig. 1** Formulation of pectin based *in situ* solution of famotidine batch S5.

**Fig. 2** Gel formation from pectin based *in situ* solution of famotidine in pH 1.2 buffer.
TABLE 1
Results of preliminary trial batches for pectin based IGS of famotidine.

<table>
<thead>
<tr>
<th>Batch No.</th>
<th>Concentration of pectin (%w/v)</th>
<th>pH</th>
<th>Viscosity (cp)</th>
<th>Drug content (%)</th>
<th>Characteristic of IGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1</td>
<td>0.5</td>
<td>7.5</td>
<td>155</td>
<td>80.20</td>
<td>Gel is not form properly and less drug content</td>
</tr>
<tr>
<td>R2</td>
<td>0.5</td>
<td>7.5</td>
<td>154</td>
<td>83.32</td>
<td></td>
</tr>
<tr>
<td>R3</td>
<td>0.5</td>
<td>7.6</td>
<td>150</td>
<td>84.45</td>
<td></td>
</tr>
<tr>
<td>R4</td>
<td>1</td>
<td>7.2</td>
<td>228</td>
<td>89.98</td>
<td></td>
</tr>
<tr>
<td>R5</td>
<td>1</td>
<td>7.3</td>
<td>227</td>
<td>91.76</td>
<td></td>
</tr>
<tr>
<td>R6</td>
<td>1</td>
<td>7.4</td>
<td>225</td>
<td>90.89</td>
<td></td>
</tr>
<tr>
<td>R7</td>
<td>1.5</td>
<td>7.1</td>
<td>314</td>
<td>96.98</td>
<td></td>
</tr>
<tr>
<td>R8</td>
<td>1.5</td>
<td>7.0</td>
<td>317</td>
<td>97.98</td>
<td></td>
</tr>
<tr>
<td>R9</td>
<td>1.5</td>
<td>7.0</td>
<td>315</td>
<td>98.25</td>
<td></td>
</tr>
<tr>
<td>R10</td>
<td>1.5</td>
<td>7.0</td>
<td>315</td>
<td>97.98</td>
<td></td>
</tr>
<tr>
<td>R11</td>
<td>2</td>
<td>6.6</td>
<td>398</td>
<td>95.11</td>
<td></td>
</tr>
<tr>
<td>R12</td>
<td>2</td>
<td>6.5</td>
<td>399</td>
<td>93.12</td>
<td></td>
</tr>
</tbody>
</table>

Note: All the batches were prepared using CaCl₂ 0.1%w/v and sodium citrate 0.25%w/v

TABLE 2
3² full factorial design layouts for pectin based IGS of famotidine.

<table>
<thead>
<tr>
<th>Batch No.</th>
<th>Variables levels in coded form</th>
<th>Viscosity (cp)</th>
<th>Drug content (%)</th>
<th>% Drug release (Q50)</th>
<th>% Drug release (Q80)</th>
<th>Similarity factor (F²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>-1 -1</td>
<td>225</td>
<td>89.99</td>
<td>99.02</td>
<td>99.02</td>
<td>30.21</td>
</tr>
<tr>
<td>S2</td>
<td>-1 0</td>
<td>238</td>
<td>91.70</td>
<td>98.00</td>
<td>98.00</td>
<td>31.38</td>
</tr>
<tr>
<td>S3</td>
<td>-1 +1</td>
<td>254</td>
<td>90.91</td>
<td>93.13</td>
<td>97.74</td>
<td>34.79</td>
</tr>
<tr>
<td>S4</td>
<td>0 -1</td>
<td>295</td>
<td>96.12</td>
<td>78.38</td>
<td>97.03</td>
<td>50.81</td>
</tr>
<tr>
<td>S5</td>
<td>0 0</td>
<td>314</td>
<td>97.96</td>
<td>53.73</td>
<td>90.18</td>
<td>72.75</td>
</tr>
<tr>
<td>S6</td>
<td>0 +1</td>
<td>345</td>
<td>95.69</td>
<td>50.52</td>
<td>85.03</td>
<td>61.99</td>
</tr>
<tr>
<td>S7</td>
<td>+1 -1</td>
<td>382</td>
<td>92.22</td>
<td>47.11</td>
<td>81.04</td>
<td>55.23</td>
</tr>
<tr>
<td>S8</td>
<td>+1 0</td>
<td>395</td>
<td>94.90</td>
<td>43.96</td>
<td>77.48</td>
<td>47.41</td>
</tr>
<tr>
<td>S9</td>
<td>+1 +1</td>
<td>399</td>
<td>93.85</td>
<td>38.56</td>
<td>74.70</td>
<td>42.42</td>
</tr>
</tbody>
</table>

Translation of coded levels in actual units

<table>
<thead>
<tr>
<th>Variables level</th>
<th>Low (-1)</th>
<th>Medium (0)</th>
<th>High (+1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration of Pectin (%w/v) (X₁)</td>
<td>1</td>
<td>1.5</td>
<td>2</td>
</tr>
<tr>
<td>Concentration of Calcium chloride (%w/v) (X₂)</td>
<td>0.075</td>
<td>0.1</td>
<td>0.125</td>
</tr>
</tbody>
</table>

Note: All the batches contained the constant amount of drug as 40 mg, viscosity measured at 150 rpm and having the same pH 7.

Optimisation by using 3² full factorial designs

On the basis of the preliminary trials in the present study a 3² full factorial design was employed to study the effect of independent variables, i.e. concentration of pectin (X₁) and the concentration of calcium chloride (X₂) on dependent variables % drug release at Q₅₀ and Q₈₀, drug content, viscosity and similarity factor. A statistical model (see equation) incorporating interactive and polynomial terms was utilized to evaluate the responses.

\[ Y = b₀ + b₁X₁ + b₂X₂ + b₁₂X₁X₂ + b₁₁X₁^2 + b₂₂X₂^2 \]

Where, Y is the arithmetic mean response of the nine runs, and b₀ is the estimated coefficient for the factor X₁. The main effects (X₁ and X₂) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X₁X₂) show how the response changes when two factors are simultaneously changed. The polynomial terms (X₁² and X₂²) are included to investigate non-linearity (Hardman et al., 2006). The results depicted in Table II clearly indicate that all the dependent variables are strongly dependent on the selected independent variables as they show a wide variation among the nine batches (S1 to S9). The fitted equations (Full model) relating the responses, i.e. % drug release at Q₅₀ and Q₈₀, drug content, viscosity and similarity factor (f₂) and to the transformed factor are show in Table II. The polynomial equation can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries, i.e. positive or negative. The high values of correlation coefficient (Table 5) for the dependent variables indicate a good fit. The equation may be used to obtain estimate of the response because small error of variance was noticed in the replicates.
Physical appearance and pH measurement

All the prepared pectin based in situ solutions of famotidine were checked for their clarity by visually and the pH of the solutions by pH meter (Sysstronic, 361 micro pH meter). After preparing solutions in pH 1.2 buffer, the time required for gel formation and consistency of gel formed was checked visually. The pH was also measured in each of the solution of pectin based in situ solutions of famotidine using pH meter at 25°C. The measurements of pH of each data were in triplicate and the average values of preliminary trial of pectin are shown in Table 1.

Determination of viscosity

The viscosities of the prepared solutions were determined using a Brookfield digital viscometer with spindle number 1. The sample temperature was controlled at 25°C ± 1°C before the each measurement. The viscosity of the solutions (drug free) prepared in water was determined at ambient condition using 2 mL aliquot of the sample.

In vitro drug release study

The drug release study was carried out using USP XXVI basket apparatus (Electrolab, TDT-06T, Mumbai, India) at 37°C ± 0.5°C and at 100 rpm using 900 mL of pH 1.2 buffer as a dissolution medium (n = 3) as per USP XXVI dissolution test prescribed IP. IGSs of famotidine equivalent to 40 mg of famotidine were used for the test. 10 mL of sample solution was withdrawn at predetermined time intervals, filtered through a 0.45 µ membrane filter, dilute suitably and analyzed UV spectrophotometrically at 265 nm (UV 1700, Shimadzu). Same amount of fresh dissolution medium was replaced immediately after withdrawal of the test sample. Percent drug dissolved at different time intervals was calculated using the Beer Lambert’s equation (Absorption = 0.0314x + 0.02, R² = 0.9996). The results of S1 to S9 are shown in Figure 3.

Comparison of dissolution profiles

(Paulo et al., 2001; Prior et al., 507)

The similarity factor (f²) given by SUPAC guidelines for modified release dosage form was used as a basis to compare dissolution profile. The dissolution profiles of products were compared using a similarity factor (f²). This similarity factor is calculated by following formula,

\[ f² = 50 \times \log \left( \prod_{j=1}^{n} \left[ \frac{R_j - T_j}{0.5 \times 100} \right] \right) \]

Where ‘n’ is the number of dissolution time and Rj and Tj are the reference (theoretical) and test dissolution values at time ‘t’. Two dissolution profiles are considered similar when the f² value is 50 to 100. The similarity factors (f²) of all the batches S1 to S9 of pectin based formulations were determined with the help of theoretical release profile as reference by the above formula.

The results of the similarity factors f² values for all the batches S1 to S9 of pectin based IGS of famotidine are mentioned in Table II.

Kinetics modeling of drug dissolution profiles

The dissolution profile of all the batches was fitted to zero order, first order (Wagner, 1969; Gibaldi et al., 1967), and Higuchi and Korsemeyer peppas model (Higuchi, 1996; 1963) to ascertain the kinetic modeling of the drug release. The dissolution pattern of the drug release form all the formulations were also checked by the following equation in which data corresponding to 60 ± 5% release were fitted using the equation proposed by Korsemeyer peppas equation:

\[ \frac{M_t}{M_\infty} = k t^n \]

Where, Mt/M∞ is the fraction of drug released at time t, k the kinetic constant and n is the release exponent that characterizes the mechanism of drug release. The correlation coefficient values of the zero-order, first order, higuchi kinetics and korsemeyer peppas kinetics are shown in Table 3.
TABLE 3
Release kinetics for pectin based IGS of famotidine batches S1 to S9.

<table>
<thead>
<tr>
<th>Batch no.</th>
<th>Zero order kinetic</th>
<th>First order kinetic</th>
<th>Higuchi kinetic</th>
<th>Krosmeyer peppas</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>0.7061</td>
<td>0.4100</td>
<td>0.8277</td>
<td>0.9101</td>
</tr>
<tr>
<td>S2</td>
<td>0.7477</td>
<td>0.5000</td>
<td>0.8624</td>
<td>0.9300</td>
</tr>
<tr>
<td>S3</td>
<td>0.8111</td>
<td>0.5000</td>
<td>0.8992</td>
<td>0.9429</td>
</tr>
<tr>
<td>S4</td>
<td>0.8859</td>
<td>0.9170</td>
<td>0.9514</td>
<td>0.9754</td>
</tr>
<tr>
<td>S5</td>
<td>0.9333</td>
<td>0.8823</td>
<td>0.9866</td>
<td>0.9731</td>
</tr>
<tr>
<td>S6</td>
<td>0.9856</td>
<td>0.9679</td>
<td>0.9793</td>
<td>0.9925</td>
</tr>
<tr>
<td>S7</td>
<td>0.9859</td>
<td>0.9609</td>
<td>0.9820</td>
<td>0.9959</td>
</tr>
<tr>
<td>S8</td>
<td>0.9956</td>
<td>0.9655</td>
<td>0.9757</td>
<td>0.9906</td>
</tr>
<tr>
<td>S9</td>
<td>0.9960</td>
<td>0.9866</td>
<td>0.9617</td>
<td>0.9805</td>
</tr>
</tbody>
</table>

Measurement of water uptake by the gel

The water uptake by the gel can be determined using a thermogravimetric analyzer. But in this present study a simple method has been adopted to determine the water uptake by the gel. The in situ gel formed in 40 mL of buffer (pH 1.2) was used for this study. From each formulation the gel portion from the buffer was separated and the excess buffer was blotted out with a tissue paper. The initial weight of the gel taken was weighed and to this gel 10 mL of distilled water was added and after every 30 minutes of the interval water was decanted and the weight of the gel was recorded and the difference in the weight was calculated and reported (Ganguly et al., 2004). The result of the water uptake study for pectin based IGS of famotidine is depicted in Figure 4.

Stability study

Prepared pectin based IGS of famotidine was stored in a glass containers (well stoppard) for three months and the stability of the aqueous solutions of the pectin based IGSs of famotidine was monitored up to 3 months at room temperature (25°C ± 1°C) and normal humidity conditions (Zatz, 1985; Tingstad, 1964 and Tas et al., 2004). Periodically (initial, 1 and 3 months interval) samples were removed and characterized by pH, viscosity and drug content. The results of the stability study for the selected batch (S5) of pectin based IGS of famotidine formulations is given in Table IV.

In vivo study

In the selected formulation (S5) of pectin based IGS of famotidine ‘pyrolus legation’ method in rats was used for in vivo study and also checked for the gel formation in collected gastric juice from the rats. Pyrolus legation method in rats: The male albino wistar rats weighing between 150-250 g, were divided into 3 groups, in which each group contain three rats.

- Group-1: Served as control
- Group-2: Served as control plus immediate treatment
- Group-3: Served as treated plus IGS of famotidine

The selected formulation (S5) was orally administered to rats (previously fasted for 24 hours) using Sandoc syringe. Then they anaesthetized with ether and a portion of the abdomen was opened by a small midline incision under the xiphoid process. The pylorus portion of the stomach was lifted and legated. During this process, care was taken to avoid the friction to the pylorus or damage to its blood supply. The stomach was closed by interrupted sutures (Robert et al., 1971).

Group-1: After 5 hours the animals were sacrificed and each stomach was removed, cut along the greater curvature and subjected to measurement of ulcer index and collect the gastric secretion for in vitro gel formation.

Group-2: In immediate treatment group, pectin based IGS of famotidine was administered orally after 5 hours of legation, after 20 minutes the animals were sacrificed and each stomach was removed, cut along the greater curvature observed whether gel is formed or not and subjected to measurement of ulcer index.

Group-3: While in treated group, the IGS of famotidine was administered orally 30 minutes before starting the experiment in 24 hours fasted rats and after 5 hours of surgery animals were sacrificed and observed for the effect of drug by counting the ulcer index.

Calculation for ulcer index

Each lesion of stomach was measured along its greatest length and breath. For circular lesion, diameter was measured and finally area was calculated. In case of petechiae, 5 of them were considered to be equivalent to 1 mm of ulcerated area. The ratio of total area of the stomach mucosa and that of ulcerated mucosa were calculated and then it was divided by 10 to obtain ulcer index (Vogel et al., 2002).

\[
X = \frac{\text{Total area of stomach mucosa}}{\text{Total area of ulcerated mucosa}} \quad \text{(3)}
\]

\[
\text{Ulcer Index} = X/10
\]
The area of ulcerated portion is calculated as per the following formula:

Area of circular lesion = \( \pi D^2/4 \)

Area of linear lesion = \( L^2B \)

Area of stomach mucosa = \( \pi D^2/8 \)

Where \( D \) = Diameter of the stomach mucosa

The results of in vivo study of the selected formulations (S5) of the pectin were presented in Figure 5 to 8. Figure 9 shows pylorus ligation induced ulcer index for pectin based IGS of famotidine formulation.

**Fig. 5** In vivo study for pectin based in situ solution of famotidine batch S5 in rat: Group 1 served as a control.

**Fig. 6** Group-2 served as control plus immediate treatment by pectin based in situ solution of famotidine batch S5.

**Fig. 7** Group-3 served as treated plus pectin based in situ solution of famotidine batch S5.


**Results and Discussion**

**Preliminary Trials**

Preliminary studies were carried out to determine the pectin concentration necessary for drug delivery. Batches R1 to R12 (Table I) were prepared to study the effect of polymer (pectin) concentration on the viscosity of the solutions, drug content, pH and the physical properties of the gel in pH 1.2 buffer. The concentration of pectin was varied from 0.5, 1, 1.5 and 2 % w/v. In the batches R1 to R3 there was improper gellation which leads to rapid flow of the formulation and also the time required for gellation and drug content was also very lower then the other batches. In the batches R4 to R6 the gellation, the flow of the formulation, the time required for gellation and the drug content were slightly better then that of R1 to R3. While in the batches R7 to R12 all the characteristics of the gels are good than that of above batches but in the batches of R10 to R12 the viscosity of the solutions were very high because of the higher concentration of pectin which was difficult to pour the solution while it was not observed in batches R7 to R9. Thus we concluded that 1.5% w/v pectin was the optimum concentration. There was no significant effect of concentration of sodium citrate hence it was kept
constant (0.25% w/v) in all the batches. Here all the batches were prepared by using 0.075% w/v concentration of CaCl₂ and 40 mg of drug. The pH of the solution was kept neutral.

**Optimization by 3² Full Factorial Designs**

On the basis of the preliminary trials in the present study a 3² full factorial design was employed to study the effect of independent variables, i.e. concentration of pectin (X₁) and the concentration of CaCl₂ (X₂) on dependent variables viscosity, drug content, Q₅₀, Q₈₀ and similarity factor. The results summarized in Table II clearly indicate that all the dependent variables are strongly dependent on the selected independent variables as they show a wide variation among the nine batches (S1 to S9). Fitted equations (full models) relating the responses i.e. viscosity, drug content, Q₅₀, Q₈₀ and similarity factor to the transformed factor are shown in Table V. The polynomial equation can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries, i.e. positive or negative. The high values of correlation coefficient (Table V) for the dependent variables indicate a good fit.

The equation may be used to obtain estimate of the response because small error of variance was noticed in the replicates.

**Factorial equation for viscosity**

The viscosity is an important variable because it affects the gellation of the solutions, the flow of the formulation and time required for the gellation. The viscosity is dependent on the concentration of the polymer and concentration of the calcium chloride. The viscosity of the pectin solutions varied from 225 cp to 399 cp which was measured at 150 rpm (Table II) and showed good correlation coefficient as 0.996 (Table V). Results of the equation indicate that the effect of X₁ (concentration of pectin) is more significant than X₂ (concentration of CaCl₂). Moreover, volume of CaCl₂ had a negative effect on the viscosity, i.e. as the volume of cross-linking agent increase, the viscosity increases and has no significant effect on drug release.

**Factorial equation for drug content**

Data of drug content for all the batches (S1 to S9) are mentioned in Table II. The drug content varied from 89.99% to 97.96% in batches S1 to S9 pectin based IGS of famotidine formulations and showed good correlation coefficient as 0.989 (Table V). Results of the equation indicated that both the concentration of the X₁ and X₂ were responsible for the drug content of the formulations but the effect of X₁ (concentration of pectin) is more significant than X₂ (concentration of CaCl₂), the effect of the X₂ was very less so it was considered non significant compared to the concentration of X₁.

**Factorial equation for Q₅₀**

The amount of drug released in an important parameter for sustained release action of the IGS of famotidine. The amount of drug released at four hours from the IGS of famotidine varied from 38.56% to 99.02% (Table II) and showed good correlation coefficient as 0.979 (Table V). Results of the equation indicated that the effect of the concentration of pectin (X₁) was very less and in minus sign while the effect of the concentration of CaCl₂ (X₂) was also in minus sign but it was higher than X₁ so the concentration of the X₂ was very less effective as controlled release action of the gels than the concentration of the X₁.

**Factorial equation for Q₈₀**

The amount of drug released of at 8 hours is also important parameters for sustained action of the formulations. The Q₈₀ for all the batches S1 to S9 varied from 74.70% to 99.02% (Table II) and showed good correlation coefficient as 0.990 (Table V). Results of the equation indicated that the effect of the concentration of pectin (X₁) was very less and in minus sign while the effect of the concentration of CaCl₂ (X₂) was also in minus sign but it was higher than X₁ so the concentration of the X₂ was very less effective as controlled release action of the gels than the concentration of the X₁.

**Factorial equation for similarity factor**

The similarity factor (f²) for all the batches S1 to S9 varied from 30.21 to 72.75 (Table II) and showed good correlation coefficient as 0.951 (Table V). Results of the equation indicated that the effect of X₂ (concentration of CaCl₂) was more significant than X₁ (concentration of pectin) as a controlled release action of the gels. Moreover, the concentration of pectin increases the release rate decreases and give effect longer period of time. Means, we conclude that the concentration of pectin and concentration of CaCl₂ directly affects the similarity factor.

**Release Mechanism**

The result from the regression from zero order, first order, Higuchi and Korsemeyer-Peppas models (Table III) showed that all the batches of pectin based IGS of famotidine S1 to S9 followed Korsemeyer-Peppas model because good correlation coefficient obtained by this model and the batch S5 containing good correlation coefficient 0.9973.

**Selection of the Best Batch**

The selection of the best batch depends on percentage viscosity, drug content, Q₅₀, Q₈₀ and similarity factor. The viscosity of batch S5 is 314 cp which is easy for swallowing and good ability for gellation immediately after oral administration. Drug content for the batch S5 is 97.96% which is highest than other batches. Dissolution data and graph are recorded in Table II and Fig. 3 respectively. In the batches S1 to S4 the rate of drug release are very high and in the batches S6 to S9 the rate of drug release are very slow while in batch S5 controlled release of drug at an appropriate time period is found. The amount of drug released for the batch S5 at

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The above text is a scientific study focusing on the optimization of drug release from a polymer-based formulation. It discusses the use of a 3² full factorial design to study the effects of concentration of pectin and calcium chloride on viscosity, drug content, Q₅₀, Q₈₀, and similarity factor. The results indicate that the concentration of calcium chloride has a more significant effect compared to pectin, with the former being more effective in controlling drug release. The study also employs various pharmacokinetic models to analyze the release mechanism of the drug, concluding that a Korsemeyer-Peppas model best fits the data for the selected batch. The selection of the best batch is based on these parameters, with batch S5 showing the most desirable properties for sustained release action.
four hours was 53.73 % which was similar to theoretical release profile and the 90.18 % drug release from the formulation within 8 hours means it is a prominent batch for sustained release formulation. The similarity factor of the batch S5 was 72.75 which was nearer to the hundred instead of other batches so, the batch S5 is selected for further study.

**Formulation of the Selected Batch**

The solution of this batch is shown in Fig. 1 which showed the pH 7 and the solution was very clear containing the viscosity 314 cp having the excellent ability for swallowing because the fluidity of the solution was maintained by addition of sufficient sodium citrate to the formulation to form a complex with all of the calcium ions present in the formulation and hence to effectively remove them from solution. After oral administration due to gastric condition pH (1.2) and temperature (37°C) the matrix type of gel is formed immediately after break down of the complex between CaCl₂ and sodium citrate, which is shown in Fig. 2. Since 1.5 % w/v solutions of pectin showed lower viscosity they should not present difficulties in swallowing. Thus they can be used as delivery vehicle (Kubo et al., 2004).

**Results of Water uptake Study and Dissolution Study**

Release of the drug from a polymeric matrix depends on the amount of water associated with the system. The release of the drug may involve the penetration of water into the matrix and simultaneous release of the drug via diffusion or dissolution as governed by Fick’s law. The water associated with the formulation at any point in time can be determined by TGA (Thermo gravimetric Analyzer) but in this present study a simple test was done for the selected batch S5 of pectin based IGS of famotidine, the graph of the water uptake study are recorded in Fig. 4. The water uptake by the pectin based IGS of famotidine at 8 hours is 62.44 % and the graph indicates good correlation coefficient 0.9942, so linearly the IGS of famotidine at 8 hours is 62.44 % and the graph for sustained release formulation. The similarity factor of the batch S5 was 72.75 which was nearer to the hundred instead of other batches so, the batch S5 is selected for further study.

**Conclusion**

The present study deals with the formulation, optimization and evaluation of pectin based IGS of famotidine. Pectin used as a polymer and CaCl₂ was used as a cross-linking agent. The IGS of famotidine formulations exhibited well, viscosity, drug content and sustained drug release; this study reports that oral administration of aqueous solutions containing pectin results in formation of in situ gel, such formulations are homogenous liquid when administered orally and become gel at the contact site. The results of a 3² full factorial design revealed that the concentration of pectin and concentration of CaCl₂ significantly affected the dependent variables viscosity, $Q_50$, $Q_90$ and similarity factor ($f_2$). The in vivo study also demonstrated the excellent gel formation takes place in the stomach of the rat and significant anti-ulcer effect of the sustained release pectin based IGS of famotidine over long period of time. These IGSs are suitable for oral sustained release of famotidine.

**References**


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