Research Article

pH Dependent Mucoadhesive *In-Situ* Gel Formulation Based on *Abelmoschus esculentus* as Sustained Release Carrier for Gastro-retentivity of Famotidine

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ABSTRACT

The major goal of this work was to develop and assess a novel in-situ gel system for sustained drug administration using natural polymers. Okra gum was extracted from the fruits of Abelmoschus esculentus using acetone as a drying agent. The physical and chemical properties of dried okra gum, including pH, solubility, viscosity, moisture content, infrared study using FTIR, and crystallinity study using XRD, were assessed. The in-situ gel was created using the powdered dried okra gum. The pH dependent gelation approach was used to generate an in-situ famotidine gel using varying concentrations of okra gum and tamarind gum. The system makes use of polymers that go through a sol-to-gel phase transition when certain physico-chemical conditions change. Viscosity and in vitro drug release were all considerably affected by the concentration of gelling agents and release retardant polymers. The results showed that the pH ranged from 6.7 to 7.4 and that the drug content ranged from 83.74 to 94.82 %. The viscosity of sol and gel strength was increased with increase in the concentration of polymer, also drug release sustaining. At the end of 8 hours, the in vitro drug release from formulations comprising various amounts of okra gum and tamarind gum was sustained. In all formulations, the drug had a retardant release.

Keywords: Famotidine, Okra gum, Tamarind gum, Gastro retentive drug delivery, in situ gel.

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INTRODUCTION

The creation of regulated and sustainable drug delivery systems has received more attention over the past 30 years. The development of polymeric drug delivery systems has received a lot of research attention. In-situ gel creation has received a lot of interest nowadays. This is mostly due to the in-situ gelling system's significant advantages, which include convenience of administration and decreased frequency of administration and assist to promote patient compliance [1]. The ability to give regulated drug delivery with improved gastro retention within the stomach is provided by gastro retentive in situ gelling systems, also known as stomach-specific systems. In situ gelling systems are liquid at room temperature but undergo gelation when in contact with body fluids or change in pH [2]. Since the gel produced by the in-situ gelling technique is lighter than gastric fluids, it floats above stomach contents or adheres to the gastric mucosa because of the bio adhesive nature of the polymer. This prolongs the time the dosage form spends in the stomach and causes gastric retention, which in turn extends the duration of time the drug is delivered to the gastrointestinal tract. The system makes use of polymers that undergo sol–gel phase transition owing to changes in specific physicochemical parameters. Several polymers are used to form in situ gel, including tamarind gum, xyloglucan, pectin, gellan gum, and sodium alginate [3,4].

Famotidine, histamine is a H2-receptor antagonist that prohibit gastric secretion both locally and systemically, is used to treat gastric ulcers. The dose frequency is twice or three times day and may vary from person to person. Famotidine is rapidly and incompletely absorbed from gastrointestinal tract with the bioavailability of about 45% having an elimination half-life (t1/2) of 3 hours [5]. The use of natural bio-degradable polymer okra gum and tamarind gum was used for this purpose at various combinations in present work. Trisodium citrate, which is a component of the formulation, aids in keeping it liquid until it reaches the stomach. When the formulation enters the stomach, the presence of an acidic environment causes Ca++ to be released, which causes the formulation to gel. The buoyancy of the in-situ gel is maintained to extend period of time due to the release of carbon dioxide in the stomach pH.

Therefore, the goal of the work was to create an in-situ gelling system containing famotidine utilising okra gum and tamarind gum by a pH dependent gelation method, and to assess its physicochemical properties including measurement of pH, viscosity, gelation time, in vitro release characteristics and drug content.

MATERIALS AND METHODS

Famotidine was gift sample from yarrow chem. Pvt. Ltd, Mumbai. Okra gum is extracted in laboratory and

Tamarind gum was obtained from Chhaya industries, Barshi and all other chemicals used were of analytical grade.

Extraction of Okra gum

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

Characterization of Extracted Okra Gum [7]

Experiments were carried out in accordance with British Pharmacopeia 2007 and altered based on prior studies.

Solubility Test

Stirring 10 mg of okra powder in 10 mL of water, acetone, chloroform, and ethanol to qualitatively assess the extracted gum's solubility (1 % dispersion). Visual examination of the solute was used to determine solubility.

pH Determination

pH metre was used to determine the pH of the sample's 1 % W/V dispersion in water after it was stirred continuously for 5 minutes.

Viscosity

Viscosity of Okra gum at 1% and 0.5% concentrations was performed using the Brook-field digital viscometer.

Moisture content

Moisture content of okra gum powder was conducted by measuring 100mg of powder using hot air oven with loss on drying at 105˚C.

Fourier Transform Infrared (FTIR)

The Fourier transform-infrared (FTIR) spectrum of the sample was recorded in FTIR Thermo Scientific range between 400–4000 cm^{-1}, in attenuated reflection mode (ATR).

X-Ray Diffraction Analysis

X-Ray diffraction was carried out on Bruker D8 Advance instrument at 250 exposures.

Pre formulation Studies

FTIR Spectroscopy of Famotidine

FTIR spectroscopy was carried out to check the compatibility between drug and polymer. The usual FTIR spectrum of the pure drug was compared to the FTIR spectra of the drug with polymers [8].

UV Spectroscopy

10 mg of famotidine transferred into 100 ml volumetric flask. 0.1 N HCL was used to get the volume assigned to 100 ml (stock-1) by using UV visible spectrophotometer in the scale of 200-400 nm UV spectrum was recorded[9].

Calibration curve of famotidine in 0.1 N HCL

50 mg of famotidine was dissolved in 50 ml of 0.1 N HCL. The solution was then diluted with 0.1 N HCL to obtain 2, 4, 6, 8, 10 and 12 µg/ml solution. It was then measured by UV visible spectrophotometer at 265 nm [10].

Melting Point

Melting point equipment was used to find out the melting point of Famotidine. Drug was placed in a glass capillary with flame-sealed end to determine melting point. Inside the melting point apparatus, which had a magnetic stirring facility, the capillary containing the drug was submerged in liquid paraffin.

Preparation of in situ gelling Sols

The in-situ gel formulations of F1 to F3 was prepared by using okra gum and tamarind gum was 69eionize in F4 to F6 formulation. The polymer solutions (sodium alginate, tamarind gum and okra gum) of various concentrations were prepared by adding to 69eionized water containing 0.17% w/v trisodium citrate and heated to 90°C with continuous stirring. After cooling to below 40°C appropriate amounts of calcium carbonate (0.05% w/v), drug solution of famotidine and preservative (methyl paraben) was added to the polymer solution and volume was adjusted to 20 ml with distilled water. The mixture was stirred by using a magnetic stirrer to ensure thorough mixing (Table 1) [11].

Table 1: Composition of the in-situ gelling formulation

Sr.no	Ingredient	F1	F2	F3	F4	F5	F6
1	Sodium alginate (%W/V)	1	1.5	2	1	1.5	2
2	Okra gum (%W/V)	0.2	0.4	0.6	-	-	-
3	Tamarind gum (%W/V)	-	-	-	0.2	0.4	0.6
4	Trisodium citrate (%W/V)	0.17	0.17	0.17	0.17	0.17	0.17
5	Calcium carbonate (%W/V)	0.05	0.05	0.05	0.05	0.05	0.05
6	Famotidine (mg)	40	40	40	40	40	40
7	Preservative (%W/V)	0.2	0.2	0.2	0.2	0.2	0.2

Characterization of the in-situ gel formulations

Determination of the visual appearance

All the preparations were visually inspected for their appearance, clarity, and consistency.

Measurement of the pH

A calibrated digital pH metre was used to measure the pH of each formulation. For each formulation, the readings were held three times, and the averages of the readings were held into consideration[12].

In vitro gelation study

The gelling capacity was determined by placing 10 ml of solution in 100 ml of stimulated gastric fluid (pH 1.2) freshly prepared and equilibrated at 37 ± 0.5°C. When the formulation came in contact with the gelation medium, it was quickly converted into a gel-like structure. The in vitro gelling capability was analyzed based on the gel's stiffness and how long it maintains its stiffness.

According to the period of time the created gel required and how long it lasts, the in vitro gelling capability was primarily categorised into three groups [10].

• (+): Gels in few second and disperse immediately.

• (++): Immediate gelation does not disperse rapidly.

• (+++): Gelation after few minutes remains for extended periods.

Determination of viscosity

The viscosities of the formulations were measured using fresh samples three times using a Brookfield digital viscometer with an S21 spindle at 50 rpm. The average reading was taken after each measurement.

In vitro buoyancy study

The in-vitro buoyancy study was carried out using stimulated gastric fluid (0.1N HCl, pH 1.2). 37 ±5°C was maintained as the medium temperature. In the dissolution media, 10 ml of the in-situ gel formulation were added. The time taken by the in-situ gel formulation to reach the medium surface (floating lag time) and how long it remained buoyant (the floating duration) was noted [1,13].

Determination of the drug content

80 ml of 0.1N HCl, pH 1.2, was combined with 5 ml of the formulation corresponding to 10 mg of the drug, and the solution was stirred for one hour in a magnetic stirrer. The solution was filtered and diluted with 0.1N HCl, pH 1.2, after 1 hour. The drug concentration was then determined by ultraviolet (UV) visible spectrophotometer at 265 nm against a suitable blank solution [14].

Measurement of density of gel

30 ml of the in-situ formulation was poured into a beaker containing 50 ml of 0.1N HCl. 10 ml of the gel formed was elevated in measuring cylinder and weight of the gel was measured. The density was determined using both the weight and volume of the gel. This method was followed for all the formulations [15].

Measurement of gel strength

30 g of the gel was elevated in a 50 ml beaker and a 50 g weight was placed on the centre of the gel surface and allowed to penetrate through the gel. The time taken by the 50 g weight to penetrate 5 cm down through the gel was noted for all the formulations. The same method was followed for 3 times for each fresh formulation and average time was noted [16].

In vitro drug release studies

A USP dissolution equipment (Type II) with a paddle stirrer operating at 50 rpm was used to assess the drug release from the formulations. This slow speed is necessary to avoid breaking of the gelled formulation. The dissolution medium was 900 ml of the simulated gastric fluid (0.1N HCl, pH 1.2), and the temperature was kept at 37±5°C. In situ gel was formed when 10 ml of the formulation were added to the dissolution vessel without disturbing the dissolving medium. At each time interval, 3 ml of the sample was withdrawn and replenished with fresh medium. The samples were collected, filtered, and suitably diluted before being analysed at 265 nm with a UV spectrophotometer [17].

In vitro mucoadhesive study [18,19]

Using a modified bioadhesion test equipment, the force necessary to separate each formulation from goat tissue was measured in order to estimate the mucoadhesive strength of each formulation.

Modified bioadhesion test apparatus

Modifying the double beam physical balance as shown in figure 1 can create the bio adhesion test apparatus. the two pans of the physical balance were removed. A light-weight plastic glass was used to replace the right-hand pan, and a glass vial was suspended from a strong thread on the left-hand side of the balance, with the height of the vial and it adjusted to allow for a lower vial to be placed beneath it. The two sides of the balance were adjusted so that the right side weighed 5 g more than the left. To determine the bioadhesive strength, a piece of goat mucosa was cut and utilised as a membrane. It was attached to both glass vials using a thread after being properly washed with physiological saline solution so that both mucosal surfaces were exposed on the outsides of the vial surfaces (figure no.1). The buffer pH 5.5 was added to the jacketed glass container, which was kept at a constant 37˚C±1˚C. The vial was then placed inside of it. The membrane was kept at this temperature for 30 minutes to allow for equilibration. the jacketed glass container containing beaker was kept below the right-hand setup of the assembly. The gel was stuck to the lower side of the beaker as a thin layer. The assembly was kept undisturbed for 1 min and the weights were slowly added to the left-hand side till the membrane surface just detached from the gel surface just detached from the gel surface. The excess weight on the left-hand side, i.e., a measurement stress in dyne/cm2 was determined from the

minimal weights that detached the tissues from the surface of each formulation using the following equations: total weight (g) minus blank (weight in gm required to detach mucosal surface without gel layer).

Detachment stress (dyne/cm^2) = m x g/A

Where, m = weight required for detachment for two vials in grams

g = acceleration due to gravity [980cm/s^2]

A= Area of tissue exposed

The goat mucosa was changed for each measurement. For each of the gel formulations, measurements were carried out times.

Stability study

The optimized formulation of in situ gel were placed in an amber colour bottle with aluminium cap as a closure. It was tightly sealed. The stability study was carried out for 1 month. Stability of the in-situ gel formulation was monitored at room temperature (25˚C+2°C). Samples were periodically removed and evaluated for viscosity, drug content, pH and in vitro release [20].

RESULTS AND DISCUSSION

FTIR and compatibility studies

All the characteristic peaks of Famotidine were present in the spectrum of drug and polymer mixture, indicating compatibility between drug and polymers. The spectrum confirmed that there is no significant change in chemical integrity of the drug.

Determination of λ $_{max}$ of Famotidine

λ $_{max}$ of Famotidine was determined by utilised stock solution and analysed spectroscopically at 265nm wavelength.

Calibration curve of Famotidine

The absorbance of the solution was recorded at 265 nm by using UV visible spectrophotometer. 0.1 N HCL was taken as blank. The graph of absorbance vs. concentration was shown to be linear in the famotidine concentration range.

Melting point determination

By using a melting point equipment, the melting point of famotidine was detected to be between 160-162˚C. The reported melting point range for famotidine 163-164˚C.

Characterization of Okra Gum

Solubility test

Okra powder was shown to be sparingly soluble in water and insoluble in acetone, ethanol and chloroform. An increase in solubility was observed when temperature was applied.

pH Determination

The pH of Okra gum is 6.59.

Viscosity

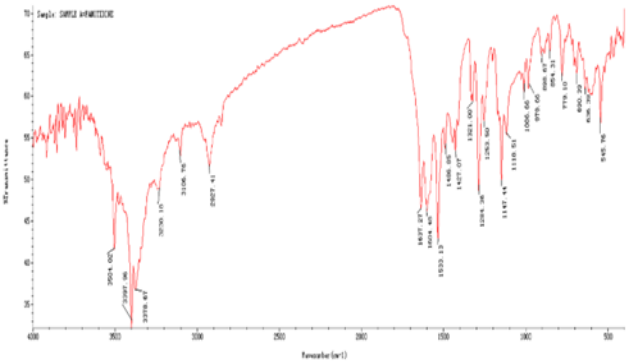
Viscosity of Okra gum 1% solution is higher (228.78cps) compared to the viscosity of Okra gum at a lower concentration (0.5% solution) which is 62.32 cps. This indicates that Okra gum has higher viscosity at a higher concentration.

Moisture content

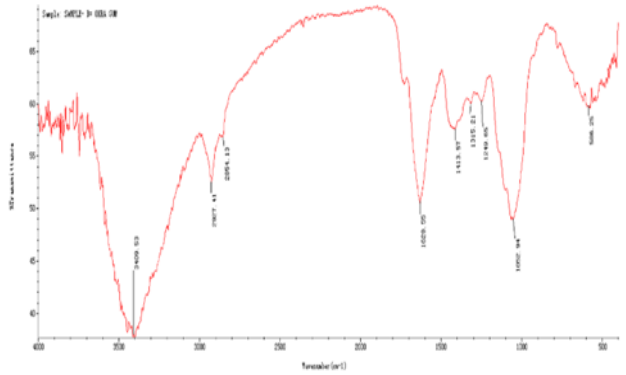
Moisture content of Okra gum is 14.83%, indicating that Okra gum contains bound moisture to the polymer. This is due to the polymer adsorption sites that is able to bind water molecules to the polysaccharide structure via hydrogen bond [9], which leads to a larger permeability of hydrophilic materials.

FTIR and compatibility studies of Okra gum

No considerable changes in the IR peaks of the extracted Okra gum as shown in figure 1.



(a)



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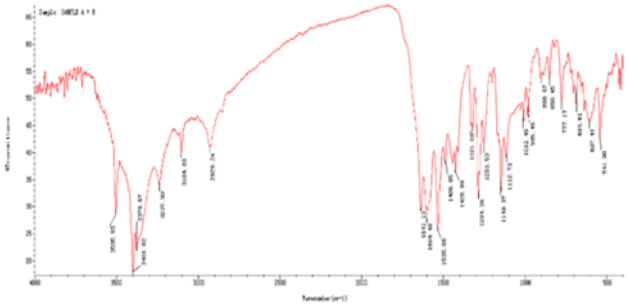

(c)

Figure 1: FTIR peak of Famotidine (a), Okra gum (b) and famotidine with okra gum (c)

X-Ray Diffraction Analysis

XRD analysis of Okra as can be seen in Figure 2 showed that it consists of crystalline structure. The sharp peak that could be seen from the X-ray diffraction spectrum indicates the crystalline nature of the polymer.

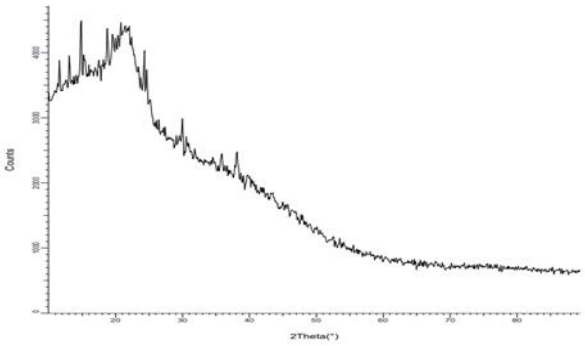

Figure 2: X-ray diffraction analysis of Okra gum

Characterization of the *in-situ* gel formulations

Visual appearance

Visual appearance was evaluated on all of the formulations. The results are shown in Table 2 for the developed formulations of in situ gel containing okra gum, which had a light brownish appearance, and tamarind gum, which had an off-white appearance. The formulations were free running and did not produce any gelation at room temperature.

pH measurements

According to Table 2, the pH of each formulation was determined to be adequate and ranged from 6.7 to 7.4. The pH of each formulation was within the orally acceptable range.

In vitro gelation study

The gelation study was conducted in 0.1N HCL, pH 1.2. On an ordinal scale between + and +++, the gelation properties of the formulations were evaluated as given in table no.2. All the formulation on contact with the gelation medium had undergone sol to gel transition. It was detected that the gel intensity was increased when the concentration of polymers was increased. Table 2 has shown that the formulation F1, F3, F5, F6 were satisfactory to cause gelation.

Table 2: Appearance, pH, Gelling capacity, Pourability

Formulation code	Appearance	pH	Gelling capacity	Pourability
F1	Light brownish	6.7±0.02	+	Easily pourable
F2	Light brownish	7.1±0.06	+++	Easily pourable
F3	Light brownish	7.3±0.03	+++	Easily pourable
F4	Off -white	7.2±0.07	++	Easily pourable
F5	Off -white	6.9±0.01	+++	Easily pourable
F6	Off -white	7.4±0.04	+++	Easily pourable

Table 3: Viscosity, Floating lag time, Floating duration, Percentage drug content

Formulation code	Viscosity (cps)	Floating lag time (s)	Floating duration (hr)	Percentage drug content (%)
F1	69.20±0.02	22	5	88.16 ± 0.34
F2	85.52±0.16	19	7	83.74 ± 0.45
F3	90.60±0.45	16	8	91.46 ± 0.53
F4	82.34±0.49	26	11	84.87 ± 0.23
F5	88.68±0.25	31	12	89.72 ± 0.41
F6	108.52±0.65	33	12	94.82 ± 0.59

In vitro buoyancy study

The floating lag time is the duration of time that the formulation required to appear on the medium's surface and the floating duration is the period of time that the formulation floated constantly. Buoyancy studies results are given in Table 3. A gel barrier forms on the plane of the formulation when it comes into contact with an acidic environment due to the calcium ions' cross-linking and gelation processes. The formulation floats because the carbon dioxide emitted is trapped in the gel matrix. The dispersing of carbon dioxide and drug release are then further constrained by the polymeric network. The floating capability of the formulations mainly depends on concentration of the gelling polymer, carbon dioxide and cation source. The formulation containing okra gum (F1-F3) is less floating lag time but more floating lag time containing tamarind gum (F4-F5).

(a) (b)

Figure 3: *In vitro* buoyancy study of (a) Okra gum and (b) tamarind gum

Viscosity

The viscosity of all the in-situ gelling formulations determined at 50 rpm using Brookfield digital viscometer. The results of viscosity measurement of each formulation are shown in Table 3. The increase in viscosity of the formulations that were observed with the increase in the concentration of polymer can be related to the increasing crosslinking of the polymer. Okra gum-based formulations have greater viscosities, which results in in situ gel and slower drug release. The all formulations of viscosity range between (69.20±0.02 and 108.52±0.65).

Drug content

Drug content is one of the important evaluation parameters for any type of dosage form. The percentage drug content of each formulation was between the range of 83.74-94.82 indicating uniform distribution of drugs in all formulations as per monograph Table 3.

Measurement of density of the gel

Regarding the gastro retentive dosage form's ability to float, density is an important evaluating parameter. The formulation must have a density that is less than or equal to the gastric content's density (1.004 gcm^3) in order to float on them. The density of each formulation given in (Table 4) has density less than the above-specified value. As a result, the floating of the gastro retentive in situ gel is promoted in the stomach.

Measurement of gel strength

All the formulations showed good gel strength in which okra gum as compare to tamarind gum ranges are same from 18.7s to 30.3s. This says the increase in polymer concentration causes an increase in gel strength (Table 4) gives the gel strength of all the formulations.

Table 4: Density and gel strength of the in-situ gel formulation

Formulation code	Density (g/cm^3)	Gel strength (s)	Mucoadhesive strength ($dyne/cm^2$)
F1	0.422±0.36	18.7 ±0.06	1191±33.41
F2	0.501±0.45	24.2±0.12	1275±33.13
F3	0.554±0.42	29.8±0.23	1511±33.41
F4	0.482±0.54	22.5±0.33	785.6±18.02
F5	0.526±0.56	26.9±0.45	915.1±18.02
F6	0.579±0.62	30.3±0.56	1011±21.31

Table 5: Stability studies of in situ gel formulation

Days	pH	Viscosity	Drug content (%)	Drug release (%)
Initial	6.7±0.02	69.20±0.26	88.16 ± 0.34	90.74
After 1 month	6.7±0.06	69.20±0.26	88.16 ± 0.34	90.74
After 2 months	6.6±0.14	67.28±0.35	87.22 ± 0.54	89.35
After 3 months	6.5±0.11	69.28±0.12	88.11 ± 0.13	88.22

***In vitro* drug release study**

The in vitro drug release studies, it was mentioned that the release of the drug from the prepared gastro retentive in situ gel reduces as the concentration of the gelling agent increases. The effect of polymer concentration on in-vitro drug release from in situ gels. The plot of % cumulative drug release v/s time (in hours) was plotted and depicted as shown in Figure no.10. Drug releasing pattern of various formulation contains a different concentration of gelling agent and drug release retardant polymers are given as follows: Okra gum: F1 > F2 > F3 and Tamarind gum: F4 > F5 > F6 as shown in Figure 4. The percentage drug release from formulations containing various concentrations of Okra gum at the end of 8 hrs was observed to be 90.74%, 86.24%, and 82.31%, respectively, for F1, F2, and F3. Similarly, percentage drug release from formulations containing various concentrations of Tamarind gum at the end of 8 hrs was observed to be 91.82%, 88.16%, and 83.74%, respectively, for F4, F5, and F6. The retarded release observes in above formulations.

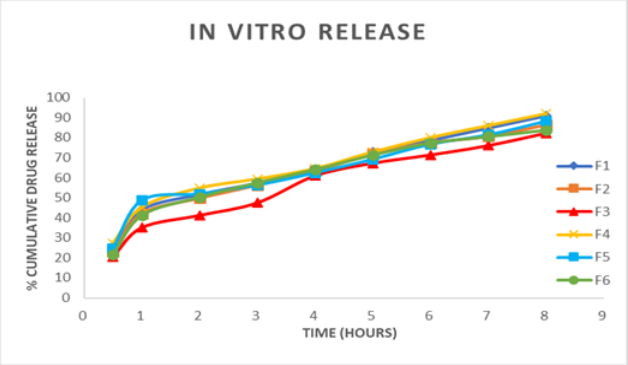

Figure 4: *In vitro* drug release

Mucoadhesive strength

Mucoadhesive strength of the in-situ gel formulation plays major role in giving the idea about gastric residence time of the formulation. Formulation must have enough mucoadhesive property so that it will remain in GIT for longer the gastric absorption of drug. The formulation containing okra gum (F1-F3) is more mucoadhesive strength but tamarind gum containing (F4-F6) less mucoadhesive strength. Result of mucoadhesive strength study is given in Table 4.

Stability studies

The stability study of optimized formulation F3 was carried out for 3 months at room temperature and humidity condition. Stability study's results designated that the there was no significant change in the pH, viscosity, drug content (%) and drug release (%) as shown in Table 5.

CONCLUSION

In the present study in situ gel of famotidine were produced by using different concentration of okra gum and tamarind gum to improve its oral bioavailability and sustained release activity. Okra gum shows less floating lag time and more mucoadhesive strength but tamarind gum shows more floating lag time and less mucoadhesive strength. Both okra gum and tamarind gum show result but okra gum shows significant result as that of tamarind gum. Based upon obtained results it concluded that prepared formulation is satisfactory for clinically use of famotidine and formulation of in situ gel using okra gum was successfully prepared.

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