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FORMULATION AND EVALUATION OF FLOATING ORAL IN-SITU GELLING SYSTEM OF FAMOTIDINE

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Abstract:

Famotidine was incorporated into an oral in situ gel formulation using sodium alginate, sodium bicarbonate, sodium citrate, and HPMC K4M as gelling agents. Conferring to FT-IR spectroscopy, there was no interaction between the medication and the excipients. All eight of the formulas were aesthetically pleasing, straightforward to work with, and did not gel at room temperature. The ideal in situ gel released an adequate dosage of medication into the stomach by flopping and gelling as intended. Observed water intake ranged from 7.36±0.28 to 29.41±0.24%, while estimated floating lag time ranged from 8.95±0.28 to 56.35±0.34s. F1 and F2 showed floating for 12 hr, whereas all formulations released more than 90% of the drug over the 8 hours.

Keywords: *Famotidine, in situ gel, HPMC K4M, Floating system.*

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INTRODUCTION:

In Situ gelling systems**, is** Polymeric formulations that enter the body as sols but transform into gels in response to the body's physiological environment are known as in situgelling systems. Multiple stimuli, including as changes in pH, temperature, solvent exchange, exposure to ultraviolet light, and the presence of certain ions or molecules, contribute to the sol-gel transition. Preparing vehicles for the continuous distribution of bioactive compounds is greatly facilitated by drug delivery systems with such characteristics. These intelligent systems' key benefits are their simplicity of use, decreased dosage frequency, and protection of the medicine against variations in its external environment. In situ gel formation occurs in a wide variety of natural and synthetic polymers, opening up the possibility of their usage in the oral, buccal, rectal, vaginal, ophthalmic, intraperitoneal, and parenteral routes of drug administration. Several triggers, including changes in pH, temperature, and solvent availability, may lead to in situ gel formation. One intriguing method involves the use of smart polymeric materials, which transform from a liquid to a solid state (a so-called sol-gel transition) when the medications are injected. Gels are an unusual material state because they combine solid and liquid properties. The liquid continuous phase is immobilized by the solid component, which is a three-dimensional network of interconnected molecules or aggregates. Chemical gels form when strong covalent bonds hold the network together, whereas physical gels form when hydrogen bonds, electrostatic, and Vander walls interaction keep the gel network together.

Materials and methods:

Famotidine was obtained as a gift sample from Dr.Deddys lab, Sodium Alginate, Gellan Gum Signet Chemical Corporation, Mumbai, HPMC K4M, Calcium Carbonate, Sodium Bicarbonate from Sigma Aldrich.

Methodology:

Preparation of Oral In Situ Gel of Famotidine

Weigh all of the components, then use a magnetic stirrer to dissolve several gelling polymers in deionized water with a measured amount of sodium citrate at 70°C. In a separate process, iota carrageenan was dissolved in Sodium Citrate-treated deionized water and heated to 80 °C with continuous stirring. The necessary amount of HPMC K4M release retardant polymer was dissolved in deionized water in another beaker. Then, while swirling constantly, the three solutions were combined. The aforementioned solution was chilled to 40 degrees Celsius before the addition of Calcium Carbonate, Sodium bicarbonate, and drug. Preservatives were used with sodium saccharin. After making any necessary adjustments to the volume with the deionized water, the resulting solution was given a good stir and placed in amber bottles for later use.

Experimental Design

The connection and interaction between independent and dependent variables may be studied using an experimental design. The optimization of the formulas was inferred to take place using a Box-Behnken design. The chosen design has enough DOF to isolate the impacts of each element and examine their interactions . Low (1) and high (+ 1) values were assigned to three independent variables (factors): sodium alginate (A), sodium bicarbonate (B), and sodium citrate (C). As reactions, we chose to assess gelation and floating times in vitro, as well as water absorption and drug release in vivo. To examine the effect of the factor's range on the outcomes (the dependent variables), that range was chosen. Design Expert® (version 12.0.3.0) by StatEase Inc., Minneapolis, MN was used to evaluate the data.

Evaluation

Physicochemical Properties

The formulas' appearance, aroma, and flavor were all chosen intuitively.

Drug Content Determination

A total of ten milliliters of the formulation (equal to forty milligrams of Famotidine) was taken from each batch and placed in a 100-milliliter volumetric flask. Using a UV-visible spectrophotometer, the concentration of famotidine was measured at 263 nm.

Measurement of pH

A calibrated digital pH meter was used to measure the pH of the final formulations by immersing its probe end in them at room temperature.

In Vitro Gelation

The ability of the produced formulations to gel in vitro was evaluated using the standard technique. One milliliter of the colored formulation was combined with five milliliters of 0.1 N HCl at 37±0.5 °C and pH 1.2 in a test tube, stirring gently to prevent breaking the gel that had formed. The gelling capacity was divided into the following categories [17] based on the stiffness of the gel that was formed, the time it took for the gel to gel, and its stability: (-) no gelation, (+) gelation after a few minutes after rapid dispersion, (++) instant gelations persist for a few hours, and (+++) immediate gelation persists for a long time.

Determination of viscosity

The Brookfield DV-II+Pro digital viscometer was used to measure the compositions' viscosities using an S21 spindle at 50 rpm throughout three separate measurements, with each sample replaced between tests.

In vitro buoyancy study

The research was done at a temperature of 37 0.5°C in a simulated gastric fluid medium (pH 1.2) utilizing a USP Type II dissolving device. The In

situ gel formulation, about 10 ml, was added to the medium. The In situ gel formulation's floating lag time and floating duration were recorded.

Measurement of water uptake by the gel

40 millilitres of 0.1N HCl (pH 1.2) were used to make the in situ gel for this experiment. By Whatman filter paper, the buffer was blotted out after the gel component of each formulation was separated from it. Once the mass of the gel was established, 10 cc of distilled water was added. In addition to the weight of the gel, the amount of time that passed between decanting the water and recording the gel's ultimate weight was also noted.

Density

Thirty milliliters of the In situ formulation were added to fifty milliliters of 0.1N HCl in a beaker. We weighed 10 ml of the gel that had formed in a measuring cylinder. The density was determined by using both the gel's mass and its volume. All formulations were made using this procedure.

In vitro drug release

The USP type II (paddle technique) dissolving equipment was used for the dissolution investigations. 900 ml of 0.1 N HCl (pH 1.2) at 37ºC was utilized as the dissolving media. The mixing speed was set at 50 revolutions per minute. This was deemed slow enough to prevent the gelled mixture from breaking and mimic the current modest agitation in vivo. 10 ml samples were taken at regular intervals using a UV-visible spectrophotometer. The dissolving media was then replaced, the samples were filtered using Whatman filter paper, diluted, and ultimately analysed for maximum absorbance at 263 nm.

Stability studies

The In situ gel, now in its optimal state, was stored in a container of amber hue. It had a good, solid seal. The stability study was conducted at an augmented temperature of 40 ±2 °C and 75 5% relative humidity for one month, as advised by the ICH. Samples were collected to assess colour, pH, gelling ability, floating behaviour, drug content, and in vitro drug release at 0 and 30 days.

Results and Discussion:

Differential Scanning Calorimetric (DSC) studies

Diffusion Imaging Figure 19 shows the results of calorimetry experiments showing a clear endothermic peak at 130.2°C, which corresponds to the melting point of pure famotidine.

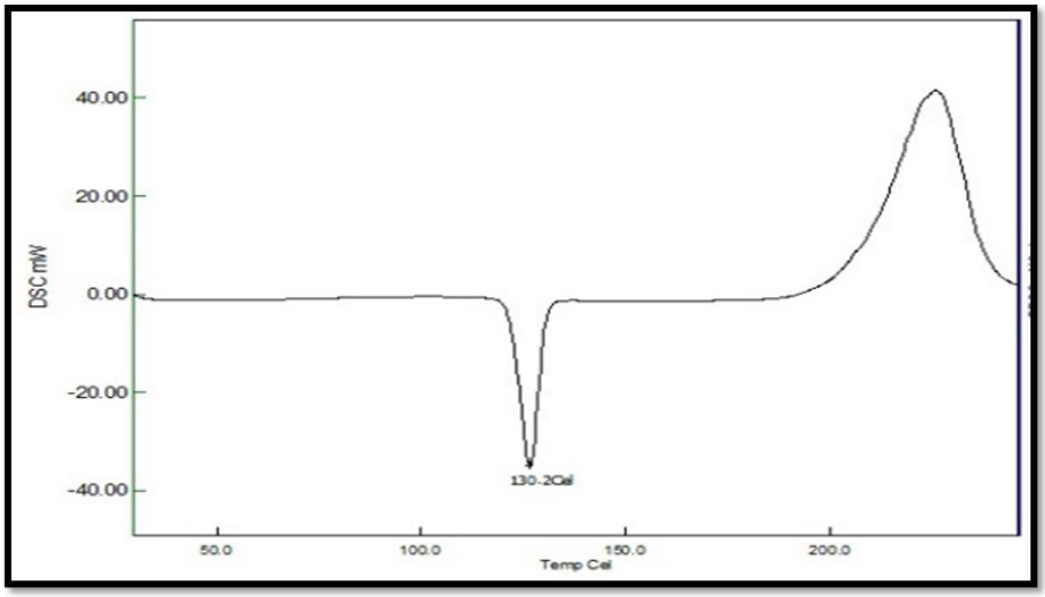

Figure 1: DSC thermogram of Pure Drug (Famotidine)

Famotidine is quickly and completely absorbed after oral administration, with a half-life of around 1 to 4 hours.

Table 1: Formulation of Famotidine in situ gel

Name of ingredient	Quantity in 100 ml (% w/v)							
	F-1	F-2	F3	F4	F5	F6	F7	F8
Famotidine	40	40	40					
Sodium alginate	3	2	2	1	2	1	3	3
Sodium bicarbonate	1.5	1.5	1.5	0.5	0.5	0.5	1	0.5
Sodium citrate	1	0.5	1	1	1	0.5	0.5	0.5
HPMC K100	0.5	0.5	0.5	1	1	1	1	1
Methyl paraben	0.5	0.5	0.5	0.8	0.8	0.8	1	1
Deionised water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Physical Appearance of Famotidine Oral In situ Gel

Patients' adherence to a treatment plan may be affected by a number of factors, one of which is how appealing the formulation is to them. Each formulation was tested for its overall aesthetic appeal, and the findings are shown in the Table below. All the finished products looked similarly lifeless and white. The formulations did not solidify or become sticky when cooled to room temperature.

pH Measurement

According to Table 3, the pH of all the finished products was between 6.23 and 7.15, which is within an acceptable range. The pH range attained was excellent for liquid-retaining compositions. Sodium alginate aqueous solutions are quite stable between pH 4 and 10. The formulations become cloudy and unattractive because sodium alginate precipitates to alginic acid at pH values below 3. Moreover, in simulated stomach juice, all formulations have shown a quick sol-to-gel transition [19].

Viscosity

All In situ gelling compositions had their viscosity measured using a Brookfield Viscometer DV-II+Pro at 50 rpm and 25 °C.

In Vitro Floating Study

Each of the finished formulations floated well in less than 1 inch of simulated stomach fluid (0.1 N HCl) and maintained their buoyancy for around 6 hours. This demonstrates that the manufactured formulations are capable of prolog-scale sustained drug delivery. Due to the added strength the polymers supplied the in situ gels, formulations F1, F4, F7, and F8 with a greater polymer content stayed afloat for at least 6 hours. Improved cross-linking density at higher polymer concentrations successfully traps the released CO2 bubbles, resulting in a less dense gel and, ultimately, superior buoyancy [22]. These formulations have also shown a floating lag time of less than 30 s.

Density

The density of the gastroretentive dose form is a critical quality indicator because of its buoyant ability. The formulation has to be lighter than the gastric contents (1.004 gcm3) or have the same density as the gastric contents to float on top of the stomach. All the formulations have densities that are lower than stomach fluid (1.004 gcm3). This encourages the In situ gastroretentive gel to float freely in the stomach.

Measurement of Gel strength

All of the preparations displayed good gel strength; values varied from 14.7 s for the formulation made solely of Iota carrageenan to 44.3 s and 52.6 s for formulations made using a combination of three polymers. A formulation with greater gel strength has a higher likelihood of remaining in place for an extended period of time.

Drug Content

One of the most crucial factors to consider when assessing a dose form is the amount of active ingredient it contains. The tabular data below details the various formulations' drug contents in percentage. All formulations had a drug content between 98.04 and 99.83%, showing that the medications were distributed evenly throughout the products.

Table 2: Evaluation parameters

F. Code	pH	Drug content (%)	In vitro gelation	Floating lag time (s)
F1	7.01±0.21	97.23 ±0.21	+++	16±0.25
F2	7.23 ±0.23	96.84±0.35	+++	8±0.43
F3	7.04 ±0.15	98.01 ± 0.14	+++	6±0.26
F4	6.95 ±0.24	97.42 ±0.16	+++	10±0.19
F5	6.83±0.22	96.31 ±0.18	+++	3±0.51
F6	6.34 ±0.19	97.28 ±0.26	+++	5±0.38
F7	6.59 ±0.16	99.02 ±0.14	+++	19±0.42
F8	7.15 ±0.13	98.24 ±0.29	+++	8±0.16

Table 3: Evaluation parameters of Famotidine floating oral in situ gelling system

F. Code	Total floating time (h)	% Drug Release (at 24 h)	Mucoadhesive strength (dyne/cm2)	Viscosity (cps)	Gel strength (sec)
F1	≥24	78.36±0.21	968.47±0.42	986.34±1.05	201.43±0.56
F2	3	79.13±0.14	1234.87±0.56	876.01±1.34	175.38±1.42
F3	6	89.01±0.16	965.84±0.38	1384.01±1.32	246.38±0.34
F4	≥24	83.64±0.18	1157.43±0.39	1126.35±1.09	300.51±0.11
F5	≤12	79.16±0.35	1068.94±0.47	891.24±0.96	264.82±0.36
F6	5	85.62±0.17	978.21±0.35	583.47±1.52	231.54±0.25
F7	≥24	91.36±0.11	895.36±0.43	326.95±0.48	115.62±0.22
F8	≤12	80.95±0.21	1136.85±0.35	1035.27±0.69	236.51±0.04

Stability Studies

Table 4: Stability data for F2

Parameter	Condition: 40±2ºC/75±5%RH	
	Initial	After 3 months
Visual Appearance	Milky-white	Milky-white
Pourability	Simply pourable	Easily pourable
pH	7.23 ±0.23	6.82
Gelling capacity	+++	+++
Floating Lag time	16±0.25	19±1.02
Floating duration	≥12	≥12
Viscosity (cps)	876.01±1.34	880.31±0.27
Drug content (% w/v)	99.02 ±0.14	98.64±0.21

CONCLUSION:

Sodium Alginate, sodium bicarbonate, sodium citrate, and HPMC K4M were used as gelling agents in the creation of an oral in situ gel containing Famotidine. FT-IR spectroscopy showed that the medicine and excipients did not interact with one another. here are a total of 8 Famotidine preparations (F1, F2, F3, F4, F5, F6, F7, and F8). All the formulations were visually appealing, easily manipulated, and did not gel when brought to room temperature. Floating lag time was less than 2 minutes across all formulations, while floating time was larger than 12 hours. Gel strength was greater in formulations F1 and F2 and their densities were lower than that of stomach fluid (1.004 gcm3). Formulations F9 and F10 had greater percentage water uptake because they included a tri-polymer blend of sodium alginate, sodium bicarbonate, and sodium citrate. The optimized in situ gel floated and gelled as desired, releasing a sufficient dose of medication into the stomach. pH values for all the preparations have been between 6.34 and 7.15, within a margin of error of 0.19 and 0.13. With immediate invitro gelation, the drug concentration was found to be between 96.31±0.18 and 99.02±0.14%, and it remained stable for a long time. There was an observed range of 7.36±0.28 to 29.41±0.24% in terms of water intake, and an estimated range of 8.95±0.28 to 56.35±0.34s in terms of floating lag time. All preparations had released over 90% of the medication during the 8-h time frame, with F1 and F2 showing floating even after 12 h.

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