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Formulation and Evaluation of Floating in Situ Gel Based Gastro Retentive Drug Delivery of Cimetidine

Vijay Kumar Damodhar[1] and Rukhsana Mahiboob Pinjari[2]

[1]Research Scholar, SunRise University, Alwar, Rajasthan, India
[2]Professor, SunRise University, Alwar, Rajasthan, India

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Abstract**—** *In this study, we formulate and evaluate an in-situ gel of cimetidine using sodium alginate and pectin. CaCO3 was employed as a cross-linking agent, while sodium alginate and pectin were used as polymers. The polymeric formulations used in in-situ gelation drug delivery systems are in sol form before injection in the body but form a gel in the body. Drug release is maintained and regulated thanks to the composition of the gel depending on elements such as temperature modulation, pH variations, the presence of ions, and ultra-violet irradiation. This research aimed to create a unique in-situ gel system for continuous medication administration by using biodegradable polymers found in nature. Polymers that undergo a sol-to-gel phase transition when certain physicochemical conditions are altered are used in this system. At a pH appropriate for life, an in-situ gel developed. Spectrophotometric analysis of the total quantity of drug release was performed during in vitro release investigations in gastric fluid models. The formulation with 1.2% sodium alginate and 1.5% pectin was able to regulate the release of the medicine for a longer period of time, as shown in a well-planned series of studies. Viscosity, drug content, pH, in vitro gelling capacity, in vitro floating ability, water absorption capacity, and sustained drug release were all characteristics of the in-situ gel that were consistent with expectations. The in-situ gels use a fickian diffusion mechanism to release the drugs.*

Keywords**—In-situ gel, gelation, natural biodegradable polymers, simulated gastric fluid, Cimetidine.**

I. INTRODUCTION

In-situ gel system development has received considerable attention in recent years. In situ forming polymeric delivery methods have garnered interest because to their many benefits, which include simple administration, decreased dosing frequency, improved patient compliance, and comfort. They form a gel in the stomach after being taken, which increases their bioavailability.

Many studies have looked at in-situ gel-forming technologies as potential vehicles for long-term drug delivery. The benefits of in situ forming polymeric delivery methods, such as simple administration, decreased dosing frequency, increased patient compliance, and comfort, have inspired this interest.1 Gels may develop in situ in response to a variety of stimuli, including changes in pH, temperature, and solvent composition. Now we may create In Situ Gelling Systems for administration by the mouth, nose, eyes, etc. Formulation development of in situ forming drug delivery systems utilizes a wide variety of natural and synthetic polymers, including gellan gum, alginic acid, xyloglucan, pectin, chitosan, poly (DL lactic acid), poly (DL-lactide-co-glycolide), and polycaprolactone. The drug's bioavailability is improved above that of a standard liquid dose form thanks to the gastro-retentive in situ gelling technology. The gel produced by the insitu gelling system is lighter than gastric fluids, so it either floats on top of the stomach contents or sticks to the gastric mucosa thanks to the bio-adhesive nature of the

polymer. This increases the gastric residence time and, in turn, the drug's half-life. Including formulation considerations to consider while developing an in-situ drug delivery system, this paper seeks to address stomach-specific in situ gelling systems in depth. Evaluation and characterization of in-situ polymeric formulations, as well as the processes of gel formation from sol forms of various smart polymers, are also covered.

In addition, it is prescribed for the treatment of GERD. It's also used for Helicobacter Pylori infections and stomach ulcers, as well as Gastroesophageal Reflux Disease (GERD). Due to its shorter half-life, this medication needs several daily doses of 15-30 mg, which often results in dose-related adverse effects and poor patient compliance. In commercial formulations, 10 ml of the formulation is typically given thrice day to counteract the effects of persistent pharmaceutical administration. A considerable decrease in stomach acid secretion is seen 2 hours after a single dosage, with further improvement with successive therapy. The peak response time ranges from 1 week to 8 weeks, depending on the disease being treated. Elderly and young people may have trouble swallowing the medication tablets.

BENEFITS OF GASTRORETENTIVE DRUG DELIVERY SYSTEM (GRDDS)

The principle of GRDDS can be used for any particular medicament or class of medicament.

One benefit of the GRDDS is that it improves the absorption of medications that are mostly absorbed in the stomach, such as ferrous salts, as well as treatments that have a local effect in the stomach and are used to treat peptic ulcer disease.

Second, using the continuous release may improve the potency of the medicines. To acquire a substantially better reaction, medication in gastro-retention may be advantageous when there is robust intestinal movement and a short transit time, as could occur in some types of diarrheas.

GRDDS has benefits, such as the administration of medicines with tiny intestinal absorption windows. Fifth, the GRDDS are not limited to medications that are mostly absorbed via the stomach. These have been proven to be just as effective as gastrointestinally absorbed medications like chlorpheniramine maleate.

Furosemide's limited absorption in the upper gastrointestinal tract contributes to its low bioavailability. The formulation of its floating dosage form is an improvement. When compared to the bioavailability of furosemide in commercial tablets (33.4%) and enteric-coated tablets (27.5%), the bioavailability of the floating system is much higher, at 42.9%.

Plasma level variations are minimized as a consequence of the delay in stomach emptying (see point 7). Incomplete absorption accounts for the discrepancy in the bioavailability of standard and HBS formulations; for example, madopar's bioavailability was reported to be 60-70%.

Floating dosage forms with prolonged release features are helpful in lowering the unpredictability in transit performance, which brings us to point number eight. Tacrine's gastrointestinal adverse effects in Alzheimer's patients are mitigated when the drug is administered as an HBS formulation, for instance. Ranitidine 150 mg twice day or 300 mg once daily is the recommended oral dose for adults. A standard dosage of 150 mg can only prevent acid production in the stomach for up to 5 hours. Changes in plasma concentration occur after 300 mg administration. By creating a ranitidine floating system, the dose may be decreased while still maintaining effectiveness.

II. LITERATURE REVIEW

Preeti Chaturvedi, Ashish Manigauha. (2022), Using sodium alginate and xanthan gum, the current work aimed to create a Gastro-retentive controlled release of floating in situ gel of Cefixime. Visual appeal, pH, gelation, viscosity, buoyancy, drug content, water absorption, gel density, gel strength, drug release, and stability were all measured for each of the six floating in situ gelling formulations (F1 to F6). All of the aforementioned metrics yielded positive outcomes. The F6 demonstrated the longest drug release, hence it was chosen as the best configuration. The F6 survived three months of storage at the specified temperature and humidity. Based on these results, it was hypothesized that the Cefixime sustained-release in situ gel that had been developed would be an appropriate vehicle for the regulated, sustained-release distribution of this antibiotic.

Devika Hegde (2021), In her next book, the purpose of this research was to use natural polymers like Gelrite and sodium alginate to create an oral floating in situ gel

of Omeprazole. The proton pump inhibitor omeprazole is prescribed to patients suffering from gastrointestinal and oesophageal conditions (GERD, ulcers, etc.). The mechanism of action is the suppression of gastric acid production. Among the symptoms it helps with include heartburn, difficulty swallowing, and a persistent cough. In this study, an oral solution of omeprazole was created that gels when exposed to an acidic environment with a pH of 1.2 and then floats. The floating oral in situ gel undergoes ion sensitive gelation. Sodium alginate (F4-F6) and Gelrite (F1-F3) were combined in varying proportions to produce these floating in situ gel compositions. Drug content uniformity, in vitro drug release, and investigations on pH, in vitro gelling capability, gelling time, water absorption, viscosity, floating lag time, and floating length were conducted on the produced formulations. The optimal formulation was found to be F5 (1.5 percent w/v Gelrite), which was evaluated across many metrics including % CDR, in vitro gelling capacity, viscosity, and so on. The formula F5 that follows Higuchi's release has a Fickian flow. In conclusion, the present study demonstrates that a stomach-specific controlled medication delivery system using a floating in situ gel containing Omeprazole is feasible.

Using sodium alginate, calcium chloride, sodium citrate, hydroxypropyl methyl cellulose K100, and sodium bicarbonate, Patel DM et al. (2019) developed and assessed a floating oral. In situ gel of Amoxicillin. The produced formulations were tested for their In vitro drug release, floating lag time, and total floating time in solution. A 32-full factorial design was used to find the optimal formulation. In situ gelling systems of amoxicillin can be formulated using sodium alginate as a gelling polymer to sustain the drug release for 10 to 12 h with zero-order release kinetics, the researchers concluded. The floating lag time, cumulative percentage drug release in 6 h and 10 h, and floating. In situ gelling system of amoxicillin were all found to be significantly influenced by the concentration of sodium alginate and HPMC K100.

Xu H, Shi M, Liu Y, Jiang J, Ma T. (2014), The primary objective of this research was to create an innovative in situ gel system for the long-term administration of ranitidine hydrochloride. Preparation, viscosity, and in vitro release characteristics of ranitidine in situ gels at gellan gum concentrations of 0.2%, 0.5%, and 1.0% (w/v) were determined. Gellan gum formulations in solution became more viscous when the concentration of gellan gum was raised. An in vitro investigation revealed that the ranitidine released from these gels went through two distinct phases: a rapid first phase (the "burst effect"), followed by a slower second phase. The amount of time a gel containing 99mTc tracer spends in the stomach was measured using single photon emission computed tomography. The animal study demonstrated the viability of in situ gel formation in the stomach and the sustained release of ranitidine from the gels for at least 8 hours. In conclusion, the in-situ gel system is an attractive method for the oral administration of ranitidine for the enhancement of therapeutic benefits.

A. Maxwell, S. Priya, M. S. S., and M. S. S. (2018), Objective: The current investigation sought to develop and assess a new in situ gel of lafutidine for gastroretentive drug administration. Methods: Using the pH-triggered ionic gelation approach and varying amounts of gelling polymer such sodium alginate, gellan gum, and xanthum gum, a gastro-retentive in situ gel of lafutidine was developed. The medication concentration, as well as the formulation's viscosity and density, were measured. All formulations were also subjected to in vitro drug release tests. The improved formulation was put through an in vivo fluorescence imaging investigation and compared to a control group. The results showed that the formulations' viscosity, floating behavior, and in vitro drug release were all considerably impacted by the proportion of gelling agents and release retardant polymers. Results showed a pH range of 6.72-7.20 and a medication concentration of 88.14%-95.33%. The time it took to float was over 12 hours, and the lag time was less than 2 minutes. The formulations with the lowest and highest in vitro drug release were F9 (51.74%) and F1 (82.76%), respectively, after 12 hours. All of the formulations showed a steady rate of drug release. The formulation was shown to be retained in the stomachs of mice for 8 hours in in vivo testing. Results from stability tests showed no discernible change in form, buoyancy, or active ingredient. To sum up, the gastro-retentive in situ gel system increased the duration of gastric residency, allowing for site-specific medication release in the stomach.

III. MATERIALS

S.D. Fine chemicals in Mumbai provided the pectin, calcium chloride, and calcium carbonate. RANKEM Ltd.

provided the sodium alginate and sodium citrate used in this study. Acron pharmaceuticals Ltd. in Ahmedabad was nice enough to send a free sample of their Cimetidine product. Surni Pharmaceuticals of Baroda, where the deionized water came from.

IV. METHOD

Preparation of Cimetidine In Situ Gel

A polymer solution was made by boiling deionized water to 60 degrees Celsius while stirring constantly. Once the temperature drops below 40 degrees Celsius, the medication and cross linking (CaCO3) of varying concentrations may be mixed together and dissolved with constant stirring. The last step is to apply the preservative and put it away.

Table 1: Cimetidine in situ gel

Ingredients	F1	F2	F3
Cimetidine	2.5%	2.5%	2.5%
Sodium alginate	0.5%	1.0%	1.5%
Pectin	1.0%	1.0%	1.0%
$Caco_3$	2.0%	2.0%	2.0%
$Cacl_2$	0.15%	0.15%	0.15%
Sodium citrate	0.45%	0.45%	0.45%
Deionizedwater	Up to 100 ml	Up to 100 ml	Up to 100 ml

Determination of UV Absorbance Maxima of Cimetidine

Cimetidine was dissolved in methanol to make a stock solution, which was then diluted to the desired concentration. The solution was then put through a UV visible spectrophotometer and scanned between 200 and 300 nm.

Preparation of Standard Calibration Curve of Cimetidine in 0.1 N HCl

100 mg of Cimetidine was dissolved in100 ml of 0.1N HCl. The solution was then diluted with 0.1 N HCl to obtain 2, 4, 6, 8 and 10 µg/ml solution. It was then measured by UV visible spectrophotometer at 218nm.

Identification of Drug by FTIR

An FT-IR spectrometer (a Shimadzu 8400S; Japan) was used to collect infrared spectra using the Fourier transform. The pure Cimetidine was extensively blended with a 1:5 (Sample: KBr) ratio of potassium bromide, an infrared transparent matrix. To make the KBr discs, the powders were pressed under 5 tons of pressure for 5 minutes in a hydraulic press. From 4000 to 400 cm-1, 40 scans were taken at a resolution of 4 cm-1.

Table 2: Cimetidine in situ gel

Ingredients	F4	F5	F6	F7	F8	F9	F10	F11
Cimetidine	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%
Sodiumalginate	0.8%	1.2%	0.8%	1.2%	0.8%	1.2%	0.8%	1.2%
Pectin	1.5%	1.5%	2.0%	2.0%	1.5%	1.5%	2.0%	2.0%
$CaCO_3$	1.5%	1.5%	1.5%	1.5%	2.0%	2.0%	2.0%	2.0%
$CaCl_2$	0.15%	0.15%	0.15%	0.15%	0.15%	0.15%	0.15%	0.15%
Sodiumcitrate	0.45%	0.45%	0.45%	0.45%	0.45%	0.45%	0.45%	0.45%
Deionizedwater	Up to 100 ml	Up to 100 ml	Up to 100 ml	Up to 100 ml	Up to 100 ml	Up to 100 ml	Up to 100 ml	Up to 100ml

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Identification of Drug By DSC

DSC60 (Shimadzu, Tokyo, Japan) was used for the analysis. Calorimeter, Flow Controller, Thermal Analyzer, and Related Software Make Up This Instrument. The medicine was processed in sealed aluminum pans at a scanning rate of 20°C/min from 50 to 300°C, with air flow (30 ml/min). A bare metal pan served as a stand-in for accuracy. The heat transfer was calculated for each sample as a function of temperature.

Viscosity of In Situ Gelling Solutions

The viscosity of formulations was determined by a Brookfield viscometer DV-III Brookfield, USA) using spindle number 21 with cup and bob setting at 50 rpm.

Floating Behavior

We used a simulated stomach fluid (0.1 mol L-1HCl, pH 1.2) to measure the formulations' buoyancy lag time and buoyancy duration. The buoyancy lag time (in minutes) and buoyancy duration (in minutes) of the formulation were recorded.

In-Vitro Gelling Capacity

Solutions of an in-situ gel forming drug delivery system were formulated, and the formulations' in-vitro gelling ability was assessed visually. Using a gelation solution (0.1N HCl, pH 1.2) and a borosilicate glass test tube with a volume of 15 ml, the in-vitro gelling capacity of the produced formulations was determined and held at 37 1 °C.

Pipette was used to add 1 ml of formulation solution. Slowly releasing the formulation from the pipette, the transfer was performed with the pipette resting on the surface of the fluid in the test tube. When the solution met the gelation solution, it was instantly transformed into a rigid gel like structure. The ability of a solution to gel was measured by observing how long a gel it produces retains its shape after being produced and how rigid it becomes. The gelation time and the duration for which the created gel persists were used to assign grades to one of three groups for the in-vitro gelling capability.

(+) Gels after few minutes, dispersed rapidly

(++) Gelation immediate remains for 12 hours

(+++) Gelation immediate remains for more than 12 hours

Drug Content

For one hour, using a magnetic stirrer, 10 mL of the solution was added to 900 mL of gastric fluid (0.1 mol L-1Cl, pH 1.2) to imitate the stomach's environment. After filtering and diluting the solution to mimic stomach acid, we measured its drug content at 226 nm using a UVvisible spectrophotometer (UV-1601 Shimadzu, Japan) and a blank solution of known concentration.

V. RESULTS AND DISCUSSION

UV ABSORBANCE MAXIMA OF CIMETIDINE

UV spectrophotometer readings between 200 and 300 nm were taken of the Cimetidine sample. The absorbance maximum of the Cimetidine spectrum was measured to be at 218.2 nm, which is close to the 218 nm value that is listed as its λmax.

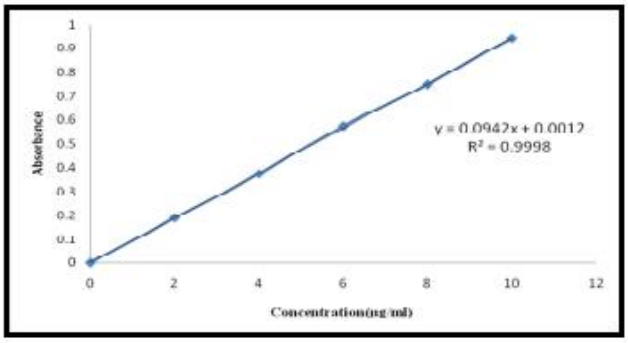

Fig.1: Standard Calibration Curve of Cimetidine

Identification of Drug by FTIR

The FTIR spectrophotometer was used to investigate the identification process. At a variety of wavelengths, Cimetidine's signature absorption peaks could be isolated. Pure drugs may be confirmed by comparing their spectra to the official British Pharmacopeia spectrum and finding that their peaks correspond.

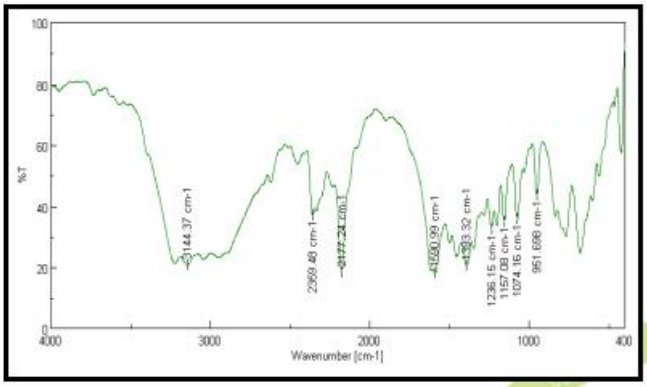

Fig.2: FTIR spectra of Cimetidine

Identification of Drug by DSC Spectra

To learn more about the melting actions of Cimetidine, a DSC thermogram analysis was performed. Cimetidine's melting point, as determined by differential scanning calorimetry (DSC), is 142.5 degrees Celsius. The melting point of cimetidine, according to the US pharmacopeia, is between 139 and 144 degrees Celsius. In other words, it was discovered to be within a hair's breadth of the certified authenticity range. Cimetidine's identification was verified in part because its IR spectra showed evidence of the existence of functional groups.

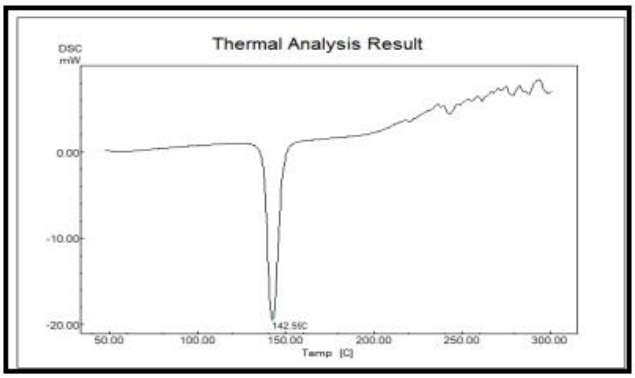

Fig.3: DSC spectra of Drug

Viscosity of In Situ Gelling Solutions

As the sodium alginate and pectin concentrations were raised, the formulations became more viscous. This effect arises because the concentration of the polymer causes the contact between the chains to grow. Increased formulation viscosity may be attributed to the addition of calcium carbonate, the cation source. The increased distributed calcium carbonate is responsible for this shift in viscosity.

Floating Behavior

The buoyancy lag time was shown to be sensitive to the formulation parameters. The buoyancy lag time was shortest for Formulation F8 (26 s) and longest for Formulation F11 (219 s). As the calcium carbonate content was raised, more CO_2 became available, and it was trapped in the newly formed gel, resulting in faster buoyancy in formulation F8. The buoyancy lasted for more than 12 hours regardless of the formulation factors.

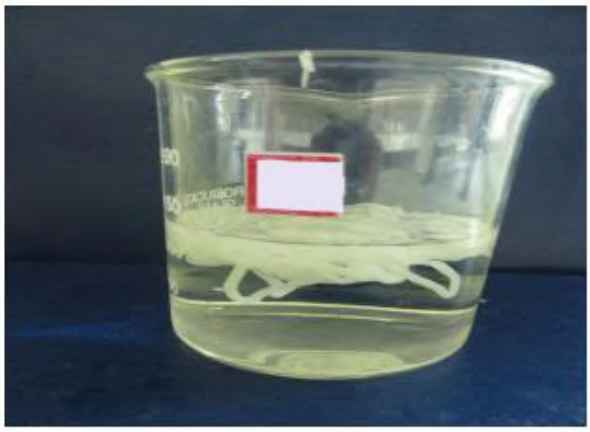

Fig.4: Floating behavior of In situ gel formulation

Table 4: Viscosity of prepared In situ gel formulation

Formulation Code	F4	F5	F6	F7	F8	F9	F10	F11
Viscosity(cp)	260	268	280	240	242	275	296	308

Table 5: Floating behavior of In situ gel formulation

Formulation Code	F4	F5	F6	F7	F8	F9	F10	F11
Floating lag time(Sec)	50	66	45	72	26	35	196	219
Floating time(hr)	>12	>12	>12	>12	>12	>12	>12	>12

Table 6: In vitro gelling capacity of In situ gel formulation

Formulation Code	F4	F5	F6	F7	F8	F9	F10	F11
Gelling capacity*	++	++	++	++	++	++	+++	+++

*(++) Gelation immediate remains for 12 hours, (+++) Gelation immediate remains for more than 12 hours

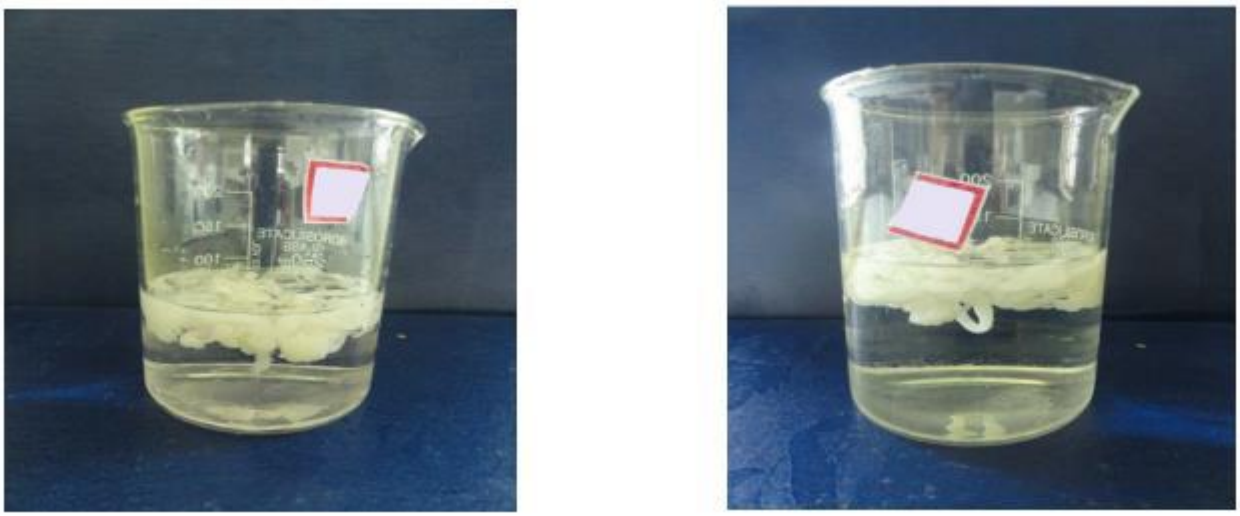

Fig.5: Gelling capacity of in situ floating gel formulation

In Vitro Gelling Capacity

In vitro gelling capacity of various formulation of in situ floating gel is reported in table no.6.

Drug Content (%)

The Drug content of all (F4-F11) formulations is given in table no 7. It ranges in between 97.68% - 98.94%. The values are acceptable as per united state pharmacopeia standards.

Table 7: Results of Drug Content of all formulation of Cimetidine

Batches	F4	F5	F6	F7	F8	F9	F10	F11
Content uniformity (%)*	98.94 ±0.40	98.94 ±0.40	99.75 ±0.33	99.75 ±0.33	97.68 ±0.27	97.68 ±0.27	98.75 ±0.42	98.75 ±0.42

VI. CONCLUSION

By analyzing the outcomes, it was shown that the various features of the created gelling technique are proportional to the concentration of polymer utilized in the formulation. Gel strength and viscosity, for example, tend to increase as polymer concentration rises, whereas the formulation's percent cumulative drug release tends to fall. Sodium alginate-based formulation

has a slower drug release rate, lesser gel strength, and greater viscosity than Gellan gum-based formulation. In conclusion, in situ gels appear promising for long-term, targeted oral administration of Cimetidine.

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