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RESEARCH ARTICLE

Screening of polymerization effect with Alginate-HPMC-Guar gum on Polymer-Based Interpenetrating Networks in Sodium Alginate Raft System for Sustained Drug Delivery

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ABSTRACT

Background: Various technologies have been developed recently, including creating controlled drug delivery systems to address several physiological challenges and gastric retention and emptying time. To combat this issue, new methods of medication delivery have been created. A recently developed technique called the raft-forming system can overcome several obstacles in the gastroretentive drug delivery system. **Materials and Methods:** This study was supervised to assess the effects of polymers like sodium alginate (SA), guar gum (GG), and hydroxypropyl methylcellulose (HPMC) and their grades in the formation of the raft. It showed the feasibility of prolonging the residence time in the stomach and the release rate of metronidazole, which was used here as a model drug. Four different HPMC grades were used (HPMC K100 M, HPMC K40 M, HPMC K15 M, and HPMC K4 M) with SA and calcium carbonate acting as divalent cation salt. The formed rafts were characterized by physical appearance, pH, *in vitro* gelling capacity, *in vitro* buoyancy study, shear stress by viscosity measurement, the density of raft, *in vitro* floating ability, raft volume, raft thickness, raft resilience, % swelling index, and Fourier transform infrared spectroscopy. **Results:** This formulation had no distinct difference in physical appearance, but HPMC 100 showed a deeper color than other formulations. pH ranged from 2 to 3, with HPMC 100 having the highest pH of 3. *In situ*, gelling capacity of HPMC 100 showed the lowest time of 5 s, and buoyancy capacity and resilience timing were the same for all more than 24 h and 4 h, respectively. **Conclusion:** The rest of the characterization of raft containing SA and HPMC 100 formulation takes the highest position. Based on the screening study, HPMC 100 demonstrated superior performance to other polymers and has been selected for further investigation.

Keywords: Floating lag time, guar gum, hydroxypropyl methylcellulose, *in situ* gel, raft volume, sodium alginate

INTRODUCTION

The oral *in situ* gel-forming system, also known as the raft-forming system, provides controlled drug delivery within the stomach in a suitable manner and enhanced gastroretention. The raft-forming system creates a persistent layer of cohesive, viscous gel that interacts with stomach contents, known as a raft. When homogenous raft-forming suspension is administered orally upon contact with the stomach fluid, it forms a thick gel-like structure, and the viscous gel density is lower than gastric fluid.[1] Various techniques have been developed earlier to enhance gastric retention, including mucoadhesive systems,[2,3] floating systems,[4-7] magnetic systems,[8] ion exchange resins,[9] and raft-forming systems.[10-12] The raft-forming drug delivery system (raft) offers distinct advantages in gastroretentive drug delivery compared to other controlled release technologies.[12]

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Raft systems are typically formed using natural cationic polymers such as sodium alginate (SA),[1,10,11,13] xanthan gum,[10,14] guar gum (GG),[15] and gellan gum,[16] as well as anionic polymers like chitosan.[17] Modified polymers such as hydroxypropyl methylcellulose (HPMC), available in various molecular weights including HPMC K100, K40, K15, and K4, are commonly used.[10-12] These polymers, individually or in combination, contribute to forming a floating layer that enhances gastric retention.

Alginate is used most among them as a parent polymer. Srinivas and Sagar reported that the combination of sodium alginate (SA) with HPMC K4 and xanthan gum formed an in-situ gel-based raft system that suitably exhibits viscosity, density lower than, gastric fluid, and their buoyancy lag time ranging from 15.34 to 26.12 seconds, and total floating duration exceeding 12 h.[10] Furthermore, SA was also combined individually with various polymers such as xanthan gum, HPMC K100, Carbopol 934, gellan gum, and HPMC K4 to develop floating raft systems. These formulations demonstrated pH ranges from 6.9 to 8.9, floating durations varied between 12 to 24 h depending on different formulation combinations. Further immediate gelation time ranged from 5 ± 2 to 16 ± 2 seconds, with short lag time. Notably, the raft system incorporating HPMC K100 exhibited a stiffer gel structure and quick gelation.[10,12-16] In addition, xanthan gum was mixed with SA and HPMC 4 to produce rafts. The formulation showed a pH of 6.9–8.9, a total floating time of over 12 h, a density of rafts from 1.051 to 1.058, and a raft thickness of 1.8 ± 0.26–3.6 ± 0.008.[10] Munusamy and Shanmugasundharam created a floating raft composition using Carbopol and GG. The gelling period of the formed raft was 12–34 s, while the overall floating time was almost 12 h. All optimized batches had raft weights and volumes between 2.052 and 2.772 g and 2.199 and 3.281 mL, respectively. At 12 h, every formulation's *in vitro* drug release varied between 74% and 88%.[18] Each polymer—sodium alginate (SA), gellan gum, pectin, guar gum (GG), and xanthan gum—was individually utilized to form raft-forming chewable tablets. According to Darwish *et al*., adding SA makes the material more rigid, brittle, mechanically stable, and raft-strong (10.25 g).[18-20]

This present work aims to screen between the different polymers. Using alginate as the parent polymer, we selected the polymer based on the intrapolymer effect and the interpolymer influence on raft formulation. We used GG, SA, and HPMC for the interpolation and HPMC with varying molecular weights, such as HPMC K100, HPMC K40, HPMC K15, and HPMC K4, for the intrapolymer. We put all six (F1-F6) formulations into practice and examined their derived qualities and how they affected the physiochemical properties. Here, metronidazole was taken as a model drug. The impact of various polymers and grades of HPMC on release kinetics and buoyancy was evaluated on a floating raft system. A more sustained drug release achieved through floating systems, using an optimal combination of polymers, can be particularly beneficial for treating local stomach infections. This approach helps maintain consistent drug levels, improves patient compliance, and does not interfere with the normal functioning of the pyloric sphincter. Additionally, it supports effective eradication of *Helicobacter pylori.*

MATERIALS AND METHODS

Materials Used

Sodium alginate (SA) and trisodium citrate were procured from Loba Chemie Pvt. Ltd. Hydroxypropyl methylcellulose (HPMC) grades K100M and K4 M were obtained from Yaddow Chem Products. HPMC K40M and K15 were sourced from MP Biomedicals, LLC. GG was purchased from Loba Chemie Pvt. Ltd.; hydrochloric acid was purchased from Merck Life Science Private Limited; potassium chloride

Table 1: Formulation table

Ingredients	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)
Sodium alginate	3	3	3	3	3	3
Tri-sodium citrate	0.25	0.25	0.25	0.25	0.25	0.25
HPMC K100	0.6	_	_	_	_	_
HPMC K40	_	0.6	_	_	_	_
HPMC K15	_	_	0.6	_	_	_
HPMC K4	_	_	_	0.6	_	_
Guar gum	_	_	_	_	0.6	_
Calcium carbonate	2	2	2	2	2	2

HPMC: Hydroxypropyl methylcellulose

was purchased from Sisco Research Laboratories Pvt. Ltd; and metronidazole was gifted from Holden Medical Laboratories Pvt. Ltd. Double-distilled water was prepared in the laboratory, and Whatman filter paper (Grade 1) was used for filtration.

Preparation of *In Situ* Gel Formulation

Suspensions were formulated according to Table 1. The formulations were prepared by combining sodium alginate (SA), guar gum (GG), and four different grades of hydroxypropyl methylcellulose (HPMC), with calcium carbonate serving both as a cross-linking agent and an effervescent component. At first, 3% SA was dispersed with 100 mL of distilled water. Then, 0.25% trisodium citrate was added to the alginate solution with continuous stirring, and the temperature was maintained until a homogeneous, viscous solution was formed. Calcium carbonate was gradually added to the mixture under continuous stirring to ensure uniform dispersion and effective cross-linking. Finally, 0.5% metronidazole (as the model drug) was added into the mixture. Following the same process, the remaining five formulations were also prepared.[1,10,15]

Physical Appearance and pH Measurement

Each formulation was physically examined by observing its appearance against a black-and-white background. A small amount (5 mL) of the sample was poured into buffer solution 0.1N HCl (pH 1.2), pH 2 (HCl acid buffer), and pH 4 (phosphate buffer). After the formation of the raft, the change of the pH was measured using a calibrated digital pH meter (pH meter CL 46+).[10,15]

In Vitro Gelling Study

An *in vitro* gelling study was conducted by adding 5 mL of the formulation to a 100 mL beaker containing 50 mL of three different pH solutions, 0.1N HCl (pH 1.2), pH 2 (HCl acid buffer), and pH 4 (phosphate buffer), as the gelation solution. The temperature was maintained at 37 ± 0.5°C. The time taken for the conversion of gel to sol (wholly dissolved) in the medium was measured.[10]

In Vitro Buoyancy Study

For the *in vitro* buoyancy study, 10 mL of the formulation was placed in a watch glass. The watch glass, containing the formulation, was then positioned in a dissolution apparatus (type II), filled with 500 mL of three different pH solutions, 0.1N HCl (pH 1.2), pH 2 (HCl acid buffer), and pH 4 (phosphate buffer), as the dissolution medium. The temperature was maintained at 37 ± 0.5°C, and the apparatus was set to a rotation speed of 50 rpm. The time it takes for the gelled mass to rise to the surface is called the floating lag time, while the duration it remains afloat is called the total floating time.[10]

Measurement of Viscosity

A rotating programmable cone and plate viscometer (Modular Compact Rheometer, 102 Anton Paar) was utilized to assess the generated formulation's viscosity at 25 ± 2°C. A small amount of the sample was poured onto the plate; then, the excess sample was trimmed to avoid interference during measurement.[1,10,16]

Density Measurement

The density of the formulation was measured using the water displacement method. To convert the formulation into a gel, 5 mL of the prepared formulation was poured into a 100 mL beaker containing 50 mL of freshly prepared three different pH solutions, 0.1N HCl (pH 1.2), pH 2 (HCl acid buffer), and pH 4 (phosphate buffer). The mixture was allowed to stand for 30 min to form a gel. After gel formation, the excess HCl was removed, and the weight of the gel was recorded. The gel was then transferred to a 50 mL measuring cylinder, and the starting volume was marked. Water was added to the cylinder up to the marked level, and the volume with the gel present was recorded. The difference between the volume of water with and without the gel was used to calculate the volume of the gel.[10,15]

Raft Volume

A 250 mL beaker was weighed and recorded before conducting the investigation. After that, 20 mL of

the prepared formulation was placed into 150 mL of three distinct pH solutions: 0.1N HCl (pH 1.2), pH 2 (HCl acid buffer), and pH 4 (phosphate buffer) and left for 30 min without any disturbance. Once the raft was fully formed, the level it reached was marked, with a marker pen on the outer wall of the beaker to indicate the final position of the raft. The weight of the liquids, beaker, and raft was measured and noted. The raft was carefully removed from the fluid, and its weight was subsequently measured on a weighing balance. After removing the beaker's fluid, water was added until the mark was reached, and the container was weighed and then determined the raft's volume.[1,15]

Raft Thickness

10 mL of the prepared formulation was added to 150 mL of gastric fluid in three different pH solutions, 0.1N HCl (pH 1.2), pH 2 (HCl acid buffer), and pH 4 (phosphate buffer) in a 250 mL beaker, with the temperature maintained at 37°C. Three separate locations around the beaker were used to measure the created raft's thickness using a digital vernier caliper.[1,15]

Raft Resilience

This test aimed to evaluate the raft's longevity under more intense movement conditions. To begin, the raft was formed in a beaker containing 50 mL of three different pH solutions: 0.1N HCl (pH 1.2), pH 2 (HCl acid buffer), and pH 4 (phosphate buffer) at a temperature of 37°C. The formed raft was placed in a tumble mixer set at 20 rpm to assess its durability. The raft was then physically inspected until it broke into at least two or more pieces, each with a diameter of at least 15 mm.[1,10,15]

Swelling Behavior: This Study is being Conducted to Measure Raft's Swelling Behavior

20 mL of the prepared formulation was placed in 250 mL of the beaker and filled with 0.1N HCl pH 1.2 at 37°C. Once the raft was constructed, it was carefully removed from the liquid and dried for 2 days. The raft was submerged in water at 30°C after drying. The raft's weight was assessed at 60, 120, 180, 240, and 300-min intervals, and the results were documented. The swelling behavior was then calculated based on the weight changes over time.[1]

Fourier Transform Infrared (FTIR) Spectroscopy

FTIR spectra of pure HPMC K100M and the dry powdered F1 formulation were recorded in the range of 4000–400 cm^{1} to investigate potential interactions between the drug and other excipients.. The samples were prepared using the KBr disk method with a hydrostatic press.[1,10]

In Vitro Release Studies

The *in vitro* release study of metronidazole from the in-situ gel raft was conducted using a United States Pharmacopeia (USP) Type II dissolution test apparatus, maintained at 37 ± 0.5°C with a rotational speed of 50 rpm. Freshly prepared 900 mL of 0.1N HCl (pH 1.2) was used as the dissolution medium. A 10 mL aliquot of the prepared formulation was carefully drawn with a syringe and slowly replaced with the same volume into the dissolution vessel to avoid any disturbances. After forming the raft, the samples (5 mL) were withdrawn at a preset time interval (5, 10, 15, 30, 45, 60, and 120 min), and the same amount of buffer was added to maintain proper sink condition in the vessel. The samples were evaluated at 277 nm using the ultraviolet (UV) spectroscopic method (SHIMADZU: UV19001).[10,16]

RESULTS

Gastroesophageal reflux disease (GERD) is one of the most common gastrointestinal conditions in which stomach contents flow backward into the esophagus, causing symptoms like heartburn and dysphagia. GERD management is based on multiple pharmacological interventions,

one of which is raft-forming formulations forming a physical barrier against reflux. It is well established that raft-forming alginate formulations effectively reduce GERD symptoms. Commercially available raft-based products for the treatment of GERD include Gaviscon Double Action, Gaviscon Original, peptic liquid, and aglycone pills.[1]

Physical Appearance and pH Measurement

All the formulations looked like cream-colored suspensions. pH is a very critical parameter for oral preparation. Otherwise, it irritates the mouth and throat. All prepared formulations possessed a pH ranging from 3 to 7, as shown in Table 2 and Figure 1.[10,15]

In Vitro Gelling Study

The *in vitro* gelling study was conducted in simulated gastric fluid at pH 1.2, pH 2 (HCl acid buffer), and pH 4 (phosphate buffer). All the formulations exhibit instant gel formation when connected to the media; in pH 2, the raft was partially floating, and pH 4 showed nonfloating. The results are shown in Table 2. Formulation F1 exhibited the shortest gelation time, approximately 4 seconds, while F6 showed a gelation time of 15 seconds, and F5 took 12 seconds, which is longer than F1 [Figure 2].[10,16]

In Vitro Buoyancy Study

This study was conducted in different pH solutions (pH 1.2, pH 2, and pH 4). The time when the formulation ultimately emerges on the medium surface is called floating lag time, and when the formed gel moves upward from the media and floats on the surface, it is called total floating time. All the formulation shows a total floating time >24 h.[10]

Viscosity

One of the crucial parameters (derived property) in this suspension formulation is viscosity. It is so because this parameter strongly affects the suspension stability at storage due to the trend of particle sedimentation. On the other hand, viscosity ought to be at a level that is simple to provide to patients. Table 3 displays the findings of tests on viscosity. The viscosity ranged from 9.88 [pa-s] to 1.43 [pa-s]. The highest viscosity belongs to F1, which had HPMC 100, and the lowest viscosity belongs to F6, which had SA. As the shear rate increased, the viscosity of each formulation

Table 2: Evaluation results of different *in situ* gel formulations

Formulation	Gelling time (s)	Gelling duration (h)	Floating lag time (h)	Floating duration (h)	pH change			Swelling %	CPR 2 h in 1.2 pH %
					1.2	2	4		
F1	4	>24	9	>24	3	4	6	93.67	33.44
F2	5	>24	12	>24	3	5	6	90.13	41.39
F3	7	>24	11	>24	2	4	5	94.55	88.57
F4	10	>24	15	>24	3	4	6	95.31	84.32
F5	12	>24	17	>24	3	4	7	95.40	43.52
F6	15	>24	18	>24	2	5	6	92.24	46.80

Table 3: Evaluation results of different *in situ* gel formulations on raft

Formulation	Density (g/cm^3)	Viscosity (pa-s)	Thickness (mm)	Raft volume (mL)	Raft resilience (h)
F1	0.939	9.88	16.32	40.18	>4
F2	0.904	8.2	13.38	34.92	>4
F3	0.763	6.1	15.12	29.24	>4
F4	0.838	5.1	14.28	19.15	>4
F5	0.893	8.1	15.34	33.64	>4
F6	0.733	1.43	12.15	18.95	>4

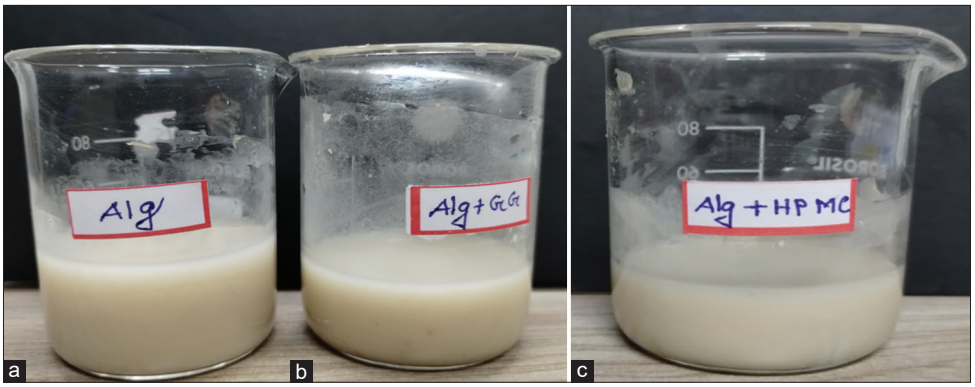

Figure 1: (a) suspension containing alginate F6, (b) suspension containing alginate with guar gum F5, (c) suspension containing alginate with K100 F1

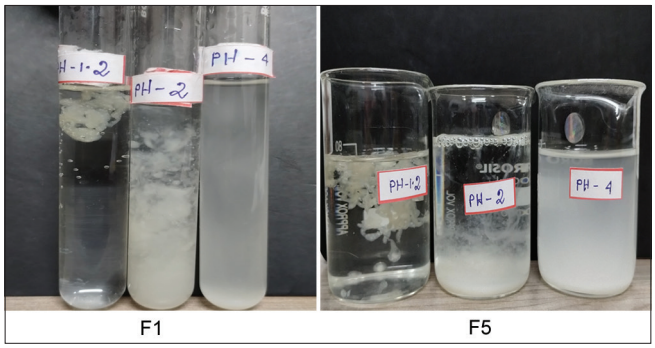

Figure 2: Raft formed in different pH levels

dropped, exhibiting shear thinning or pseudoplastic behavior. Pharmaceutical items benefited from this characteristic, reducing sedimentation volume and making pouring liquid formulations easier [Figure 3].[1,10,16]

Density Measurement

The densities of all formulations (F1–F6) after gelation ranged from 0.733 to 0.939 g/cm³. These results indicate that the formulations can float on gastric contents because raft density was consequently much less than gastric fluid (1.004 g/cm³), thereby fulfilling the requirements for gastric floating.[1,15]

Raft Volume

Production of CO_2 is a crucial parameter in raft volume confined in raft structure. The dissociation of calcium carbonate in an acidic solution is believed to produce CO_2. Table 3 displays the raft volume results for each formulation. With a minimum amount of roughly 18.95 mL, F6 had the lowest raft volume, which the formulation's reduced viscosity could explain. Moreover, F1 observed the highest raft volume, 40.18 mL, which results in a higher amount of entrapment of CO_2.[1,15]

Raft Thickness

The thickness of all the formulations was 16.32–12.15 mm. Rafts F1 and F6 had the highest and lowest thicknesses because they contained fewer and more polymers. No noticeable change in the thickness was observed in formulations F1, F2, F3, F4, F5, and F6.[1,10,15]

Raft Resilience

Raft resilience is the ability to stay disintegrated in conditions that mimic movement in the stomach. This characteristic depends on the drug's dosage, component quality, polymer concentration, and raft strength. Table 3 displays the raft resilience findings for prepared suspensions. For all formulations in our experiment, the raft resilience was roughly >4 h.[1,10,15]

Swelling Behavior

The swelling behavior assessed the dried Raft's ability to absorb water when immersed in distilled water at room temperature. The rafts' water absorption profiles are displayed in Table 3. All formulations exhibited enhanced swelling behavior

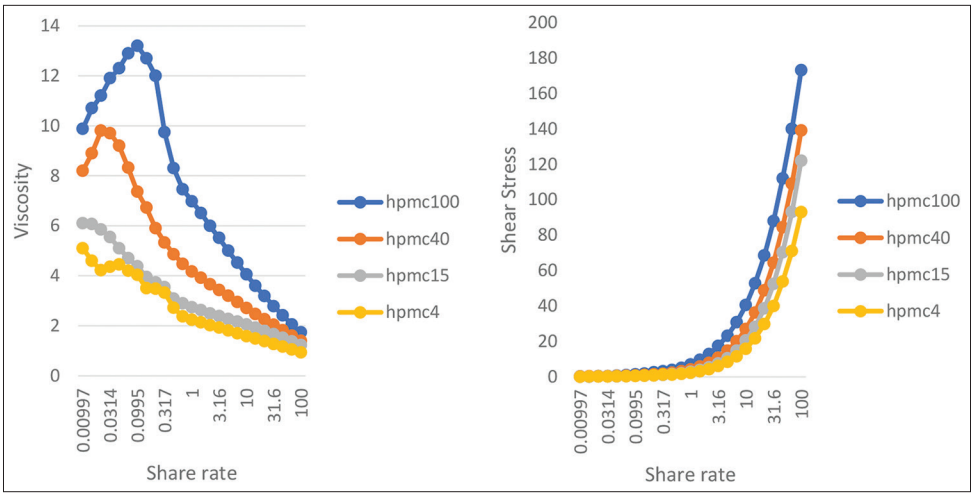

Figure 3: Viscosity of formulation F1–F4

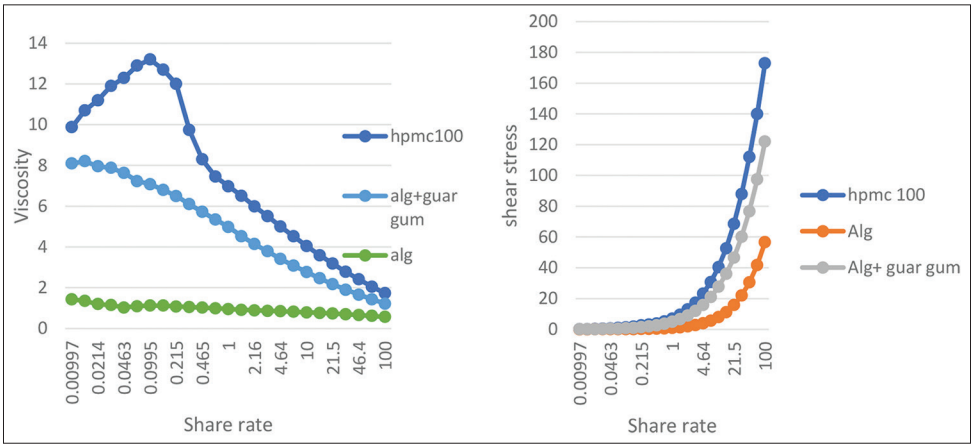

Figure 4: Viscosity of formulation F1, F5, and F6

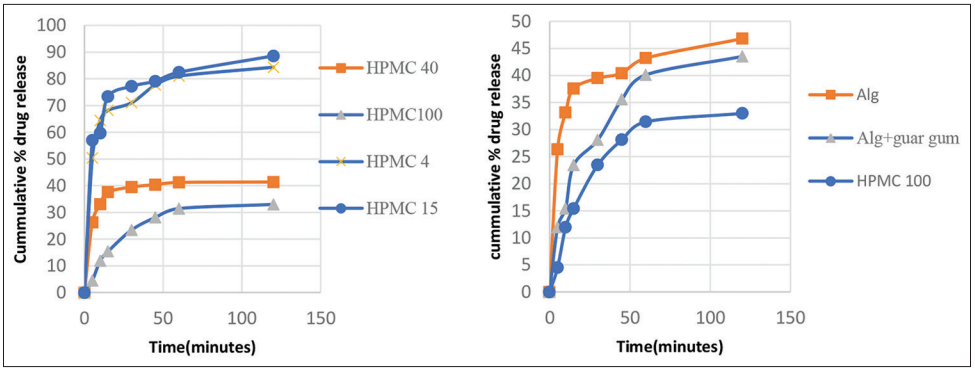

Figure 5: Dissolution study

due to more porous spaces, ranging from 92.24% to 95.31%.[1]

In Vitro Drug Release Profile

Designing a floating raft with various polymers and grades of HPMC with a release profile suitable to sustain sufficiently high local/systemic concentration was the study's primary goal during the *in vitro* release profile. To understand the range and kind of polymers employed in the final formulation design, preliminary formulations using different polymers, either separately or in combination, provide a range of release profiles. SA, GG, HPMC K 100M, HPMC K 40M, HPMC

K 15M, and HPMC K 4M were chosen as release modifier polymers based on these investigations.

The *in vitro* release profile of the formulation was investigated at 1.2 pH conditions. In this gastroretentive formulation, the drug release range was between 33.44 and 88.57%. The drug release of all the formulations was cheeked for 2 h. Using polymer and preferably a combination of polymers gave better control release for a prolonged time. F1, F2, F3, F4, F5, and F6 showed the drug release of 33.44%, 41.39%, 88.57%, 84.32%, 43%, and 46% after 2 h, respectively. F1 shows the lowest drug release, and F3 shows the highest drug release after 2 h. All the data are shown in Table 2. Here, the difference is in the molecular weight of the four varieties of HPMC. HPMC K100 M, being the higher molecular weight, forms a gel of higher viscosity compared to HPMC K40, HPMC K15 M, and HPMC K4 M [Figure 5].

The higher viscosity gel layers of HPMC K100 M matrices provided a more tortuous and resistant barrier to diffusion, resulting in a slower release of drugs from these matrices. The drug release decreased in the rank order of HPMC K4 M > HPMC K15 M > SA > SA + GG HPMC K40 M > HPMC K100 M.[11,21]

Fourier Transform Infrared Spectra

HPMC K100 M polymer peaks at 1515.29, 2893.40, and 3729.48 cm^{-1} due to C–O, C-H, and O–H stretching vibration, respectively. The FTIR spectrum of the dried HPMC 100 formulation reveals a broad peak at 3374.77 cm^{-1}, attributed to N-H stretching, as well as peaks at 1629.95 cm^{-1} and 1030.65 cm^{-1}, which correspond to the presence of alkene and amine groups, respectively. These characteristic peaks indicate the chemical composition and functional groups present in the formulation. There was no discernible interaction between the raft formulation (F1) and polymers in the FTIR spectra [Figure 6].[22,23]

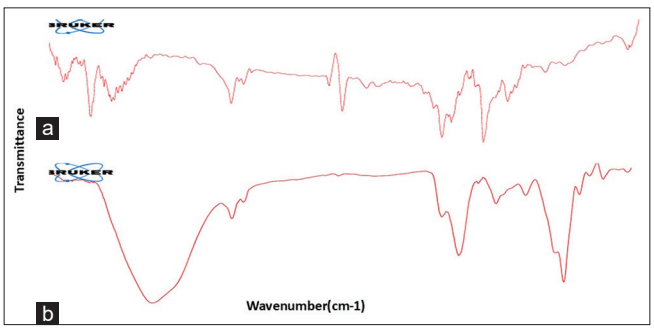

Figure 6: (a) Fourier transform infrared spectroscopy of hydroxypropyl methylcellulose 100 and (b) F1 formulation

DISCUSSION

In this study, gastroretentive *in situ* gel fabricated with SA, GG, and HPMC was successfully developed. All formulations demonstrated suitable viscosity, gelling capacity, quick floating characteristics, and prolonged drug release over a long period. Polymers with higher viscosity were more beneficial than those with lower viscosity in controlling drug release. In our study, formulation F1 demonstrated the most effective control of drug release, with a 33% release after 2 hours, compared to the other formulations (F2, F3, F4, F5, and F6). The gel formulation F1, which contained HPMC K100 M, exhibited excellent buoyancy, maintaining a long flotation time of over 24 hours in simulated gastric fluid. This extended flotation time improves gastric retention, making F1 a promising candidate for sustained drug release. Overall, this study concluded that developing a raft-forming system containing SA with HPMC 100 has a better impact on the sustained release of the drug, and viscosity is a significant factor affecting the drug release and floating properties of floating drug delivery systems.

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CONFLICT OF INTERESTS

The authors declare no conflict of interests in the current work.

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