Ind. J. Pharm. Edu. Res., 2023; 57(3s):s540-s547.
https://www.ijper.org

Original Article

Multiparticulate Floating Beads an Aid to Enhance Therapeutic Efficacy of Rabeprazole

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ABSTRACT

Background: Rabeprazole sodium is a newer generation anti-ulcer drug with short half-life and low bioavailability. Present research work is an attempt to design novel floating beads of Rabeprazole sodium in multiparticulate dosage form to increase residence time and modulate its release behavior for stomach-specific delivery. **Materials and Methods:** In this present study, Rabeprazole sodium beads were formulated by ionotropic gelation method and effect of variation in sodium alginate and gellan gum concentrations alone and in combination on release properties was examined. **Results:** Formulated beads were analyzed for particle size, density, entrapment efficiency, swelling index, *in vitro* buoyancy properties, surface topography, *in vitro* drug release and release kinetics study. The percentage content and entrapment efficiency of Rabeprazole sodium in beads ranged from 77.06±3.612 to 92.88±5.723 and 57±1.543 to 89±1.089 respectively. *In vitro* drug release of Rabeprazole sodium from the beads at the end of 12 hr ranged from 69.373% to 97.0142%. The release behavior was best fitted in Korsemeyer-Peppas equation. F9 was optimized depending on entrapment efficiency, *in vitro* buoyancy properties and *in vitro* drug release. Modified formulation F9 was also subjected to a series of tests. mucoadhesive study, *in vivo* X-ray imaging in rabbits and stability study. **Conclusion:** These studies revealed that beads exihibited 84% mucoadhesion, floating up to 12 hr as well as stability at 25±2°C. Hence Floating bead formulation of Rabeprazole sodium will be a promising drug delivery system to improve drug residence time and patient compliance.

Keywords: Floating beads, Rabeprazole, Buoyancy, *In vivo* Radiography, Mucoadhesion.

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Received: 27-07-2022;
Revised: 22-02-2023;
Accepted: 24-06-2023.

INTRODUCTION

Oral drug delivery though most preferred route of drug administration is subjected to many adversities such as short residence, invariable gastric emptying time which in turn causes fluctuations in drug plasma concentrations leading to unpredictable absorption of drugs, rapid gastrointestinal transit prevents complete absorption of drugs in absorption zone. Constraints of oral route also includes difficulty in localization of drug to the specific target site decreasing efficacy of administered dose.[1-5]

In order to deal with the above-mentioned issues, recent trends of novel drug delivery system such as gastroretentive drug delivery systems are formulated which would release effective amount of drug from the protected supply at a controlled rate for prolonged period of time.

Floating drug delivery systems is one of the innovative approach of gastroretentive system which have a lower bulk density than stomach fluid (1.004gcm^{-3}) hence remains floating in the stomach bypassing gastric emptying, releasing drug in a sustained manner along with increase in gastric residence time and confers flexibility of blending different excipients to attain different release pattern.[6-10] The medication is slowly released from the system while it is floating in the stomach juice at the desired rate. The release rate can be controlled depending on the type and concentrations of polymers which involves swelling and ultimate diffusion and erosion of drug. These benefits of floating drug delivery formulations can further be extended by modifying it into multiple-unit dosage forms. These delivery systems are primarily reservoir-type oral dosage forms with a large number of small various independent subunits, each with a distinct characteristic, and where the active component is in the form of distinct units. Due to these subunits multiparticulate systems overcomes the problem of "all or none" emptying associated with the single-unit dosage form, augments drug safety.

Rabeprazole sodium is a newer PPI that claims to provide the most rapid acid suppression. When it reaches pH 5, it rearranges into two charged cationic forms (a sulphenic acid and a sulphenamide

DOI: 10.5530/ijper.57.3s.62

structure), which react covalently with the SH groups of the H+K+ATPase enzyme and effectively inactivate it. After diffusing into the parietal cell from blood, it concentrates at the acidic pH of the canaculi because the charged forms generated there are unable to diffuse back and instead become securely bound to the enzyme.[11-16]

These characteristics, together with the unique localization of H+K+ATPase to the apical membrane of parietal cells, confer a high degree of Rabeprazole selectivity.[17,18] Rabeprazole sodium has a short half-life of 1-2 hr, a low bioavailability of 52%, and is rapidly metabolized. Taking these facts into account, Rabeprazole sodium has been formulated into a floating multiparticulate system using an ionotropic gelation method to provide stomach specific sustained drug delivery while minimizing inter and intra subject variability.

MATERIALS AND METHODS

Rabeprazole sodium is obtained as gift sample from Cipla Pvt. Ltd., Mumbai. Sodium alginate was purchased from Bombay Research Laboratory, Poona. Gellan gum was purchased from Sisco Research Laboratories Pvt. Ltd., Calcium carbonate was purchased from Loba Chemie Pvt. Ltd., Mumbai. All other reagents used were of analytical grade.

Experimental methods

Formulation of floating beads

The ionotropic gelation process was used to develop nine different floating bead formulations. Rabeprazole sodium, 20 mg, was dissolved in distilled water first. Different ratios containing sodium alginate and gellan gum were dissolved in distilled water (1:1,1:2,1:3). The drug solution, as well as the polymer solution, were added to this mixture. Calcium carbonate was added and stirred on a magnetic stirrer to form a homogeneous solution. The drug-loaded polymeric solution was extruded into a calcium chloride solution (5% w/v) that was kept under gentle agitation on a magnetic stirrer using a 22G syringe needle. The beads were left in the same solution for about an hour to increase hardness and mechanical strength, as well as to complete the reaction that formed gas within the beads. The resulting beads were filtered and dried overnight at room temperature. Then, using a combination of sodium alginate and gellan gum in various ratios, three more formulations were created. Formulation codes were allocated to the designed formulations, as shown in Table 1.

Evaluation of floating beads

Practical yield

The efficiency of any methodology is measured using practical yield, which facilitates in the selection of the most appropriate production process. Practical yield was calculated using the weight of beads retrieved from each batch in relation to the total starting material.[19-21]

The equation was used to calculate the practical yield of the beads produced.

$$\text{Practical yield} = \frac{\text{Practical mass(Beads)}}{\text{Theoretical mass(Polymer + drug)}} \times 100$$

Determination of particle size

Optical microscopic techniques were used to assess particle size using an ocular and a stage micrometer. A total of 100 particles were seen, and the mean diameter was calculated by counting the number of divisions covered by beads with an ocular micrometer that had been calibrated with a stage micrometer. Each sample was examined three times, with each time the mean and standard deviation recorded.[22-25]

Density measurement

Density of floating beads was assessed by mercury porosimetery (Autopore IV GA, USA). Pore diameter was measured by scanning electron microscopy.[26]

Determination of swelling index

50 mg of floating beads were soaked in 900mL of buffer (0.1N HCl) at 37± 0.5°C in a (USP XXIII type 2) dissolving test device (Paddle type). After that, the beads were removed at predetermined intervals, dried, and weighed to determine the swelling index. The following equation was used to calculate the swelling ratio.[27]

$$\text{Percent swelling index} = \frac{W2 - W1}{W1} \times 100$$

Where, W1 - Weight of dried beads.

W2 - Weight of swollen beads.

Determination of buoyancy of beads

In a USP XXIII type 2 dissolution test apparatus, the floating properties of beads were examined using 900mL of 0.1N HCl at a specified temperature of 37°C±0.5°C. Visual observation was used to determine the time it took 50 beads to float on the surface (lag time) and total floating time in the medium. Filtration was used to separate the layer at the bottom from the layer of floating beads. The following equation was used to compute buoyant time.[28,29]

$$\text{Percent buoyancy} = \frac{\text{Weight of floated beads(Wf)}}{\text{Weight of floated beads(Wf)} + \text{Weight of settled beads(Ws)}} \times 100$$

Drug content

The drug content was determined in order to ensure that the dose in the formulation was uniform. 20 mg of rabeprazole sodium floating beads were dissolved in 100mL of 0.1N HCl, which was mechanically agitated on a shaker. This sample was filtered and dilute to a concentration of 10g/mL before being analyzed using a

double-beam UV at 272.5nm against a blank of 0.1N HCl solution and the percentage of drug present in the sample was determined.

Entrapment efficiency

For 10 min, a homogeneous solution of swollen beads (incubated with water) was sonicated. After proper dilution with 0.1N HCl, the solution was centrifuged for 10 min at a rotational speed of 10000 rpm and the supernatant was examined by UV at 272.5nm. The entrapment efficiency percentage was calculated as follows:[30]

$$\text{Percent entrapment efficiency} = \frac{\text{Practical drug loading}}{\text{Theoretical drug loading}} \times 100$$

Morphological analysis

Scanning electron microscopy was used to examine surface and cross-sectional morphologies. The dried sample was gold coated and tested further after being put on double adhesive carbon tape.[31]

In vitro drug release studies

The *in vitro* release characteristics of floating beads were investigated using a USP XXIII dissolution apparatus type 2 (Paddle apparatus) in 900mL of 0.1N HCl as the dissolution medium and a temperature range of at 37±0.5°C, stirring at 50rpm for 12 hr and spectrophotometrically at 272.5 nm (UV Shimadzu UV-1700 pharmaspec).[11] Triplicates of the *in vitro* drug release tests were performed.

In vitro drug release kinetics

In vitro drug release data was fitted into various kinetic models, including zero-order, first-order, Higuchi, and Hixon, to explore release kinetics. Korsmeyer-Peppas and Crowell.[32]

In vitro Mucoadhesive study

The prepared slide was hung onto one of the groves of a USP pill dissolving test device, and beads were dispersed onto the wet, washed tissue specimen. The dissolving test apparatus was set up so that the tissue specimen was moved up and down in a beaker containing 0.1N HCl on a regular basis. The number of beads remained adhered to the tissue at the conclusion of each time period was counted.[13,16]

$$\text{Percent Adhesive strength} = \frac{NO - NS}{NO} \times 100$$

Where, No = denotes the number of beads that first spread from the mucosal surface.

Ns = denotes the number of beads that have detached from the mucosal surface.

In vivo X-ray imaging

The buoyant qualities of Rabeprazole sodium beads were confirmed *in vivo* using X-ray imaging in rabbits, which was recommended as a model to confirm the buoyancy properties of beads. The *in vivo* radiography examinations were performed on 12 young, healthy male albino rabbits weighing 2.0 kg to 2.5 kg that were housed in conventional laboratory settings [temperature (25±2°C). To guarantee that the conditions of gastrointestinal motility were consistent, the animals were fasted for 12 hr prior to the commencement of the experiment, and they were only given free access to water *ad libitum*. To guarantee that the dose form was present in the stomach region, the rabbits were given rabeprazole sodium beads containing barium sulphate orally along with 5-10 mL of water. Approximately every hour. Throughout the investigation, the animals were given 10mL of water to drink. X-ray images acquired at various time intervals were used to investigate the floating efficiency and behaviour.[15-20]

Stability study

Formulation tweaked F9 was submitted to a 60-day stability evaluation in a humidity control oven at room temperature (25±2°C/60±5%) and accelerated settings (40±2°C/75±5%) (Lab Control, Ajinkya IM 3500 Series, India).[33,34]

RESULTS AND DISCUSSION

Evaluation of formulated beads

Practical yield (%)

Practical yield (%) of formulated beads F1 to F9 was calculated and yield was found to be ranging from 80% to 90%. The loss of material during formulation of beads may be due to process parameters as well as during filtration of beads and hence yield was not 100%. Among all formulations F9 showed maximum practical yield. Practical yield of all batches is shown in Table 2.

Particle size

When compared to gellan gum, the particle size of sodium alginate formulations was found to be smaller. This could be due to changes in polymer molecular weight and structure, resulting in viscosity discrepancies in polymeric solutions. It was observed that when the polymer content grew, so did the average particle size. It's possible that this is due to the scorching impact of higher polymer concentrations. The average particle size was found to be between microns 1.213±0.017 to 1.671±0.053 (Table 2).

Density

The beads are buoyant for 12 hr because their density is less than 1.004 gcm-1. Table 2 shows the density of all formulations.

Determination of swelling index

The swelling capacity was calculated using the beads' water absorption capacity. The swelling behaviour of the beads was assessed in terms of swelling ratio by incubating them in 0.1N HCl at 37°C for 12 hr. Due to the conversion of Ca-alginate into alginic acid gel, all formed Rabeprazole Sodium beads stayed intact in 0.1N HCl during the trial time and appeared more

transparent at the end of 12 hr. As the polymer concentration rises, the swelling index rises as well, owing to an increase in viscosity, which reduces drug release. Alginate beads have a larger swelling index than gellan gum beads, and the same can be said for formulation F9, which has a higher swelling index than F7 and F8. This could be related to alginate's increased water absorbing capability, which induces swelling and as a result, an increase in size. The swelling index was found to be in the range of 7.22±1.76 (mean±SD) to 7.63±1.23(mean±SD) (Table 2).

Drug content and entrapment efficiency

The amount of drug and the effectiveness of the entrapment are essential factors to consider. The amount of medication in the formulation shall not differ from the indicated amount beyond prescribed limits. As the polymer concentration was increased, the actual drug content and entrapment efficiency both ascended. As polymer concentration grows, cross-linking increases, inhibiting drug diffusion. Alginate gel beads had a higher entrapment efficiency than gellan gum with a low calcium chloride content. F3 entrapment efficiency was determined to be the highest in the case of alginate beads and F6 in the case of gellan gum beads. Among all formulations, the F9 formulation had the highest release (Table 2). This could be owing to a larger sodium alginate content, which promotes increased polymer cross-linking and prevents drug diffusion out of the system.

Determination of buoyancy of beads

With a floating lag time of 80-160 sec, good integrity, and a floating endurance of more than 12 hr, all of the manufactured beads floated promptly. This shows that the examined polymers' gel layers allowed for effective trapping of the produced gas bubbles. All formulations' floating lag time, floating duration, and buoyancy percentage are presented in (Table 3). As shown in Figure 1.

Table 1: Composition of gastroretentive floating beads of Rabeprazole sodium.

Formulation code	Rabeprazole sodium (mg)	Sodium alginate (mg)	Gellan gum (mg)	Calcium carbonate (mg)	Calcium chloride (w/v)
F1(1:1)	20	20	-	60	5%
F2(1:2)	20	40	-	60	5%
F3(1:3)	20	60	-	60	5%
F4(1:1)	20	-	20	60	5%
F5(1:2)	20	-	40	60	5%
F6(1:3)	20	-	60	60	5%
F7(1:1.5:1.5)	20	30	30	60	5%
F8(1:2:1)	20	40	20	60	5%
F9(1:1:2)	20	20	40	60	5%

Table 2: Characterization of floating beads.

Formulation Code	Practical Yield (%)	Particle size (mm)	Density (gcm^{-3})	Drug entrapment efficiency (%)*	Drug content (%)	Swelling index (%) (At the end of 12 hr)	Pore diameter (µm)
F1	80.0±4.012	1.231±0.015	0.901±0.004	76±1.743	85.53±3.601	7.22±1.76	0.481
F2	84.5±2.323	1.451±0.023	0.920±0.020	78±2.187	90.93±4.871	7.54±2.11	0.372
F3	86.5±2.045	1.571±0.018	1.001±0.120	85±2.090	91.46±6.343	7.61±2.08	0.195
F4	87.0±2.665	1.213±0.017	0.915±0.0891	57±1.543	77.62±5.989	7.41±1.87	0.175
F5	83.5±2.576	1.517±0.069	0.961±0.0912	63±2.198	77.06±3.612	7.54±1.09	0.131
F6	84.0±3.698	1.671±0.053	0.980±0.006	69±1.576	80.45±7.154	7.59±1.14	0.117
F7	85.0±1.754	1.513±0.027	0.889±0.127	87±1.764	91.75±6.576	7.61±1.25	0.193
F8	89.0±2.798	1.619±0.024	1.034±0.135	76±1.878	82.71±3.698	7.51±1.88	0.117
F9	90.0±3.632	1.318±0.020	0.868±0.0718	89±1.089	92.88±5.723	7.63±1.23	0.195

Data are expressed as mean (n=3).

Table 3: ***In vitro*** **buoyancy study.**

Formulation Code	Percentage Floating (%) ± SD	Floating Lag Time (Secs)	Floating Duration (hrs)
F1	95±5.601	120	>12
F2	92.5±6.887	140	>12
F3	90.4±7.607	150	>12
F4	93.6±2.512	80	>12
F5	91.2±2.343	85	>12
F6	91.±6.601	90	>12
F7	86.5±2.923	150	>12
F8	95±2.001	160	>12
F9	95.5±2.523	130	>12

Table 4: **Model fitting data of release profile for formulations F1-F9.**

Formulation Code	Zero Order (R^2)	First Order (R^2)	Higuchi Matrix (R^2)	Hix crowell	Peppas Model		Best fit Model
					(R^2)	(n)	
F1	0.9727	0.9641	0.9687	0.9808	0.9907	0.5800	Peppas
F2	0.9703	0.9631	0.9708	0.9805	0.9914	0.5880	Peppas
F3	0.9518	0.9089	0.9485	0.9089	0.9908	0.5326	Peppas
F4	0.9558	0.9606	0.9743	0.9799	0.9901	0.5598	Peppas
F5	0.9899	0.9121	0.9765	0.9635	0.9921	0.5792	Peppas
F6	0.9485	0.9493	0.8999	0.9521	0.9532	0.9384	Peppas
F7	0.9564	0.9871	0.8971	0.9821	0.9947	0.5111	Peppas
F8	0.9432	0.9440	0.9063	0.9495	0.9561	0.8107	Peppas
F9	0.9514	0.9875	0.9741	0.8947	0.9899	0.5232	Peppas

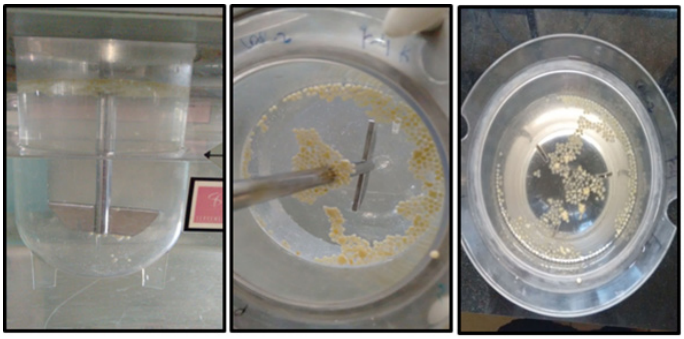

Figure 1: Images of floating beads which remained buoyant in 0.1N HCl.

Scanning electron microscopy

The surface morphology of the generated beads was examined using scanning electron microscopy. According to morphological study, beads had a nearly spherical shape and a rough outer surface. The cross-sectional morphologies of floating beads were studied using SEM. The surface was found to be slightly porous, which could be linked to the concentration of gas-forming agents. Figure 2 shows scanning electron micrographs of the exterior and cross-sectional surfaces.

In vitro drug release

Rabeprazole sodium was released from beads *in vitro* using a USP XXIII dissolving equipment type 2 (Paddle device) in 0.1N HCl. The medication release profiles were created by plotting the amount of Rabeprazole sodium released against time. It was observed that as the polymer concentration was increased, the rate and extent of drug release decreased significantly. This was attributed to an increase in the density of the polymer matrix, an increase in the diffusion path length that the drug had to traverse, and it's possible that at higher polymer concentrations, the drug is trapped in smaller polymer cells and is structured by its close proximity to the polymer molecules, resulting in a longer period for the drug to be released.

Gellan gum preparations (F4, F5, F6) released drugs at a lesser rate than sodium alginate preparations (F4, F5, F6) (F7, F8, F9). This is due to gellan gum's ability to form double helical junction zones, which are followed by aggregation of the double helical segments to form a three-dimensional network by complexation with cations and hydrogen bonding with water, allowing it to form strong clear gels under physiological conditions, which can entrap the drug firmly and cause further drug release retardation. Calcium carbonate also contributed to drug release retardation

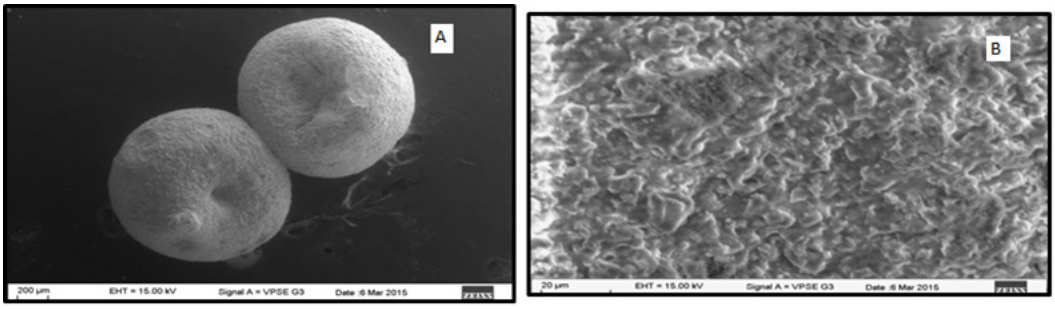

Figure 2: Scanning electron microscopy photographs of beads a) Spherical shape of beads, b) Rough surface.

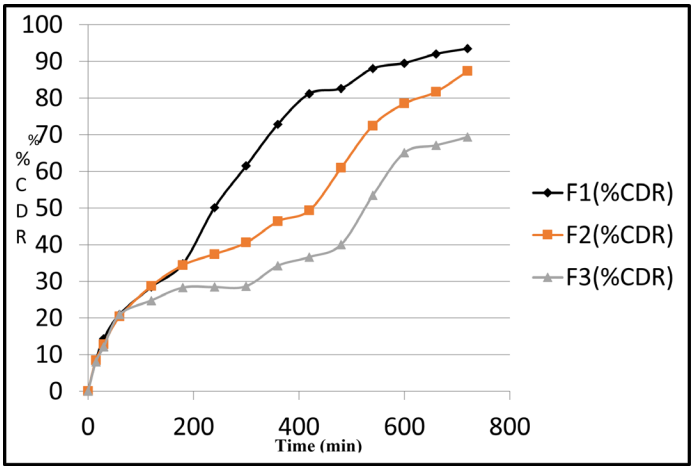

Figure 3: Comparative *in vitro* drug release profile of Rabeprazole sodium beads for formulation F1-F3 in 0.1N HCl.

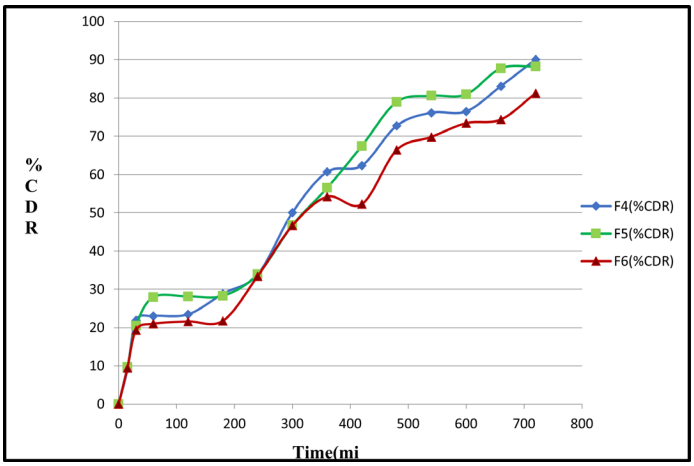

Figure 4: Comparative *in vitro* drug release profile of Rabeprazole sodium beads for formulation F4-F6 in 0.1N HCl.

due to gelation, which was mostly caused by calcium ions. The maximum drug release was seen in Formulation F9, possibly due to a lower gellan gum concentration than in Formulations F7 and F8 (Figures 3, 4 and 5).

Release kinetics

The release data was evaluated with release kinetics mathematical models such as Zero order, first order, Higuchi's,

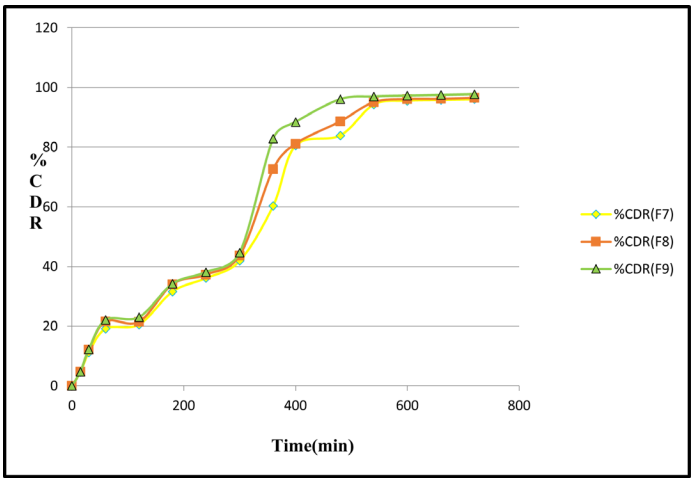

Figure 5: Comparative *in vitro* drug release profile of Rabeprazole Sodium beads for formulations F7-F9 in 0.1N HCl.

Korsemeyers-Peppas, and Hixson-Crowell in order to investigate the manner of drug release from floating beads. In order to calculate the release constant and Regression coefficients (R^2), the release data were fitted to various kinetic models (Table 4). The drug release patterns for formulations (F1-F9) were fitted in the Korsemeyers-Peppas model with regression coefficients of 0.9907, 0.9914, 0.9908, 0.9901, 0.9921, 0.9532, 0.9947, 0.9561, and 0.9899 among the models analyzed. The plot's linearity indicated that the release was controlled via diffusion. The diffusion exponent (n) values for formulations (F1, F2, F3, F4, F5, F7, F9) were greater than 0.5, indicating a non-fickian mechanism of drug release in which the rate of drug release is due to the combined effect of drug diffusion and polymer relaxation, and formulations (F6 and F8) were greater than 0.89, indicating that drug release is due to polymer relaxation and diffusion is the mechanism of release.

In vivo gastroretentive radiographic study

The barium sulphate-loaded floating beads were seen in the stomach after oral administration of the dose form. After an hour, radiographic images revealed that all of the beads had been disseminated throughout the stomach. Images of floating beads could be seen at first, but as time passed, the images of beads became lighter. It could be due to the way beads are dispersed throughout the gastrointestinal tract. According to radiographic

Table 5: Stability study of optimized formulation (F9) stored at room temperature and accelerated conditions.

Evaluation Parameters	Optimized Formulation F9				
	Initial (Zero days)	Room Temperature (25± 2°C/60±5%)		Accelerated conditions (40± 2°C/75±5%)	
		30 Days	60 Days	30 DAYS	60 DAYS
Entrapment efficiency (%)	89	88	88	87.89	87.81
Drug release %	97.77	96.89	96.89	96.71	96.68
Floating lag time (secs)	130	120	120	120	120
Density (gcm^{-3})	0.868	0.867	0.865	0.860	0.860

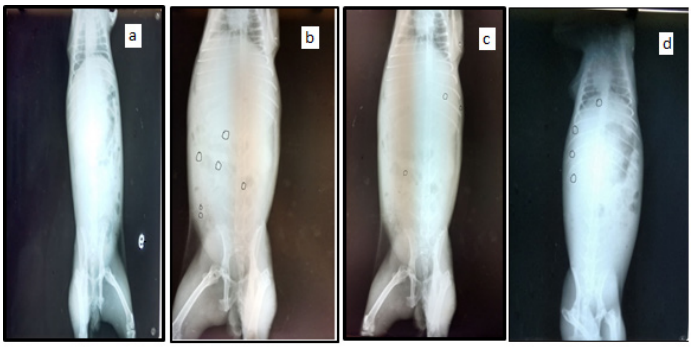

Figure 6: Radiographic images showing the presence of barium sulphate loaded floating beads in the stomach at different time intervals.

Note: Images were taken at 1 hr, 6 hr, 12 hr. a) control b) Test at 1 hr c) Test at 6 hr d) Test at 12 hr.

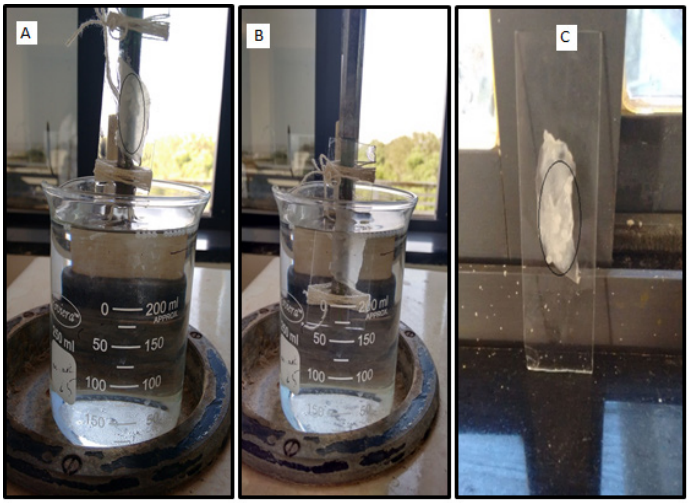

Figure 7: Photographs showing mucoadhesive study of optimized formulation F9 in 0.1N HCl.

A) And B) Beads adhered to the mucosa immersed in 0.1N HCl. C) Beads remaining adhered to mucosa after immersing in 0.1N HCl.

tests, floating beads can be retained in the stomach for up to 12 hr. Figure 6 shows X-ray images.

Mucoadhesion study

By targeting drugs at specific areas, a mucoadhesive drug delivery system can improve treatment effectiveness. The mucoadhesion test on the optimized formulation F9 (Figure 7) revealed that sodium alginate and gellan gum help with stomach adherence. The percentage of beads that adhered to the mucosa was determined to be 84%. The mucoadhesion of floating beads could be due to the mucoadhesive properties of alginate and gellan gum.

Stability study

Stability tests were conducted on the formulation for two months at room temperature and under accelerated settings due to its potential application. The formulations were examined for drug entrapment, floating behavior, and *in vitro* release after 30 and 90 days. Table 5 summarizes the results.

CONCLUSION

The ionotropic gelation process was used to efficiently prepare nine formulations containing Rabeprazole sodium beads. Particle size was dependent on the kind of polymer and was directly proportional to the rise in polymer concentration, however practical yield was independent of polymer concentration and was dependent on experiment characteristics such as drug loss during formulation. The swelling index, which measures entrapment efficiency, was found to be proportionately dependent on polymer concentration. Almost all formulations had a density of less than $1.004gcm^{-3}$, allowing the beads to float for more than 12 hr. SEM revealed that the beads were spherical in shape with a slightly rough external surface, which could be owing to shrinkage caused by drying. Drug release *in vitro* tends to decrease as polymer concentration rises. The maximum release of Formulation F9 was discovered after 12 hr. The drug content, entrapment efficiency, floating lag time, and *in vitro* drug release of Formulation F9 were all optimised. The best match kinetic model was found to be Korsemeyer Peppas (non-fickian and case II transport). *In vivo* (X-ray) testing in rabbits revealed that the beads remained buoyant in the stomach for up to 12 hr, while a mucoadhesion analysis of the improved formulation revealed that it can stick to the gastric mucosa. Formulation F9 was tested for stability and found to be stable for up to 60 days. According to the results of the research, the gastroretentive floating beads of Rabeprazole sodium had good buoyancy and sustained drug release for up to 12 hr, demonstrating their potential for site-specific drug delivery, which leads to improved Rabeprazole absorption and bioavailability.

ACKNOWLEDGEMENT

Authors are thankful to KLE College of Pharmacy, Belagavi for providing all the necessary equipment's and facilities for the conduct of research work. Authors are also thankful to Cipla Pvt. Ltd., for providing gift sample of Rabeprazole Sodium and to Government Veterinary Hospital, Belagavi for extending their help for animal studies.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

PPI: Proton Pump Inhibitor; **RPM:** Rotations Per Minute; **SEM:** Scanning Electron Microscopy.

SUMMARY

Thus, it can be summarized that the novel floating beads of Rabeprazole sodium can be successfully prepared by ionotropic gelation method which due to their low densities showed good floating ability due to which it can remain buoyant for 12 hr, thus providing site specific delivery of drug for prolonged period of time by increasing residence of drug in the stomach which can in turn give long term relief from peptic ulcer.

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Cite this article: Magdhut P, Dandagi PM, Kokatanur UA, Patil AS. Multiparticulate Floating Beads an Aid to Enhance Therapeutic Efficacy of Rabeprazole. Indian J of Pharmaceutical Education and Research. 2023;57(3s):s540-s547.