Research Paper

PREPARATION AND OPTIMIZATION OF ORAL FLOATING ALGINATE GEL BEADS OF FAMOTIDINE

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ABSTRACT:
The objective of present investigation is to prepare and optimize an oral floating alginate gel beads of famotidine using gas generating agent like sodium bicarbonate and Corn oil was utilized as a dispersed phase to generate a uniform emulsion to create multiple tiny chambers in the alginate matrix for better buoyancy. The effect of different concentrations of sodium alginate, calcium chloride and famotidine were used and their Morphological analysis, Buoyancy, Encapsulation efficiency and In vitro drug release behavior in simulated gastric fluid were carried out. Size of all the beads was found spherical and uniform and percentage yield of all formulation was found approximate 80%. Buoyancy study showed that only F-3 to F-13 was floating. It was clearly seen that famotidine release from uncoated beads in a considerable "burst" during the first 30 min, due to rapid water ingress and creation of aqueous channels.

KEY WORDS: Famotidine, Corn oil, Sodium Alginate, Buoyancy, In vitro drug release etc.

INTRODUCTION

Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation etc. From immediate release to site specific delivery, oral dosage forms have really progressed. Gastro retentive dosage forms significantly extend the period of time, over which drug may be released and thus prolong dosing intervals and increase patient compliance. Such retention systems are important for those drug that are degraded in the intestine like antacids or certain antibiotics enzymes that act locally in the stomach. This system can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have absorption window in a particular region of the gastrointestinal tract, thus ensuring optimal bioavailability.[1,2] Various gastro retentive techniques were used, like floating, swelling, high density, and bioadhesive system. Out of these floating have been explored to increase the gastroretention of dosage forms.[3, 4] Floating systems having low density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach without affecting the gastric emptying rate for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastric retentive time and reduces fluctuation in plasma drug concentration.[5, 6]

Formulation of floating beads containing famotidine as a drug candidate, which remain in stomach or upper part of GIT for prolonged period of time, therefore the maximum drug release is maintained at desired site. Famotidine is readily but incompletely absorbed from the gastrointestinal tract with peak concentrations in plasma occurring 1 to 3 hours after oral doses. The bioavailability of oral famotidine is about 40 to 45% and is not significantly affected by the presence of food. The elimination half-life from plasma is reported to be about 3 hours and is prolonged in renal impairment. Famotidine is weakly bound, about 15 to 20%, to plasma proteins. A small proportion of famotidine is metabolized in the liver to famotidine S-oxide. About 25 to 30% of an oral dose, and 65 to 70% of an intravenous dose, is excreted unchanged in the urine in 24 hours, primarily by active tubular secretion. Famotidine is also found in breast milk.[7] Low viscosity hydrophilic polymers ethyl cellulose were found to be more beneficial to improving floating properties. Hydrophilic polymer slowly forms thick gel, which retains integrity of the formulation and promotes drug release through thick gel which control the burst release.[8] For the present study famotidine was selected as drug candidate, and Ethylcellulose as polymer, both the drug and polymer fulfills the above characteristics, which indicate its suitability for fabrication into the floating drug delivery system.

MATERIALS AND METHODS:

Famotidine, Ethylcellulose and Corn oil were purchased from RS enterprises Jaipur.

Characterization of Famotidine:

- **Description:** The sample of famotidine was analyzed for its nature, color and taste.
- **Melting Point:** The melting point was taken by open capillary method.
- **Standard Curve of Famotidine:** Famotidine has been quantitatively analyzed by various techniques. In present studies, Famotidine was estimated by UV Spectrometry method.

Preparation of Alginate Gel Beads

All alginate gel beads were prepared following the same gelation procedure.[11] A pre-gelation liquid was prepared by mixing sodium alginate solution, the prescribed amount of corn oil, and the drug, famotidine. Twenty milliliters of each of the pre-gelation liquid was then added, through a 26 G syringe, into 100 ml of different concentration [0.5% (w/v), 1%(w/v), 5% (w/v) ,10%(w/v)] of $CaCl_2$ solution and kept for 30 min. The beads were then recovered from the $CaCl_2$ solution and washed with deionized (D.I.) water and air dried for 48 hours. Different formulations were prepared by varying the sodium alginate concentrations, corn oil concentrations and drug concentrations. The prepared formulations are given in table 1.

Table 1 Different formulations of alginate gel beads

S. No.	Formulation Code	Conc. of corn oil [(v/v) of alginate solution]	Conc. of sodium alginate [(v/v) of alginate solution]	Conc. of $CaCl_2$ solution (w/v)	Famotidine conc.[(w/v) of alginate solution]
1	F-1	0	3	0.5	0.5
2	F-2	10	3	0.5	0.5
3	F-3	20	3	0.5	0.5
4	F-4	30	3	0.5	0.5
5	F-5	40	3	0.5	0.5
6	F-6 [Not formed]	20	1	0.5	0.5
7	F-7	20	2	0.5	0.5
8	F-8	20	4	0.5	0.5
9	F-9	20	3	1	0.5
10	F-10	20	3	5	0.5
11	F-11	20	3	10	0.5
12	F-12	20	3	1	1
13	F-13	20	3	1	2
14	F-14	20	3	1	5

Characterization and Optimization of Floating Alginate Beads:

1. Morphological Analysis

Surface and cross-sectional morphologies of beads were examined with a Scanning Electron Microscope (SEM Leo 430, England)**.** Beads were mounted on metal grids using double-sided tape and gold coated under vacuum. Figure 3 and 4 reveals the surface and cross-sectional details of the calcium alginate beads with drug, respectively. Figure 3 shows beads with nearly spherical shape and a rough surface without any pore. Drug particles are seen on the surface. Figure 4 showing cross-sectional bead reveals no cavity but uniform matrix within the bead. Drug particles are also seen embedded within the matrix of the bead.

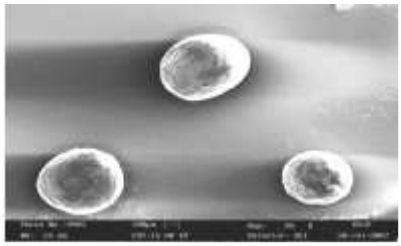

Fig 1. SEM photomicrograph of calcium alginate beads

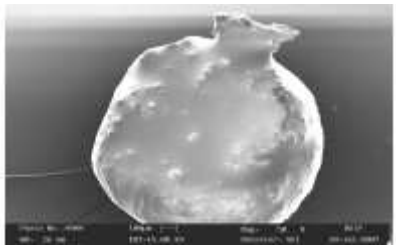

Fig 2. SEM photomicrograph of cross-sectional calcium alginate bead

2. Size analysis:

The size of the 10 prepared floating alginate beads was measured by traveling microscope (Harrison, New Delhi) with the main and vernier scale. Least count of the instrument was found to be 0.01mm.The observations were recorded in table 2.

3. Percentage Yield and Percentage Drug entrapment

Percentage Yield: % Yield for the different formulations was calculated by the formula

$$\% \text{ Yield} = \frac{\text{Total weight of floating beads produced}}{\text{Total weight of drug and polymer}} \times 100$$

Percentage Drug entrapment: 200 mg of prepared floating alginate beads of famotidine were dissolved in 50 ml of phosphate buffer saline (pH 7.4) and the drug content was analysed at 286 nm using a UV/visible spectrophotometer (Shimadzu-1700). Encapsulation efficiency was calculated as the percentage (w/w) of the theoretical drug content. Results were given in table and based on triplicate determinations.

$$\% \text{ Drug Entrapment} = \frac{\% \text{ Drug content} \times \text{amount (dried floating beads)}}{\text{Amount drug added- amount drug remaining in apparatus}}$$

Table 2 Percentage Yield, Percentage drug entrapment and average size of different formulations

S. No.	Formulation Code	% Yield	% Drug entrapment	Average size (mm)
1.	F-1	77.89	70.19	1.53
2.	F-2	79.23	68.53	1.51
3.	F-3	82.34	64.34	1.52
4.	F-4	83.56	63.67	1.49
5.	F-5	85.35	61.17	1.48
6.	F-7	81.14	62.78	1.49
7.	F-8	84.52	69.44	1.54
8.	F-9	86.67	75.63	1.53
9.	F-10	90.02	78.12	1.57
10.	F-11	94.48	80.32	1.61
11.	F-12	87.32	76.48	1.55
12.	F-13	88.78	78.32	1.53
13.	F-14	90.53	79.89	1.56

4. Buoyancy:

The floating ability was determined using USP dissolution test apparatus II (paddle method). Fifty beads were introduced in the vessels and the paddles were rotated at 100 rpm in 500 ml of simulated gastric fluid (SGF) without pepsin, maintained at 37 0.5 °C for 24 h. The floating ability of the beads was measured by visual observation. The preparation was considered to have buoyancy only when all beads floated on the test solution.[9,10] immediately or within a lag time which did not exceed 2 min and all beads remained afloat after the prescribed time period. Buoyancy of the different formulations are given in table 3.The experiment was conducted thrice. The observations were recorded in table 3 Beads are shown floating in figures 3 and 4.

Fig 3. Calcium alginate beads (F-13) floating in (SGF) without pepsin in a beaker (top view).

Fig 4. Calcium alginate beads (F-13) floating in (SGF) without pepsin in a beaker (side view).

Table3 Buoyancy of different formulations

Formulation Code	Buoyancy
F-1	Non-floating (0% float after 24 h)
F-2	Non-floating (40% float after 24 h)
F-3	Floating
F-4	Floating
F-5	Floating
F-7	Floating
F-8	Floating
F-9	Floating
F-10	Floating
F-11	Floating
F-12	Floating
F-13	Floating
F-14	Non-floating (12% float after 24 h)

Formulations F-1 with no oil incorporation and F-2 with 10% oil incorporation were found non-floating. Also, F-14 with 5% famotidine was found non-floating. So, these formulations were discarded from further characterizations.

5. Bead water uptake:

Bead water uptake in this case was presented as normalized weight gain ratio as defined below:

$$Y = m_w/m_d$$

Where,

Y is the normalized weight gain ratio,

m_w the bead weight after swelling (including water uptake), and

m_d is the initial dry bead weight[11].

Bead water uptakes of the different floating formulations are given in table 4. It is the average of the three determinations.

Table 4 Bead water uptake of different formulations

Formulation Code	Weight gain ratio
F-3	1.0614
F-4	1.0396
F-5	1.0207
F-7	1.0309
F-8	1.1167
F-9	1.0373
F-10	1.0218
F-11	1.0109
F-12	1.0802
F-13	1.1209

Leaching of oil from beads was seen in formulations F-4 and F-5 containing 30% and 40% oil, respectively. As beads of these formulations were found sticking to each other so formulations F-4 and F-5 were discarded from further characterization. Also, further formulations were prepared with 20% corn oil incorporation.

5. In vitro drug release studies:

The *in vitro* drug release studies of the different formulations (F-3, F-7, F-8, F-9, F-10, F-11, F-12 and F-13) were conducted to ensure the effect of sodium alginate concentration, calcium chloride concentration and drug loading concentration on the release of famotidine from the formulations.

The *in vitro* dissolution studies of the floating formulations were carried out using USP dissolution test apparatus II (paddle method). The paddle of USP dissolution test apparatus II, each containing an amount of beads equivalent to 10 mg famotidine, were rotated at 100 rpm in 500 ml of simulated gastric fluid (SGF) without pepsin, maintained at 37 °C 0.5 °C. An aliquot of 5 ml of the solution was withdrawn at predetermined time intervals and replaced by fresh dissolution medium. The withdrawn samples were analyzed for famotidine content spectrophotometrically at λ_{max} 266 nm. The results expressed were the mean of two experiments.

a. Effect of sodium alginate concentration

Formulations F-3, F-7 and F-8 were prepared by 3%, 2% and 4% sodium alginate concentrations (v/v of alginate solution), respectively. *In vitro* drug release study (figure 5) was performed to observe the effect of sodium alginate concentration on famotidine release.

Table 5 Cumulative % drug released from floating beads (F-3, F-7 and F-8) of different sodium alginate concentration

Time (hour)	Cumulative % drug release		
	F- 3 (3%)	F -7 (2%)	F- 8 (4%)
0.0	0.00	0.00	0.00
0.5	40.00	41.53	35.14
1.0	58.46	59.03	54.24
2.0	86.55	88.50	74.57
3.0	95.17	95.46	89.91
4.0	96.50	96.92	95.34
5.0	97.34	97.35	95.81
6.0	97.91	97.91	96.37
7.0	98.33	98.47	96.93
8.0	98.75	99.03	97.21

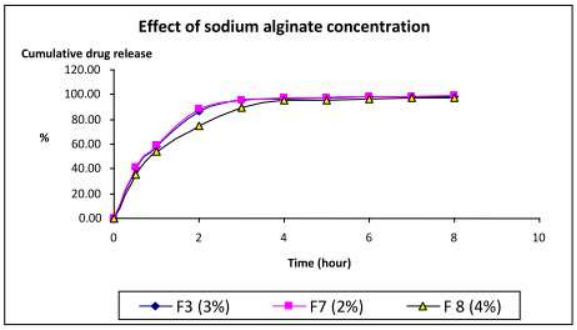

Figure 5 Famotidine release from floating beads (F-3, F-7 and F-8) of different sodium alginate concentration

Formulation F-3 prepared with 3% sodium alginate and 20% corn oil was selected and further observed for the effect of calcium chloride concentrations on drug release.

b. Effect of calcium chloride concentration

Formulations F-3, F-9, F-10 and F-11 were prepared by syringing the pre-gelation liquid in 0.5%, 1%, 5% and 10% $CaCl_2$ concentration (w/v) solutions, respectively. *In vitro* drug release study (figure) was

performed to observe the effect of calcium chloride concentration on famotidine release.

Table 6 Cumulative % drug released from floating beads (F-3, F-9, F-10 and F-11) prepared in different calcium chloride concentration

Time (hour)	Cumulative % drug release			
	F- 3 (0.5%)	F- 9 (1%)	F- 10 (5%)	F -11 (10%)
0.0	0.00	0.00	0.00	0.00
0.5	40.00	40.69	48.89	52.22
1.0	58.46	59.57	86.88	89.83
2.0	86.55	87.12	94.89	96.59
3.0	95.17	96.98	98.58	96.79
4.0	96.50	97.91	97.92	98.04
5.0	97.34	98.47	98.47	98.33
6.0	97.91	98.89	98.89	98.47
7.0	98.33	98.90	99.03	98.75
8.0	98.75	99.03	99.31	99.03

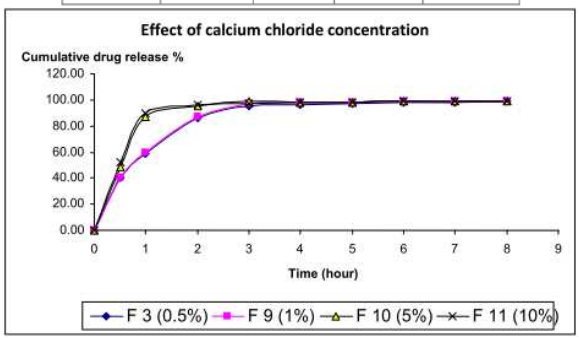

Figure 6 Famotidine release from floating beads (F-3, F-9, F-10 and F-11) prepared in different calcium chloride concentration.

Formulation F-9 prepared with 3% sodium alginate, 20% corn oil and syringing in 1% calcium chloride solution was selected and further observed for the effect of drug loading on famotidine release.

c. Effect of drug loading

Formulations F-9, F-12 and F-13 were prepared with 0.5%, 1% and 2% famotidine drug concentrations (w/v of alginate solution), respectively. *In vitro* drug release study (figure 7) was performed to observe the effect of drug loading on famotidine release.

Table 7 Cumulative % drug released from floating beads (F-9, F-12 and F-13) of different drug loadings

Time (hour)	Cumulative % drug release		
	F- 9 (0.5%)	F- 12 (1%)	F- 13 (2%)
0.0	0.00	0.00	0.00
0.5	40.69	35.00	29.58
1.0	59.57	57.29	55.57
2.0	87.12	83.63	75.83
3.0	96.98	95.69	91.45
4.0	97.91	96.50	94.10
5.0	98.47	96.93	96.49
6.0	98.89	97.35	97.34
7.0	98.90	98.05	97.77
8.0	99.03	98.61	98.33

Formulation F-13 prepared with 3% sodium alginate, 20% corn oil, 2% drug loading and syringing in 1% calcium chloride solution was selected as optimized batch based on drug release studies. But, this formulation has shown (figure 7) to release 96.49% famotidine in 5 hours.

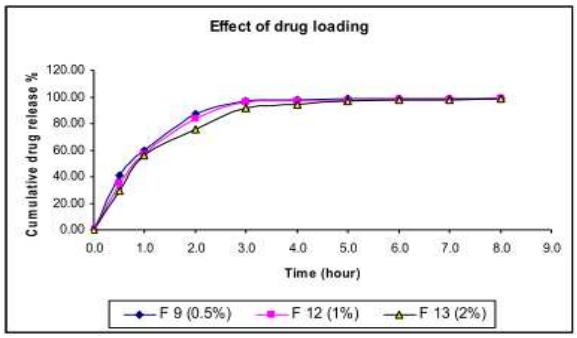

Figure 7 Famotidine release from floating beads (F-9, F-12 and F-13) of different drug loadings.

Results and Discussion:

1. Bead dimension and morphology:

Most beads were found nearly spherical in shape. There were no large differences in size between the samples with different alginate and oil concentrations or by gelation in different $CaCl_2$ concentrations. However, formulation F-14 loaded with 5% famotidine concentration was found elliptical in shape. This was due to the increased viscosity of the pre-gelation liquid with increased famotidine concentration. Also, tailing of beads were found in formulation F-8 containing 4% alginate concentration due to increase in viscosity of the pre-gelation liquid. Figure 1 and 2 reveals the surface and cross-sectional details of the calcium alginate beads with drug, respectively. Figure 1 shows beads with nearly spherical shape and a rough surface without any pore. Drug particles are seen on the surface. Figure 2 showing cross-sectional bead reveals no cavity but uniform matrix within the bead. Drug particles are also seen embedded within the matrix of the bead.

2. Encapsulation efficiency:

Encapsulation efficiency of the different prepared formulations is given in table2. Figures show the effect of corn oil concentration, sodium alginate concentration, $CaCl_2$ concentration and drug loading, respectively, on encapsulation efficiency. Encapsulation efficiency was found to be decreased with the increase in oil concentration from 0% to 40% (v/v) due to the hydrophilic nature of drug, famotidine. But encapsulation efficiency was found to be increased with the increase in sodium alginate concentration from 2% to 4% (w/v) due to the hydrophilic nature of famotidine. The drug partitions more in alginate matrix than in corn oil. Encapsulation efficiency was found to be increased with the increase in concentration of gelation ($CaCl_2$) solution from 0.5% to 10% (w/v). There was an abrupt rise in value of encapsulation efficiency from 64.34% to 75.63% in formulation F-3 to F-9 on increase in concentration of gelation liquid from 0.5% to 1% (w/v) than 1% to 10% (w/v). The reason for this is still unclear. Encapsulation efficiency was found to be increased with the increase in drug loading from 0.5% to 5% (w/v).

3. Buoyancy :

Table 3 shows how the oil loadings affect the buoyancy of the alginate beads. All non-oily beads failed the buoyancy test as several specimens began sedimentation either upon contact with the SGF or soon after agitation started. Only 40% beads of formulation F-2 containing 10% corn oil was found

to float for 24 hours. As the oil concentration was increased from 20%, 30% or 40%, all beads were found floating for 24 hours. But leaching of oil from beads was seen in formulations F-4 and F-5 containing 30% and 40% oil, respectively. So, 20 % oil was incorporated in rest of the formulations. There was no effect of the increase in alginate concentration from 2% to 4% or increase in $CaCl_2$ concentration from 0.5% to 10% on the buoyancy of the beads.

Drug loading was found to impair buoyancy as only 12% beads of formulations F-14 containing 5% famotidine was found to float after 24 hours. Therefore, the results show that the buoyancy decreased for the beads with less oil inclusion or more drug incorporation. All the floating formulations immediately float as soon as they were put in the SGF. Therefore, no lag time in floatation was seen.

Emulsification of corn oil in the alginate solution and fast gelation encapsulation of the oil with the alginate gel matrices resulted in a large number of tiny oil pockets either on the gel bead surface or deep within the bead matrices. This was the reason for the beads buoyancy. The oil pockets spread evenly over the surface and in the kernel so leakage of a certain number of these tiny compartments would not necessarily result in a failure of the referred gel bead. This feature thus increases the margin of safety against premature sedimentation.

4. Bead water uptake

In general, the beads achieved relatively low degrees of swelling, probably because the ionization of –COOH in alginate hydrogel was suppressed in acidic pH. Oil encapsulation inhibits bead water uptake (figure) as equilibrium weight gains of beads of the same crosslink density decreases with increasing initial oil concentration. Famotidine incorporation seemed to have made the beads more hydrophilic compared with beads that contain less drugs and the equilibrium weight gain increased (figure) with more famotidine. This was possibly due to the increased osmotic pressure caused by the hydrophilic famotidine incorporation. As the sodium alginate concentration increased from 2% to 4% (figure), equilibrium weight gain ratio increased because the crosslink density of the beads increased with increase in alginate concentration.

5. Drug release studies:

The release profile (figure 5, 6, 7) shows that famotidine releases from uncoated beads in a considerable “burst” during the first 30 min, due to rapid water ingress and creation of aqueous channels for the niacinamide to permeate out. Figure 5 shows the effect of sodium alginate concentration increased from 2 to 4%, famotidine was released in a slow manner. But due to the tailing of the beads (as earlier stated) in formulation F-8 containing 4% alginate, further formulations are prepared in 3% alginate concentrations.

Figure 6 shows the effect of $CaCl_2$ concentrations on famotidine release. As the concentration of CaCl2 increased (0.5%, 1%, 5%, 10%) in formulations (F-3, F-9, F-10, F-11, respectively), the famotidine was found to be released rapidly. The reason for the result is still unclear. The formulation F-9 prepared in 1% $CaCl_2$ solution released famotidine faster than the formulation F-3 prepared in 0.5% $CaCl_2$ solution but the encapsulation efficiency of formulation F-9 was much higher than the formulation F-3 so further formulations were prepared by gelation in 1% $CaCl_2$ solution.

Figure 7 shows the effect of drug loading on drug release. Formulation F-13 was found to release drug in a sustained manner than formulation F-12 and formulation F-9. The release profiles seemed dependent on the initial drug concentration C_0. Higher drug loadings achieved longer and sustained release. If less drug is loaded as in formulation F-9 (0.5% famotidine), the excessive drug particles were exposed and there would have been a considerable burst effect, considering fast water infiltration into the porous alginate matrix. Wherever, if drug loading is increased as in formulation F-13 containing 2% famotidine, drug particles were exposed to comparatively less amount of water so water infiltration into m^{th} porous alginate matrix decreased.

It is clearly seen that famotidine releases from uncoated beads in a considerable “burst” during the first 30 min, due to rapid water ingress and creation of aqueous channels for the niacinamide to permeate out.

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