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Formulation development and characterization of alginate beads of ranitidine hydrochloride

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ABSTRACT

The objective of this investigation is to develop a multi-unit gastroretentive sustained release dosage form of a water soluble drug, Ranitidine hydrochloride, from a completely aqueous environment avoiding the use of any organic solvent, which could cure peptic ulcer more efficiently by releasing the drug especially in stomach and also for a prolonged duration of time. A new emulsion gelation technique was used to prepare emulsion gel beads using sodium alginate as a polymer. The gel beads containing oil was prepared by gently mixing or homogenizing oil and water phase containing sodium alginate which was then extruded in to calcium chloride solution. The effects of factors like concentration of oil, curing time, drug: polymer ratio, alginate: pectin ratio and curing agent on drug entrapment efficiency, floating lag time, morphology and drug release were studied. Minimizing the curing time of beads leaded to enhanced drug entrapment efficiency. The use of sodium alginate and combinations of sodium alginate and pectin were used to study the effect on the sustaining property of the formed beads. It was found that sodium alginate was not sufficient to sustain the drug release at gastric pH. Instead of it, appropriate combination of alginate and pectin could provide the sustain release of drug. The results show that these beads can entrap even a water soluble drug as Ranitidine hydrochloride in sufficient amount and also can successfully deliver the drug in stomach for a prolong duration of time without using any organic solvent and any time consuming step in the preparation.

Keywords: Floating Beads, Ranitidine hydrochloride, Floating Drug Delivery

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INTRODUCTION

A drug that is released from a dosage form in a controlled manner in the stomach will empty together with fluids and will have the whole surface area of the small intestine available for absorption [1]. These considerations have lead to the development of oral controlled gastro retentive dosage forms possessing gastric retention capabilities. Thus Gastroretentive dosage forms, i.e. those designed to exhibit a prolonged gastric residence time (GRT), have been a topic of interest in terms of their potential for controlled drug delivery [2,3,4,5]. Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs [6,7]. Such retention systems are important for drugs that are degraded in the intestine or for drugs like antacids or certain antibiotics, enzymes that should act locally in the stomach [8]. If drug is poorly soluble in intestine due to alkaline pH and then its retention in gastric region may increase the solubility before they are emptied, resulting in increased bioavailability [9]. Such systems are more advantageous in improving G.I. absorption of drugs with narrow absorption windows as well as for controlled release of the drugs having site-specific absorption limitation. Retention of drug delivery system in stomach prolongs over all G.I. transit time, thereby resulting in improved bioavailability for some drugs [6,10] The patient always wants to minimize the frequency of dosing without compromising the therapeutic benefit. Use of sustained release dosage forms can fulfill this requirement .Ranitidine hydrochloride is an antiulcer drug and works on H2-receptor mainly in stomach. The primary absorption region of this drug is stomach. Since it is an antiulcer drug, it will be beneficial to retain the drug in gastric region. The halflife

of RHCL is approximately 2.1 hr and the dose of drug is also low which make it a suitable candidate for sustained release dosage form. By retaining it in stomach and by sustaining its release, the absorption of drug and its efficacy can be enhanced. Formulation of RHCl as a sustained release dosage form can also minimize the loss of drug in comparison of conventional tablets. The design of gastroretentive drug delivery systems depends upon physicochemical properties, dose and purpose of controlling the drug release, constraining pathophysiological factors. Various approaches have been pursued including low density dosage form that remains buoyant above gastric fluid or high density dosage form that is retained at the bottom of the stomach, imparting bioadhession to the stomach mucosa, utilizing ion-exchange resin which adheres to mucosa, expending the dosage form by swelling or unfolding to a large size which limits emptying of dosage form through pyloric sphincter, using modified shape system, or other effervescent systems using a gas generating material like sodium bicarbonate and calcium carbonate or the same with citric acid [11-16]. Preparation of floating alginate beads is more suitable because it is a multiparticulate system, utilizes cheap and nontoxic polymers and there is no use of any organic solvent. These beads having a sustained release composition and formulation of ranitidine hydrochloride capable of providing release drug release over 12 hr was formulated using expandable, gelling, swellable, hydrocolloid polymer along with light liquid paraffin. Sodium alginate has been used as thickening and gelling agent. Additionally it also reduces interfacial tension between an oil and water phase and is efficient for preparation of emulsion. Alginate is a linear co-polymer composed of two monomeric units. D-mannuronic acid and L-guluronic acid. They occur in alginate molecule as regions made up exclusively of one unit or the other referred to M block or G block or as a region in which monomer approximates an alternating sequence. Gels form when a calcium salt is added to a solution of sodium alginate in water. The gel forms by chemical reaction, the calcium displaces the sodium from the alginate, holds the long alginate molecules together and a gel is the result [17,18,19]. No heat is required and the gels do not melt when heated. The polyguluronate block of alginate is known to be responsible for this gelling feature [20]. Pectin was also used in combination with alginate to study its effect on different parameters. It is a complex polysaccharide comprising mainly esterified D-galacturonic acid residues in an α-(1–4) chain. The acid groups along the chain are largely esterified with methoxy groups in the natural product. The USP 28 describes pectin as a purified carbohydrate product obtained from the dilute acid extract of the inner portion of the rind of citrus fruits or from apple pomace. It is also gelled when react with calcium ion.

MATERIAL AND METHODS

MATERIALS

Ranitidine hydrochloride, Sodium alginate, HPMC K100 M, Calcium chloride, Hydrochloric acid, Hydrochloric acid, Sunflower Oil, UV/Visible spectrophotometer, Electronic balance, Digital pH meter, Dissolution apparatus, Magnetic Stirrer, Homogenizer, Hot air oven and Desiccators.

PREPARATION AND OPTIMIZATION OF ALGINATE GEL BEADS

All alginate gel beads were prepared following the emulsion gelation procedure. A pre-gelation liquid was prepared by mixing sodium alginate solution and HPMC K100M by dissolving in water with stirring. Sunflower oil was added to the polymer solution followed by drug. Twenty millilitres of each of the pre-gelation liquid was then added, through a 26 G syringe (0.8 mm diameter, into 100 ml of different concentration [1 %(w/v), 2% (w/v)] of $CaCl_2$ solution dropped from 5 cm dropping at the rate of 2 ml/min. and kept for 20 min. The beads were then recovered from the $CaCl_2$ solution and washed with distilled water and air dried. Different formulations were prepared by varying the sodium alginate concentrations, sunflower oil concentrations and drug concentrations. The prepared formulations are given in Table1.

Table1: Different formulations of alginate gel beads

Sr. No.	Formulation Code	Amount of Ranitidine HCl (mg)	Amount of HPMC K100M (mg)	Amount of Sodium alginate	Amount of Calcium chloride	Amount of Sunflower oil (ml)
1	F1	300	250	1%	1%	0.5
2	F2	300	250	2%	1%	0.5
3	F3	300	250	3%	1%	0.5
4	F4	300	250	1%	2%	0.5
5	F5	300	250	2%	2%	0.5
6	F6	300	250	3%	2%	0.5
7	F7	300	250	1%	3%	0.5
8	F8	300	250	2%	3%	0.5
9	F9	300	250	3%	3%	0.5

CHARACTERIZATION OF FLOATING ALGINATE BEADS

Physical Appearance and Morphological Analysis

All the batches of Ranitidine HCl beads were studied for colour and physical appearance. 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 coated with gold under vacuum.

Size Analysis

The size of the 10 prepared floating alginate beads was measured by occular microscope. Least count of the instrument was found to be 0.01mm.

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 50 rpm in 500 ml of 0.1 N HCl, maintained at 37±0.5 °C for 10 hr. The floating ability of the beads was observed visually. The preparation was considered to have buoyancy only when all beads floated on the test solution for the prescribed time period. The experiment was conducted thrice.

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. Weight gain ratio at equilibrium, Y of different floated formulations is the average of three determinations.

% Yield and % Drug Entrapment

% Yield

% Yield for the different formulations was calculated by the formula given below.

% Yield =Total weight of floating beads produced × 100 / Total weight of drug and polymer

% Drug entrapment

30 mg of prepared floating alginate beads of Ranitidine were dissolved in 50 ml of SGF (pH 1.2) and the drug content was analyzed at 313.5 nm using a UV/visible spectrophotometer (Shimadzu-1700). Encapsulation efficiency was calculated as the percentage (w/w) of the theoretical drug content.

% Drug Entrapment = (Actual drug content / Theoretical drug content) x 100

In Vitro Drug Release Studies

The *in vitro* drug release studies of different formulations (F-3, F-6, and F-9) were conducted to ensure the effect of sodium alginate concentration, calcium chloride concentration and drug loading concentration on the release of Ranitidine HCl from the formulations. The *in vitro* dissolution studies of the floating formulations were carried out using USP dissolution test apparatus I (basket method). The basket of USP dissolution test apparatus I, each containing an amount of beads equivalent to 300 mg Ranitidine HCl, were rotated at 100 rpm in 900 ml of simulated gastric fluid (SGF) without pepsin, maintained at 37 °C±0.5 °C. An aliquot of 10 ml of the solution was withdrawn at predetermined time intervals and replaced by fresh dissolution medium. The withdrawn samples were analyzed for Ranitidine content spectrophotometrically at λmax 313.5 nm.

Table 2: Value of 'n' and corresponding mechanism of drug release

Value of 'n'	Mechanism of drug release
n = 0.5	Case – I (Fickion) diffusion or square root of time kinetics
0.5 < n < 1	Anomalous (non-Fickion) diffusion
n = 1	Case – II transport
n > 1	Super Case – II transport (Costa and Mannual, 2001)

RESULTS AND DISCUSSION

PREPARATION AND OPTIMIZATION OF ALGINATE GEL BEADS

Nine formulations were prepared with the optimization of sodium alginate concentration, sunflower oil and calcium chloride. The variations of calcium chloride and sodium alginate were 1%, 2% and 3% with varying combinations. Also Oil concentration is changed to 0.5 and 1mL. The drug loading and HPMC K100M concentration was constant in each formulation.

CHARACTERIZATION OF FLOATING ALGINATE BEADS

Physical Appearance and Morphological Analysis

Physical appearance of various formulations of Ranitidine beads by using different carrier (in different ratio) was given in (Table 3).

Table 3: Physical appearance of Ranitidine HCl beads

Formulation Code	Physical Appearance	
	Colour	Appearance
F-1	Creamy white	Oval
F-2	Creamy white	Round
F-3	Creamy white	Round
F-4	Creamy white	Oval
F-5	Creamy white	Oval
F-6	Creamy white	Round
F-7	Creamy white	Oval
F-8	Creamy white	Round
F-9	Creamy white	Round

Size Analysis

The size analysis was done by Occulometer and the average size for each formulation was found out as shown on Table 4.

Table 4: Average size of different formulations

S. No.	Formulation Code	Average size (mm)± SD
1	F-1	1.536±0.056
2	F-2	1.512±0.039
3	F-3	1.527±0.045
4	F-4	1.491±0.068
5	F-5	1.483±0.073
6	F-6	1.493±0.038
7	F-7	1.543±0.051
8	F-8	1.531±0.069
9	F-9	1.574±0.047

Buoyancy

The buoyancy of each of the nine formulations were found out and the maximum floating time found was of formation F-6 and F-9, since the oil was in optimized concentration and sodium alginate concentration was more, which binds water. Both the constituents help in maximum floating time. Formulations F-7 and F-8 with less oil and varying concentrations of sodium alginate and calcium chloride. So, these formulations were discarded from further characterizations.

Table 5: Buoyancy of different formulations

S. No.	Formulation Code	Buoyancy	Floating time (hrs)
1	F-1	Floating	7
2	F-2	Floating	8
3	F-3	Floating	9
4	F-4	Floating	8
5	F-5	Floating	6
6	F-6	Floating	10
7	F-7	Non-floating	-
8	F-8	Non-floating	-
9	F-9	Floating	10

Bead water uptake

Weight of bead was taken before and after putting in SGF, the weight gained showed which formulation shows sticking and leaching of oil, thus the stability of formulation can be found out.

Leaching of oil from beads was seen in formulations F-1, F-4 and F-5 containing 1% and 0.5% oil, respectively. As beads of these formulations were found sticking to each other so formulations were discarded from further characterization. Also, further formulations were prepared with 0.5% sunflower oil incorporation only.

Table 6: Bead water uptake of different formulations

S. No.	Formulation Code	Weight gain ratio at equilibrium, Y ± SD
1	F-1	1.0207±0.009
2	F-2	1.0302±0.019
3	F-3	1.0309±0.022
4	F-4	1.0373±0.014
5	F-5	1.0396±0.012
6	F-6	1.0614±0.023
7	F-9	1.1167±0.018

Drug content uniformity studies and % practical yield

Drug content is found to be between 85.79 % and 96.75 %. All the formulations show presence of high drug content and low standard deviations of results. It indicates that the drug is uniformly dispersed in the formulations. Therefore, the method used in this study appears to be reproducible for the preparation of beads.

Table 7: Drug content uniformity studies and percentage practical yield of Ranitidine beads

Formulation Code	Drug Content uniformity %				% Practical Yield
	1st	2nd	3rd	Mean ± SD	
F-2	92.62	92.37	92.12	92.57 ± 0.25	85.63
F-3	85.75	86.37	85.25	85.79 ± 0.56	28.11
F-6	96.75	97.0	96.5	96.75 ± 0.25	29.33
F-9	91.25	91.75	91.37	91.45 ± 0.26	31.24

Table 8: % Yield and % drug entrapment of different formulations

S. No.	Formulation Code	% Drug loading	% Drug entrapment± SD
1	F-2	85.63	97.62±1.99
2	F-3	28.11	87.66±3.21
3	F-6	29.33	97.99±3.36
4	F-9	31.24	75.97±2.23

Fig 1: *In Vitro* Drug Release Studies

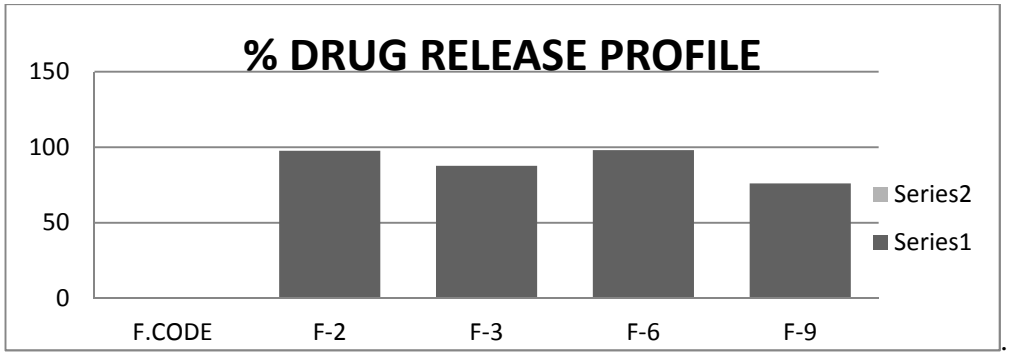

Fig 2: SEM F3

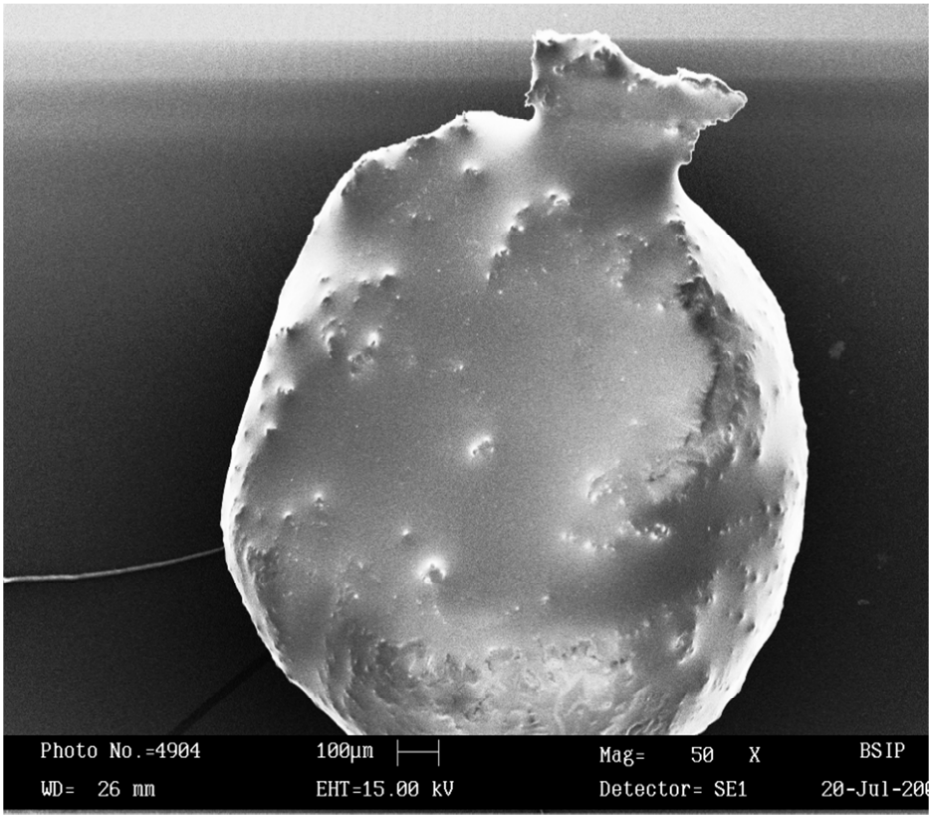

Fig 3: SEM F6

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