Research Article

FORMULATION AND EVALUATION OF GASTRORETENTIVE BEADS OF RANITIDINE HYDROCHLORIDE

RAJKUMAR PATEL, RITESH S. BATHE*, DEEPAK KHOBRAGADE, SACHIN JADHAV

Dept. of Pharmaceutics, Sahyadri College of Pharmacy, Methwade, Sangola, Dept. of Pharmaceutics, NRI Institute of Pharmacy, Bhopal, Dept. of Pharmaceutics, Bharat School of Pharmacy, Hydrabad. Email: riteshbathe@gmail.com

ABSTRACT

The gastro retentive system can remain in gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Objective of this study was to develop an intra gastric multi unit floating drug delivery system of RHCl and also attempts were made to sustain the release of RHCl. This could cure peptic ulcer more efficiently by releasing the drug especially in stomach and also for a prolonged duration of time. The emulsion gelation method was used and calcium chloride was used for entrapment. Drug identification test for RHCl were carried which includes physical appearance, melting point, and FT-IR identification. The melting range of RHCl was 69 – 70 $^{\circ}$C which is in conformity with reported literature. IR spectra of RHCl showed all the characteristic peaks of RHCl. The results of drug identification tests confirm the purity of the procured sample of RHCl. The FT-IR of RHCl, sodium alginate and HPMC showed compatibility. The partition coefficient showed the drug is hydrophilic. UV scan, linearity range and validation (interday and intraday precision) were done. The R^2 value was found to be 0.9997. The formulation is based on change in ratio of polymers and sunflower oil. The evaluation was based on size analysis, buoyancy, bead water uptake, %yield, %drug loading, *In Vitro* tests, and statistical analysis. The final batch found was F-6, which has drug 300mg, sodium alginate 3%, HPMC 300mg, Sunflower oil 0.5ml, and Calcium chloride 2%. It showed a bouncy of 10hrs and *In Vitro* release of 94.8%.

Keywords: Floating, Ranitidine hydrochloride, Beads, SEM.

INTRODUCTION

Oral controlled release (CR) formulations have been developed in an attempt to release the drug slowly into the GIT and maintain a constant drug concentration in the serum for longer period of time. Such oral drug delivery devices have a restriction due to the gastric retention time (GRT), a physiological limitation. Approaches to increase the GRT include: (i) Bioadhesive delivery systems, ii) Swellable delivery systems and (iii) Density-controlled delivery systems, which either float or sink in gastric fluids. The floating system is intended to float in and over the gastric contents resulting in prolonged GRT [1]. Furthermore, as the total gastrointestinal transit time of the dosage form is increased by prolonging the gastric residence time; these systems can also be used as sustained release devices with a reduced frequency of administration and therefore, improved patient compliance. Unfortunately, floating devices administered in a single-unit form such as hydrodynamically balanced systems (HBS) are unreliable in prolonging the GRT owing to their 'all-or none' emptying process and, thus, they may cause high variability in bioavailability and local irritation due to a large amount of drug delivered at a particular site of GIT. In contrast, multiple-unit particulate dosage forms (e.g. microspheres, gel beads) have the advantages that they pass uniformly through the GIT to avoid the vagaries of gastric emptying and provide an adjustable release, thereby, reducing the inter subject variability in absorption and risk of local irritation. Various types of drug delivery systems for oral administration such as drug release rate-controlled delivery systems, time-controlled delivery systems and site-specific delivery systems have been extensively developed. Controlled-release drug delivery systems (CRDDS) provide drug release at a predetermined, predictable, and controlled rate. An important requisite for the successful performance of oral CRDDS is that the drug should have good absorption throughout the gastrointestinal tract (GIT), preferably by passive diffusion, to ensure continuous absorption of the released drug. The average time required for a dosage unit to traverse the GIT is 3–4 h, although slight variations exist among various dosage forms. Certain types of drugs can benefit from using gastro retentive devices. These include: Drugs acting locally in the stomach, Drugs that are primarily absorbed in the stomach, Drugs those are poorly soluble at an alkaline pH, Drugs with a narrow window of absorption, Drugs absorbed rapidly from the GI tract, Drugs that degrade in the colon. Thus, when a drug possesses a narrow 'absorption window, design of the controlled release preparation requires both prolongation of gastrointestinal transit of the dosage form and controlled drug release. The prolongation of gastric residence time (GRT) is expected to maximize drug absorption from Floating Drug Delivery Systems (FDDS) due to increased dissolution of drug and longer residence at the most favorable sites of absorption. It is evident from the recent scientific and patent literature that an increased interest in novel dosage forms that are retained in stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time. Gastro retentive Dosage Forms (GRDFs) will provide us with new and important therapeutic options. Thus control of placement of a DDS in a specific region of the GI tract offers numerous advantages, especially for drug exhibiting an 'absorption window' in the GI tract [2]. The intimate contact of the DDS with the absorbing membrane and also the potential to maximize drug absorption may influence the rate of drug absorption. These considerations have led to the development of oral controlled release (CR) dosage forms possessing gastric retention capabilities. Drug may not be absorbed uniformly over the length of the gastrointestinal tract, because dosage form may be rapidly transported from more absorptive upper regions of the intestine to lower regions where the drug is less absorbed and drug absorption from colon is usually erratic and inefficient. Moreover, certain drugs are absorbed only from the stomach or the upper part of small intestine [3].The rate of drug absorption may not be constant in spite of the drug delivery system delivering the drug at constant rate into the gastrointestinal fluids. The drug is absorbed only from specific regions of the stomach or upper parts of the small intestine in case when the drug has a clear cut "absorption window". Absorption windows in the proximal gut can limit the bioavailability of orally administered compounds and can be a major obstacle to the development of CDDS. It is apparent that for a drug having such an absorption window, an effective oral controlled drug delivery system should be designed not only to deliver the drug at a controlled rate, but also to retain the drug in the upper parts of the gastrointestinal tract for a long period of time. The real issue in the development of oral controlled release dosage forms is not just to prolong the delivery of drugs for more than 12 hrs but also to prolong the presence of dosage forms in the stomach or somewhere in the upper part of small intestine [4].

Sodium alginate gel beads have been developed in recent years as a unique vehicle for drug delivery system. Various categories of drug have been encapsulated such as nonsteroidal anti-inflammatory drugs, enzymes, peptides/proteins, and acid labile drugs[5]. Ranitidine was selected as a model drug for incorporation in sodium alginate beads. Ranitidine, is a antihistaminic, H2 selective drug competitively inhibits the action of histamine on the H2 receptors of parietal cells, reducing gastric acid secretion and concentration under daytime and nocturnal basal conditions and also when stimulated by food, histamine, or pentagastrin[6]. The beads were evaluated with respect to micromeretic properties, floating property, drug content, entrapment and encapsulation efficiency, in vitro drug release.

In the present investigation, a controlled release formulation of Ranitidine capable of providing detectable blood levels over 10 hr was formulated using expandable and swellable hydrocolloid polymer along with the sunflower oil [7]. The polymer used was HPMC K100M. 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. Hydroxypropylmethylcellulose (K100M) was used to achieve a controlled drug release [8, 9]

MATERIAL AND METHODS

Materials

Sunflower Oil, hydroxypropylmethylcellulose (K100M) and calcium chloride were obtained from Peekay scientific center Bhopal. Ranitidine and Sodium alginate was donated by Alpha Pharmaceutical Ltd. Indore. All other chemicals used were of analytical grade.

Pre-formulation of Ranitidine Hydrochloride

Pre-formulation studies for the selected drug Ranitidine HCl include, test for identification, examination of physical appearance, melting point determination, IR spectroscopy (Figure 1), solubility studies and determination of partition coefficient.
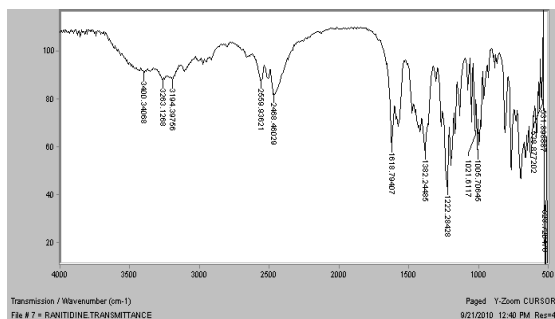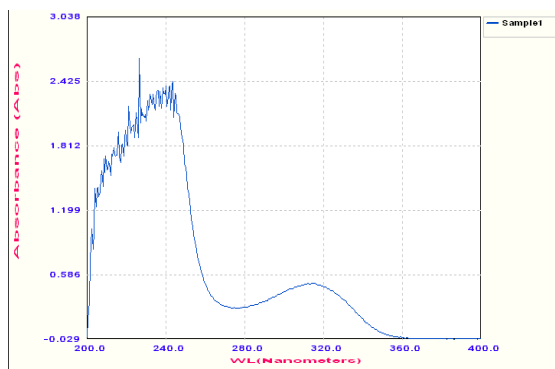

Fig.1: FT-IR Spectra of Ranitidine HCl

Fig.2: UV absorption spectra of Ranitidine HCl in SGF

Quantitative estimation of drugs

UV spectrophotometric method was used to estimate the drug concentration in simulated gastric fluid (SGF -pH 1.2)

Preparation of SGF (Simulated Gastric Fluid) without Pepsin: 2 g of NaCl was dissolved in 7 ml of HCl and sufficient water to make 1000 ml. This test solution was checked for a pH of about 1.2.

Determination of Absorption Maximum (λmax) in SGF: Absorption maximum was determined by dissolving 10mg of Ranitidine HCl in 5 ml of SGF and then volume was made up to 100 ml with SGF[10]. From this stock solution, 1 ml solution was added to the 10 ml of volumetric flask and volume was made up to 10 ml with solution of SGF. The solution was scanned in the range of 200 – 400 nm in the Shimadzu- 1700 UV/Visible spectrophotometer. The scan was recorded in Figure 2.

Preparation of Standard calibration Curve: 10 mg accurately weighed Ranitidine HCl was dissolved in the 5ml SGF and volume was made up to 100 ml in volumetric flask with SGF. From this stock solution different dilutions were prepared in the concentration range of 20, 40, 60, 80 and 100 μg/ml in 10 ml volumetric flask and absorbance was taken at 313.5 nm. Standard curve was prepared by the observations recorded in Table 3.3 and seen in Figure 3.
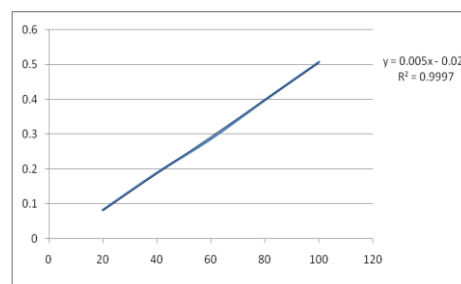

Fig. 3: Calibration curve of Ranitidine HCl in SGF

Validation of Calibration curve

Validation of calibration curve of Ranitidine HCl conducted in SGF (pH 1.2), for three days for interday and intraday variation (Table, Figure 4, 5).
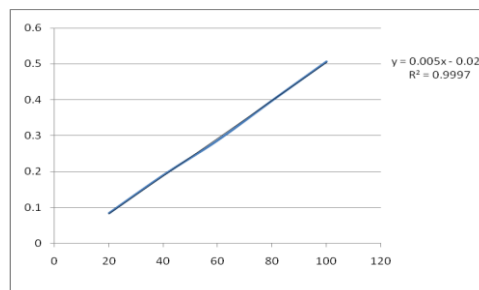

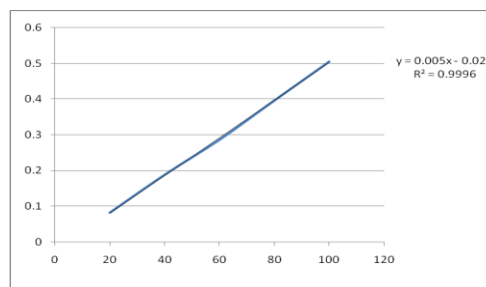**Fig. 4: Interday Calibration curve of Ranitidine HCl in SGF**

Fig. 5: Intraday Calibration curve of Ranitidine HCl in SGF

Compatibility studies

IR studies were done with drug and various polymers in the ratio of 1:1 and then by the interpretation compatibility studies are done.

Formulation of Ranitidine floating 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 milliliters 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 CaCl2 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 CaCl2 solution and washed with deionized (D.I.) water and air dried for 48 hours. Different formulations were prepared by varying the sodium alginate concentrations, sunflower 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	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%	1
2	F2	300	250	2%	1%	0.5
3	F3	300	250	3%	1%	1
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

Process variables and process optimization

To investigate the contribution of formulation variables on the release profile of Ranitidine from alginate beads, the different batches were produced and analyzed for size, shape, ease of preparation, drug loading, entrapment efficiency, buoyancy and drug release. The formulation parameters investigated are concentration of sodium alginate, concentration of calcium chloride, amount of sunflower oil, % entrapment efficiency, % drug loading and buoyancy.

RESULTS

Physical Appearance and Morphological Analysis

All the batches of Ranitidine HCl beads were studied for color 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 ocular microscope. Least count of the instrument was found to be 0.01mm.

SEM of floating beads

Morphological characterization of the floating alginate beads of Ranitidine was done by taking scanning electron micrograph (Model Jeol JSM-5200). Cross-sectional views were obtained by cutting the bead with a razor blade. The samples were coated to 200 Aº thickness with gold- palladium prior to microscopy. A working distance of 20 nm, a tilt of 0º and accelerating voltage of 15 KV were the operating parameters. Photographs were taken within the range of 20- 500 magnifications (Figure 6).
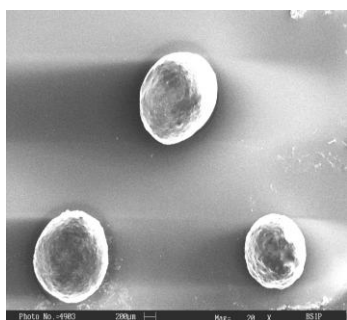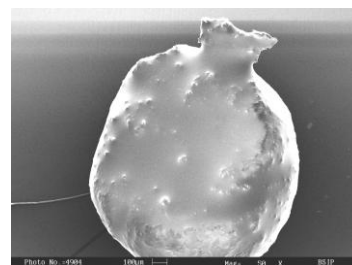

Fig.6a

Fig. 6b

Fig. 6: a) SEM photomicrograph of alginate beads (F-6) b) SEM photomicrograph of cross-sectioned alginate bead (F-6)

Buoyancy

The floating ability was determined using USP dissolution test apparatus I (basket method). Fifty beads were introduced in the vessels and the baskets were rotated at 100 rpm in 900 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 (Table 2).

Table 2: 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

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

$$Y = mw/md$$

Where Y is the normalized weight gain ratio, mw the bead weight after swelling (including water uptake), and md is the initial dry bead weight. Weight gain ratio at equilibrium, Y of different floated formulations is the average of three determinations (Table 3, Figure 7, 8).
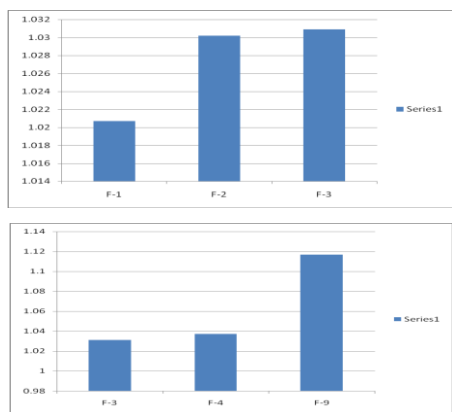
Fig. 7& 8: Bead water uptake of different formulations

% 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 (Table 4).

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

Table 3: Drug content uniformity studies and percentage practical yield of Ranitidine beads

S. No.	Formulation Code	Drug Content uniformity %				% Drug loading	% Drug entrapment± SD
		1st	2nd	3rd	Mean ± SD		
1	F-2	92.62	92.37	92.12	92.57 ± 0.25	85.63	97.62±1.99
2	F-3	85.75	86.37	85.25	85.79 ± 0.56	28.11	87.66±3.21
3	F-6	96.75	97.0	96.5	96.75 ± 0.25	29.33	97.99±3.36
4	F-9	91.25	91.75	91.37	91.45 ± 0.26	31.24	75.97±2.23

Table 4: Cumulative % drug released from floating beads (F-3, F-6 and F-9) prepared in different calcium chloride concentration

Time (hr)	Cumulative % drug released ± SD		
	F- 3	F- 6	F- 9
0.5	42.1±0.15	25.8±0.43	25.8±0.34
1.0	50.9±0.15	42.5±0.40	42.5±0.20
2.0	59.8±0.11	55.6±0.23	64.1±0.56
3.0	61.2±0.20	64.5±0.11	75.8±0.34
4.0	63.3±0.26	72.3±0.20	78.7±0.40
5.0	72.1±0.30	78.5±0.20	80.5±0.30
6.0	82.3±0.41	86.9±0.40	86.9±0.25
7.0	89.1±0.36	91.7±0.26	87.3±0.32
8.0	96.8±0.30	92.3±0.27	88.2±0.43

Table 5: Kinetic data of Ranitidine beads

Formulation code	Zero order R^2	First order R^2	Higuchi R^2	Peppas R^2
F-3	0.967	0.885	0.959	0.937
F-6	0.879	0.986	0.964	0.975
F-9	0.745	0.934	0.875	0.916

Table 6: One way ANOVA (t_{50} %) followed by Post hoc Tukey's test

Source of variation	Degree of freedom	Sum of square	Mean sum of square	F Ratio	Significant
Between treatment	2	4.44	2.22	0.0025	Highly significant
Within treatment	15	13240.425	882.695	-	-
Total	17	13244.865	-	-	-

Table 7: Post hoc Tukeys HSD Value

F-3 Vs. F-6	F-6 Vs. F-9	F-9 Vs. F-3
0.0082	0.0906	0.0824

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 [11, 12]. The withdrawn samples were analyzed for Ranitidine content spectro-photo metrically at λmax 313.5 nm.

Statistical analysis for *In Vitro* release at time 5 hour of Ranitidine floating beads

It is clearly evident that the dissolution of Ranitidine Floating beads is clearly higher of formulation F-6. But to find its statistical significance we have performed the one way ANOVA analysis followed by tukeys post hoc test to evaluate the effect of different treatments i.e. formulations F-3, F-6 and F-9 (Table 6, 7, 8 and Figure 10-13).
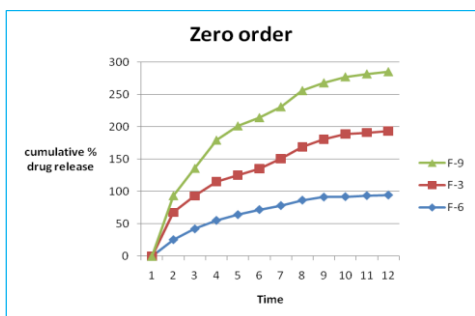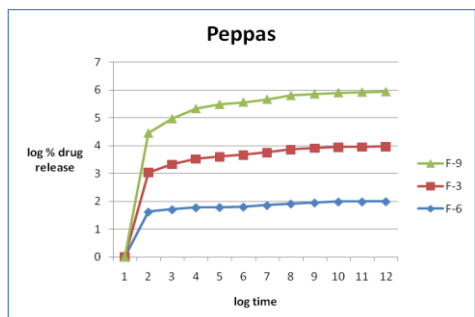

Fig. 9: Cumulative % drug release

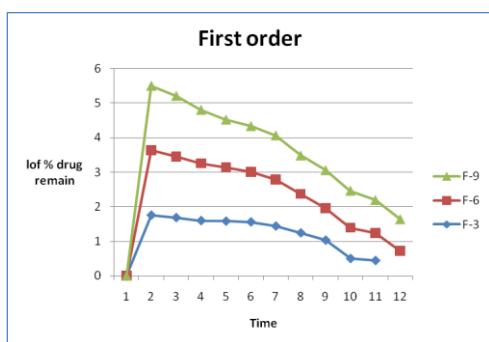**Fig. 10: Peppas exponential plot of Ranitidine from F3, F6 and F9.**

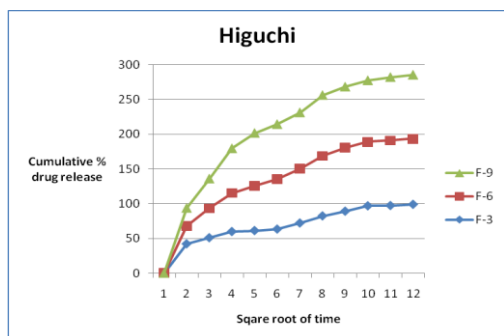**Fig. 11: First order plot of Ranitidine from F3, F6 and F9.**

Fig. 12: Higuchi diffusion plot of Ranitidine from F3, F6 and F9.

DISCUSSION

The floating beads of Ranitidine were prepared by emulsion-gelation method and influence of amount of sunflower oil on floating property and particle size of the beads, as well as concentration of hydroxypropylmethylcellulose (K100M) and Sodium alginate on the release profile of Ranitidine from floating alginate beads was studied.

Pre-formulation studies for the selected drug Ranitidine HCl were conducted. The Physical appearance and melting point of drug were found to be concordant with that mentioned in USP, 29 and Clarke's Analysis of Drugs and Poisons, 2006 respectively which shows purity of the sample. IR spectrum of the drug sample confirmed its identity. The drug was found to be soluble in distill water, dimethylformamide, glacial acetic acid, and SGF without pepsin. The partition coefficient value (Log Po/w) of ranitidine was found to be 0.3 in n-octanol: water indicating hydrophilic nature of drug. The standard curves of drug were prepared in SGF (Simulated gastric fluid) without pepsin in the concentration range of 20-100 µg/ml. A straight line with $R^2 = 0.9997$ for SGF (Simulated gastric fluid) without pepsin was found indicating that the drug follows Beer's law within the specified concentration range.

All floating alginate gel beads were prepared following the same gelation procedure. A pre-gelation liquid was prepared by mixing sodium alginate solution, the prescribed amount of sunflower oil, and the drug, Ranitidine HCl. The pre-gelation liquid was then added, through a 26 G syringe, into $CaCl_2$ solution to form the beads which were filtered and air dried. Different formulations were prepared by varying the sunflower oil concentration, sodium alginate concentration, Ranitidine concentration and concentration of $CaCl_2$ solution. All prepared formulations were characterized and optimized based on morphological analysis, size analysis, % yield, % drug entrapment, buoyancy, bead water uptake and in vitro drug release studies.

SEM photomicrograph shows beads with nearly spherical shape and a rough surface without any pore. Drug particles were seen on the surface as well as embedded within the matrix of the bead.

The % Yield of prepared formulations was found to be between 28.11 to 85.63%. Encapsulation efficiency was found to decrease with the increase in oil concentration from 0.5% to 1% (v/v) but it was found to increase with the increase in sodium alginate concentration from 1% to 3% (w/v) due to the hydrophilic nature of ranitidine as the drug partitions more in alginate matrix than in sunflower oil. Encapsulation efficiency was found to increase with the increase in concentration of gelation (CaCl2) solution from 1% to 3% (w/v).

Gel beads made solely of sodium alginate was found to lack sufficient and consistent buoyancy over 10 hours of study. Oil encapsulation inhibits bead water uptake but equilibrium weight gain ratio increased with the sodium alginate concentration from 1% to 3% (w/v).

As the concentration of sodium alginate increased from 1% to 3% (w/v), Ranitidine HCl was found to be released in a slow manner. Also, as the concentration of $CaCl_2$ increased from 1% to 3% (w/v), the Ranitidine HCl was found to be released rapidly.

Formulation F-6 prepared with 3 % (w/v) sodium alginate, 0.5% (v/v) sunflower oil, and syringing in 2% (w/v) calcium chloride solution was selected as optimized batch. But, this formulation has shown to release 94.80% Ranitidine HCl in 10 hours.

CONCLUSION

The drug was found to be soluble in distill water, ethanol, methanol, glacial acetic acid, SGF without pepsin (pH 1.2). The partition coefficient value (Log Po/w) of Ranitidine HCl was found to be 0.3 in n-octanol: water indicating the hydrophilic nature of drug. The λmax for drug in SGF (Simulated gastric fluid) without pepsin was 313.5 nm (pH 1.2). A straight line with $r^2 = 0.9997$ for SGF (Simulated gastric fluid) without pepsin was found indicating that the drug follows Beer's law within the specified concentration range. Formulation F-9 loaded with high polymer concentration was found elliptical in shape. This

was due to the increased viscosity of pre-gelation liquid with increased polymer concentration. Tailing of beads were found in formulation F-8 containing 2% alginate concentration due to increase in viscosity of the pre-gelation liquid. Encapsulation efficiency was found to decrease with the increase in oil concentration from 0.5% to 1% (v/v) due to the hydrophilic nature of drug, Ranitidine. Encapsulation efficiency was found to increase with the increase in sodium alginate concentration from 1% to 3% (w/v) due to the hydrophilic nature of Ranitidine as the drug partitions more in alginate matrix than in sunflower oil.

Encapsulation efficiency was found to increase with the increase in concentration of gelation and curing ($CaCl_2$) solution from 1% to 3% (w/v). The buoyancy decreased for the beads with less oil inclusion. All the floating formulations immediately float as soon as they were put in the SGF.

Therefore, no lag time in floatation was seen. Oil encapsulation inhibits bead water uptake as equilibrium weight gains of beads of the same crosslink density decreases with increasing initial oil concentration. As the sodium alginate concentration increased from 1% to 3%, equilibrium weight gain ratio increased because the crosslink density of the beads increased with increase in alginate concentration. Ranitidine HCl incorporation seemed to have made the beads more hydrophilic and the equilibrium weight gain ratio increased.

The concentration of sodium alginate increased from 1 to 3%, Ranitidine HCl was found to be released in a slow manner. As the concentration of $CaCl_2$ increased (1% to 3%) in formulations the ranitidine was found to be released rapidly. The formulation F-9 prepared in 1% $CaCl_2$ solution released Ranitidine faster than the formulation F-3 prepared in 0.5% $CaCl_2$ solution but the encapsulation efficiency of formulation F-9 (75.63%) was much higher than the formulation F-3 (64.34%) so further formulations were prepared by gelation in 1% $CaCl_2$ solution.

CONFLICT OF INTEREST: No any

REFERENCES

1. Streubel, A., et al*., Floating microparticals based on low density foam powder.* Int. J. Pharm, 2002. **241**: p. 279-292.
2. Chawla, G., et al., *Gastroretention: A Means to Address Regional Variability in Intestinal Drug Absorption.* Pharmaceutical Tech, 2003.p.50-68.
3. Arora, A., et al., *Floating Drug Delivery Systems: A Review.* AAPS PharmSciTech, 2005.**06**(03).
4. Hilton, A.K., and Deasai, P.B., *Invitro and In vivo evaluation of an oral sustained release dosage form of Amoxycillin trihydrate.* Int J Pharm, 1992. **86**: p. 79-88.
5. Badve, S.S., et al., *Development of hollow/porous calcium pectinate beads for floating-pulsatile drug delivery.* Eur. J. Pharm. Biopharm, 2007. **65**: p.85-93.
6. Chavanpatil, M.D., et al., *Novel Sustained release, Swellable and bioadhesive gastroretentive drug delivery system for ofloxacin.* Int. J. Pharm, 2006. 216: p. 86-92.
7. Gattani, Y.S., et al., *Formulation and evaluation of intragastric floating drug delivery system of diltiazem hydrochloride.* A. J. Pharm, 2009. P. 228-231.
8. Gattani, Y.S., et al., *Formulation and evaluation of gastro retentive multiparticulate drug delivery system of aceclofenac.* Int. J. ChemTech Res, 2009.**1**: p.1-10.
9. Patel, D.M., et al., *Floating granules of ranitidine hydrochloride-gelucire 43/01: Formulation optimization using factorial design.* AAPS Pharm. Sci.Tech, 2007. **8**: E1-E5.
10. Martindale, *The Complete Drug Reference*, 33rd Edn., Sweetmann, S.C. Edt., The Pharmaceutical Press, London, 2002. p. 979.2-889.1.
11. *Indian Pharmacopoeia*, Published by the Indian Pharmacopoeia Commission, Ghaziabad, 2007. p. 1037-1038.
12. *British Pharmacopoeia*, Published by the stationary office, 2007.p. 328- 329.