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PREPARATION AND *IN VITRO* EVALUATION OF CHITOSAN BASED GASTRIC FLOATING SYSTEM OF RANITIDINE HYDROCHLORIDE

RAKESH PAHWA[*,a], VIPIN KUMAR[a,b] and KANCHAN KOHLI[c]

[a]Institute of Pharmaceutical Sciences, Kurukshetra University, KURUKSHETRA – 136119 (Haryana) INDIA
[b]Department of Pharmacy, School of Chemical Sciences and Pharmacy, Central University of Rajasthan, AJMER – 305801 (Raj.) INDIA
[c]Department of Pharmaceutics, Faculty of Pharmacy, Jamia Hamdard, NEW DELHI – 110062, INDIA

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ABSTRACT

The objective of the current study was to prepare and evaluate gastroretentive floating system of ranitidine hydrochloride. The floating beads of ranitidine hydrochloride were prepared by employing ionotropic gelation technique. The designed floating beads were characterized for particle size analysis, percentage yield, entrapment efficiency and *in vitro* buoyancy profile. Findings demonstrated that all prepared beads containing gas forming agent showed excellent buoyancy profile. Formulated beads remained buoyant even after the buoyancy test period in a simulated gastric fluid (pH 1.2). Furthermore, it was also revealed that the concentration of chitosan influenced the physicochemical characteristics of prepared floating beads.

Key words: Gastroretentive, Floating system, Ranitidine hydrochloride, Chitosan, Gas forming agent.

INTRODUCTION

The primary aim of an oral controlled release dosage form is to release the drug in a very predictable manner and to increase its bioavailability[1,2]. However, the developmental process is precluded by various physiological adversities such as an inability to restrain and localize the dosage form within desired region of the gastrointestinal tract, fluctuation in the gastric emptying process etc. This variability may lead to an unpredictable bioavailability of an orally administered dosage form[3]. To enhance the gastric retention time of drugs, various attempts have been made for the development of controlled release gastroretentive dosage forms, which can remain in the gastric region for several hours[4]. Prolonged residence time in the gastric region is highly desirable for drugs that are locally active in the stomach, or are unstable in the intestinal or colonic environment, and/or have low solubility at higher pH values [5].

Important approaches for gastric retention that have been examined so far includes floating system, mucoadhesion or bio-adhesion system, high density system, magnetic system, raft forming system, and floating ion exchange resins, unfoldable, extendable or expandable systems[6,7]. Among the various approaches employed to increase the retention of an oral dosage form, floating drug delivery system is a considerably acceptable and logical approach in the development of gastroretentive dosage forms. Gastroretentive floating drug delivery system is one of the promising approach for enhancing the

Available online at www.sadgurupublications.com
[*]Author for correspondence; E-mail: rakesh_pahwa2407@yahoo.co.in

bioavailability and controlled delivery of drugs that exhibit narrow absorption window[8]. These drug delivery systems have revealed better efficacy in controlling the release rate of various therapeutic molecules along with site specific absorption[9].

In this study, sodium alginate and chitosan were utilized for the development of gastroretentive floating drug delivery system. Alginate, natural polymer is a non-toxic, biodegradable, biocompatible and linear polysaccharide consisting of alternating blocks of 1-4 linked α-L-guluronic and β-D-mannuronic acid residues. Chitosan is a naturally occurring polysaccharide comprising D-glucosamine and N-acetyl-D-glucosamine units via β-(1-4) linkages with unique polycation characteristics. It has various favourable biological properties such as non toxicity, biocompatibility and biodegradability[10-12]. The objective of present study was to prepare floating drug delivery system of ranitidine hydrochloride by using sodium alginate and chitosan. The prepared beads were also evaluated for particle size, percentage yield, percentage entrapment efficiency and *in vitro* buoyancy profile.

EXPERIMENTAL

Preparation of floating chitosan-sodium alginate beads

The beads were prepared by employing ionotropic gelation technique. Alginate solution was prepared by dissolving sodium alginate in distilled water and the solution was stirred thoroughly. Ranitidine hydrochloride and varying concentration of calcium carbonate were dissolved/dispersed uniformly in alginate solution under continuous stirring. The stirring was continued after complete addition until a uniform dispersion was obtained. The resultant homogenous bubble free alginate dispersion was extruded using a 21G syringe needle into the gelation medium, which was kept under stirring to prevent aggregation of the formed beads. The gelation medium was prepared by dissolving calcium chloride in acetic acid glacial. The small gelled beads formed were left in the solution with gentle stirring for 10 min at room temperature to be cured. Thereafter, beads were collected by filtration and oven-dried at 40°C. The alginate beads coated with chitosan were prepared by transferring the alginate slurry containing drug and different concentrations of calcium carbonate into the calcium chloride solution with chitosan dissolved in it at various concentrations. Afterwards, the beads were collected, allowed to harden before washing them twice with distilled water and were dried accordingly[13,14]. Composition of prepared formulations is listed in Table 1.

Table 1: Formulation design of chitosan-sodium alginate floating beads

Formulation code	Chitosan (% w/v)	$CaCO_3$ (% w/v)	Calcium chloride (% w/v)
F1	0.2	0.5	0.5
F2	0.2	1.0	0.5
F3	0.2	2.0	0.5
F4	0.4	0.5	0.5
F5	0.4	1.0	0.5
F6	0.4	2.0	0.5
F7	0.6	0.5	0.5
F8	0.6	1.0	0.5
F9	0.6	2.0	0.5

All batches were also composed of drug (1% w/v) and sodium alginate (3% w/v)

Characterization of floating beads

Particle size analysis

Particle size of the prepared floating beads was determined using an optical microscope fitted with an ocular micrometer. Mean diameter of beads was calculated by measuring twenty dried beads of each formulation[15-17].

Percentage yield

The yield was calculated by dividing the weight of the collected beads by the total weight of all the non-volatile components used for the preparation of beads and expressed in the terms of percentage[18-20].

$$\text{Percentage yield} = \frac{\text{Actual weight of floating beads}}{\text{Total weight of excipients and drug}} \times 100 \quad \ldots(1)$$

Drug entrapment efficiency

Accurately weighed quantity of the dried beads were crushed in a glass mortar and pestle, and dissolved in a simulated gastric fluid (pH 1.2). The resulting mixture was also continuously agitated for 24 h to extract the drug from beads completely. The solution was filtered and an aliquot was analyzed spectrophotometrically for ranitidine hydrochloride. Each sample determination was made in triplicate. The drug entrapment efficiency was calculated according to the following relationship[21-23].

$$\text{Drug entrapment efficiency (\%)} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100 \quad \ldots(2)$$

Test for buoyancy

In vitro floating test was performed by spreading the floating beads on a simulated gastric fluid (pH 1.2) containing the surfactant in USP type II dissolution test apparatus. The media was stirred at 37 ± 0.5°C. After specific intervals of time, both the fractions of beads (floating and settled beads) were collected, dried and weighed. Buoyancy percentage of the floating beads was determined by using formula[24-26].

$$\text{Buoyancy (\%)} = \frac{Q_f}{Q_f + Q_s} \times 100 \quad \ldots(3)$$

where, Q_f is the weight of floating beads and Q_s is the weight of settled beads collected at different time intervals, respectively.

RESULTS AND DISCUSSION

Preparation of floating chitosan-sodium alginate beads

In the present work, ranitidine hydrochloride loaded floating beads were successfully prepared by using the ionic gelation technique. Sodium alginate was selected as a polymer for the preparation of floating beads owing to its non-toxicity, non-irritancy and excellent biocompatibility. The carboxylic acid groups on these units attribute negative charges of alginate, and thus, being able to interact electrostatically with the positively charged molecules to form gels. Divalent cation (Ca^{2+}) induces gelation by binding mainly to the guluronic blocks of alginates. Calcium ions diffuse into the alginate drops, forming a three dimensional lattice of ionically cross linked alginate. Formation of beads was due to the cross linking of the sodium

alginate with divalent calcium ions of the $CaCl_2$ solution. Therefore, the beads were produced by dropping drug loaded alginate solution into calcium chloride solution. The prepared alginate gel beads were collected and dried. Moreover, polyelectrolyte complexation with oppositely charged polyelectrolyte (i. e. chitosan) was also carried out to increase the mechanical strength of the prepared hydrogel and to provide a permeability barrier. Polyelectrolyte complex membrane was developed on the surface of alginate beads. In this study, well packed chitosan layer around the alginate particle was formed. The developed microparticles consisted of drug entrapped within sodium alginate and finally coated with chitosan as an outer layer.

Characterization of floating beads

Particle size analysis

It has been observed that the mean diameter of the prepared floating beads marginally increased with an increase in the concentration of chitosan and was in the range of 0.83 ± 0.011 mm to 1.34 ± 0.037 mm. This may be attributed to the formation of a thicker chitosan layer with the increase of chitosan concentration in the gelation medium due to its ionic interaction. The mean diameter of formulations **F1** to **F3** containing 0.2% w/v of chitosan was found to be between 0.83 ± 0.011 mm to 0.99 ± 0.024 mm; **F4** to **F6** containing 0.4% w/v chitosan was 1.01 ± 0.028 mm to 1.16 ± 0.018 mm and for **F7** to **F9** with 0.6% w/v chitosan was found to be 1.19 ± 0.038 mm to 1.34 ± 0.037 mm. The data are represented in Table 2.

Table 2: Diameter and percentage yield of prepared chitosan-sodium alginate floating beads

Formulation code	Diameter of beads (mm)[a]	Percentage yield (%)[b]
F1	0.83 ± 0.011	77.75 ± 0.055
F2	0.90 ± 0.034	78.30 ± 0.479
F3	0.99 ± 0.024	78.71 ± 0.247
F4	1.01 ± 0.028	83.11 ± 0.035
F5	1.09 ± 0.025	83.53 ± 0.305
F6	1.16 ± 0.018	84.04 ± 0.025
F7	1.19 ± 0.038	88.20 ± 0.167
F8	1.26 ± 0.026	89.06 ± 0.015
F9	1.34 ± 0.037	89.84 ± 0.145

Data are presented as mean value ± SD; (a) n = 20, (b) n = 3

Moreover, the number of the gas bubbles observed appears to be directly related to the amount of incorporated gas forming agent, $CaCO_3$. It is clearly revealed that as more $CaCO_3$ was added, the more CO_2 was produced by reacting with glacial acetic acid in the gelation medium. It was observed that the mean size of beads increased prominently with the increasing weight ratio of $CaCO_3$/Alginate. This was probably due to the effect of more gas bubbles formed after the addition of more $CaCO_3$.

Percentage yield

Percentage yield of different formulations of floating beads was determined by weighing the prepared beads after drying. The percentage yield of the prepared beads ranged between 77.75 ± 0.055% to 89.84 ± 0.145%. The percentage yield showed an increase in its value with the increase in the polymeric concentration. This might be due to the increased amount of coating polymer protecting the beads against coalescing. This increases the microencapsulation process yield. In addition; at low concentration, transient

beads might be broken before hardening resulting in low yield. No considerable effect was observed with calcium carbonate on percentage yield of beads. The percentage yield of different formulations is depicted in Table 2.

Drug entrapment efficiency

The entrapment efficiency of the prepared beads was found to be in the range of 53.86 ± 2.138% to 72.54 ± 2.120%. The values for various formulations are tabulated in Table 3. The entrapment efficiency was found to be proportionally increased with the increasing concentration of chitosan. This is due to the increasing thickness of chitosan coat formed over the beads, which may encapsulate a larger amount of drug. This can be explained well because of the strong electrostatic interactions between carboxyl groups of alginate and amino groups of chitosan. Alginate-chitosan complex block up the large pore of calcium-alginate gel matrix and form a polyelectrolyte complex membrane on the surface of the beads and thereby; reduce the permeability of the beads. Therefore, the diffusion of drug is effectively prevented during the gelation process and ultimately increases entrapment efficiency. Increase in the concentration of chitosan that impede the drug diffusion leads to increased drug entrapment efficiency. This effect became more evident owing to the formation of a denser membrane at higher chitosan concentration. No considerable effect was observed with calcium carbonate on encapsulation efficiency of prepared beads.

In vitro buoyancy studies

The buoyancy studies were carried out in order to investigate the floating characteristics of the beads. The floating ability of the prepared formulations was evaluated in simulated gastric fluid (pH 1.2) using USP type II dissolution apparatus. The time the formulation took to emerge on the surface of dissolution medium is known as floating lag time. In addition, the percentage floated on the surface of dissolution medium known as buoyancy percentage was determined and are depicted in Table 3. Calcium carbonate was used as an effervescent agent for the floating behaviour and the buoyancy percentage of prepared beads was observed to increase proportionally with an increase in the amount of effervescent agent.

Table 3: Physicochemical characteristics of prepared chitosan-sodium alginate floating beads

Formulation code	Entrapment efficiency (%)[c]	Percentage buoyancy (%)[d]
F1	54.92 ± 2.070	72.54 ± 2.110
F2	54.39 ± 2.585	80.37 ± 2.072
F3	53.86 ± 2.138	88.59 ± 1.025
F4	65.04 ± 3.020	75.21 ± 1.852
F5	64.89 ± 4.215	82.45 ± 2.439
F6	63.75 ± 3.017	90.34 ± 1.567
F7	72.54 ± 2.120	77.37 ± 2.593
F8	71.82 ± 2.920	84.87 ± 1.862
F9	72.11 ± 3.986	92.51 ± 2.163

Data are presented as mean value ± SD; (c) n = 3, (d) n = 3

Upon contact with an acidic medium, gelation and cross-linking by calcium ions occurred to provide a gel barrier. The calcium carbonate effervesced, releasing both carbon dioxide and calcium ions. The released carbon dioxide was entrapped in the network of gel producing buoyant formulation and also calcium ions reacted with alginate forming a cross-linked three dimensional gel network that restricted

further diffusion of carbon dioxide and resulted in an extended duration of floating. Increase in the proportion of gas forming agent resulted in the production of more gas bubbles and thus, increased buoyancy percentage of prepared floating beads was observed.

On increasing the calcium carbonate concentration, the floating lag time was reduced and the duration of floating was increased. Increase in the amount of calcium ions and subsequently in the amount of carbon dioxide evolved is responsible for the observed reduction in the floating lag time and increased duration of floating. Therefore, inclusion of calcium carbonate in the beads resulted in the creation of calcium ions and carbon dioxide and ultimately played a pivotal role in buoyancy.

Increase in chitosan concentration from 0.2% w/v to 0.6% w/v lead to increased percentage buoyancy of prepared beads. This may be accounted to increased gel strength of the polymeric matrices through rapid hydration and swelling ensuring floatation in the simulated gastric fluid. The buoyancy can also be associated with swelling and volume expansion in media, leading to reduction in beads density. The superior floating ability of the alginate gel coated beads might be due to their low densities. It was observed that all formulated floating beads demonstrated excellent percentage buoyancy as overall floating characteristics is primarily controlled by the apparent density of the prepared beads, which in turn is influenced by the effect of both; quantity of calcium carbonate and concentration of chitosan. Formulated beads containing gas generating agent (calcium carbonate) were floating in a simulated gastric fluid (pH 1.2). It is also pertinent to note that beads remained buoyant even after the buoyancy test period. Moreover, it has been found that the control beads (without calcium carbonate) sank consistently in the dissolution medium.

CONCLUSION

In the present endeavour, ranitidine hydrochloride loaded chitosan floating beads were successfully prepared utilizing the ionotropic gelation technique. From the findings, it has been observed that developed floating beads revealed satisfactory physicochemical characteristics. Particle size, entrapment efficiency and production yield were influenced by the concentration of chitosan. *In vitro* data obtained for floating beads of ranitidine hydrochloride showed excellent buoyant ability owing to the incorporation of gas generating agent. Thus, the prepared floating multiple-unit delivery devices may prove to be potential candidate for effective and safe therapy of stomach ulcer. It is also anticipated that further research with a variety of gas-forming agents will ensure the development of more effective gastric floating system.

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