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# Ranitidine hydrochloride multiparticulate floating drug delivery system: Formulation and evaluation

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## Abstract

Gastroretentive Drug Delivery Systems (GFDDS) are retained in the stomach for a longer time and assist in improving the oral controlled delivery of drugs that have an absorption window in the particular region of the GI tract as well as for controlling the release of the drug having site-specific absorption limitation. 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. In the present work, an attempt was made to prepare GFDDS of Ranitidine HCl using different polymers by ionotropic gelation method with sodium alginate, pectin and HPMC as polymers, and $CaCO_3$ as the buoyancy providing agent. All the prepared HBS formulations were evaluated for size, morphology, drug content, drug-polymer interaction, in-vitro floating studies, in-vitro drug release and short term stability studies. IR spectroscopic studies indicated that there was no incompatibility between drug, polymer and co-excipients. The drug-polymer ratio, type of polymer, and ratio of buoyancy providing agent were found to influence the drug release and floating properties of the prepared GFDDS. Decrease in polymer concentration and $CaCO_3$ proportion was found to enhance the drug release from the GFDDS. The drug release was faster in case of GFDDS containing pectin (3A-C) when compared to GFDDS prepared with HPMC (10A-C). The floating lag time was found to be more when the $CaCO_3$ ratio was less. Addition of $CaCO_3$ as buoyancy providing agent showed considerable reduction in the floating lag time. The in-vitro dissolution profiles of all the GFDDS formulations of Ranitidine HCl were controlled for a period of more than 14 hours. The drug release data showed a good fit to Higuchi model indicating that diffusion is the predominant mechanism controlling the drug release. Among the various GFDDS formulations studied, formulation 3C containing drug-polymer ratio (1:1) prepared with pectin showed promising results releasing ≈ 88% of the drug in 14 hours with a floating lag time of 1 sec and floating time of more than 24 hours.

**Keywords:** HPMC, Ranitidine hydrochloride, Drug-polymer Interaction, GFDDS.

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## 1. Introduction

There are different types of dosage forms, which are being administered through different routes. However oral route is the most preferred route of administration because of its patient compliance. Now a days oral controlled system are designed offering a number of advantages including improvement in patient compliance, therapeutic efficacy and safety, Decreased side effects and reduced dose frequency. Majority of the drugs are having site specific absorption In the G.I. tract and parameters like pH dependent solubility, stability and ionization of the drug in different portions of the G.I. tract. Influence such absorption. Gastric retention time is one of the important factors, which adversely affect the performance of these drugs when administered simply by an oral controlled drug delivery system. The novel dosage forms that can be retained in the stomach for a prolonged and predictable period of time. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profiles in the gastrointestinal tract is to control the gastric residence time, using gastro-retentive dosage forms that will provide us with new and important therapeutic options. From the formulation and technological point of view, the floating drug delivery system is considerably easy and logical approach. An attempt has been made in this research work to introduce the current technological developments in controlled drug development delivery floating drug delivery system. For many drugs, increased or more predictable availability would result if controlled release systems could be retained in the G.I. tract for extended periods of time. Thus, control of placement of drug delivery systems in a specific region of the G.I. offers numerous advantages, especially for drugs exhibiting an absorption window in the G.I tract or drugs with a stability problem or for drugs locally active in the stomach. Overall, the intimate contact of the drug delivery system with the absorbing membrane has the potential to maximize drug absorption and may also influence the rate of drug absorption. These considerations have led to the development of oral controlled release dosage forms possessing gastric retention capabilities.

Gastric retention systems are such systems, which increase the gastric retention time of the dosage forms at the stomach and upper parts of the small intestine and suitable for the drugs having site-specific absorption from the above sites. The controlled release of the drugs from these systems at the preferred absorption site optimizes delivery of the drug, maximizing its therapeutic benefits and reduces side effects by permitting a large portion of the drug to be absorbed before passing through the lower G.I tract. Many attempts have been made in the recent years to provide a dosage forms with a longer retention time and therefore a more efficient absorption. These approaches include floating during delivery systems, swelling and expanding systems, polymeric bio adhesive systems, modified-shape systems, high density systems and other delayed gastric emptying devices, Compared to these approaches the gastric floating drug delivery systems (GFDDS) developed has provided several advantages as shown by the encouraging results reported earlier. Furthermore, the buoyancy action provided by the GFDDS seems to offer a greater safety for clinical uses than some of the above-mentioned approaches. In fact, no adverse effects due to floating devices have been reported till date, but the sudden gastric emptying often affects their therapeutic efficacy.In the present investigation the drug Ranitidine HCl was selected for the design of GFDDS. The drug has its absorption window in stomach and upper small intestine. There are no reports on the use of sustained release formulations or floating concept in the formulation of gastric retention systems of Ranitidine HCl. Hence, it is aimed to Design and evaluate GFDDS of Ranitidine HCl effervescent floating beads with different natural polymers like sodium alginate and pectin, and $CaCO_3$ as the agent responsible for floating of beads. Post GATT era encourages product patents, so as very few drug molecules come out from R&D labs; it is time to exploit the existing drugs whose patent is expired by formulating new drug delivery systems. Moreover WHO recommends and encourages that dosage forms which are cost effective and with the best technology should be available to the patients. Hence this was an attempt to formulate the beads using sodium alginate and pectin which are easily available and cost effective, biodegradable and natural polymers which were designed in such a way that they both give controlled release rates.

**The major objectives of the investigation are as follows:**

1. To formulate the GFDDS of Ranitidine HCl using natural polymers and optimize them in once-a-day GFDDS beads, as natural excipients proposed to be used are very cost effective.
2. Evaluation of the prepared GFDDS for their floating lag time and total floating time.
3. To evaluate the prepared GFDDS of Ranitidine HCl for various properties like drug content, hardness, weight variation etc.
4. To carry out the *in vitro* dissolution studies of the GFDDS in simulated gastric environment.

## 2. Materials and Methods

**Materials:** Ranitidine HCl received as a gift sample from Cadila Pharmaceuticals, Ahmedabad, HPMC,Calcium Carbonate and Hydrochloric acid receive from Central Drug house PVT, LTD,New Delhi. Sodium alginate andPectin received from Gift sample of Venus Pharmaceuticals, Baddi, H.P

**Method Analytical Steps:**

**Analysis of Excipients used in the formulation:**
The following excipients HPMC, Sodium Alginate, Pectin as polymers and Calcium Carbonate as a floating are selected for formulating GRFDDS and these have been evaluated and analyzed for the physico-chemical characters.
**Analysis of the Model Drug:**
Description: Drug was observed for its general appearance.
Melting point: Melting point was determined using melting point apparatus.
UV spectroscopy: A stock solution of Ranitidine HCl (100 µg/ml) was prepared in
0.1N HCl. Then UV spectrum was scanned in the range of 313 nm using shimadzu 1800.
IR Spectroscopy: The IR spectrum of drug was obtained from B R Nahata College of Pharmacy, M.P.
**Preparation of Standard curve:**
A stock solution of Ranitidine HCl (100 µg/ml) was prepared in 0.1N HCl. Then UV spectrum was scanned in the range of 313 nm using. The solutions of 10 to 70 µg/ml were prepared from stock solution by appropriate dilution with 0.1 N HCl. The absorbance of each of solution was recorded using Shimadzu 1800 at wavelength of maximum absorption.

## 3. Results and Discussion

**Table1. Calibration** data of the UV spectrophotometer method for determination of Ranitidine HCl in simulated gastric fluid (pH 1.2) at 313 nm

| S.No. | Concentration (µg/ml) | Mean Absorbance at 313 nm |
|---|---|---|
| 1. | 10 | 0.041 |
| 2. | 20 | 0.074 |
| 3. | 30 | 0.109 |
| 4. | 40 | 0.152 |
| 5. | 50 | 0.189 |
| 6. | 60 | 0.228 |
| 7. | 70 | 0.259 |

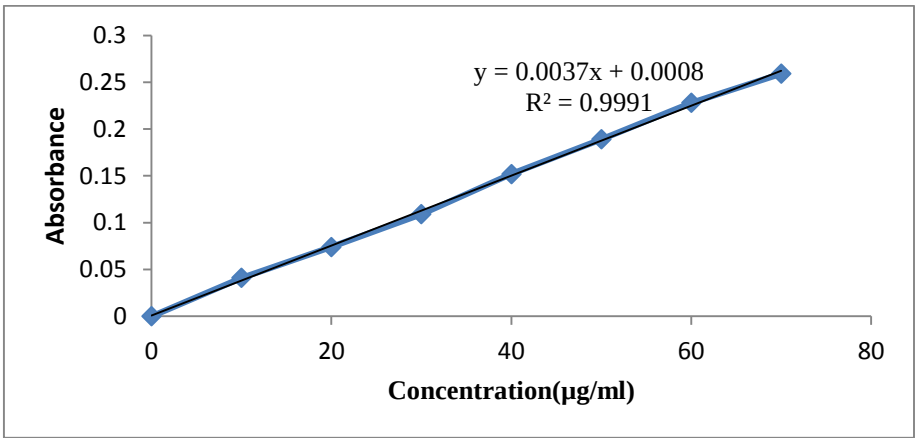


**Fig 1. Standard Curve for the UV spectrophotometric method for determination of Ranitidine HCl.**

**Fabrication of Beads: Preparation of Ranitidine HCl floating beads with sodium alginate, HPMC and pectin:**
Different concentration mixture of polymer was dissolved in distilled water with agitation. $CaCO_3$ was added to the above solution and dispersed thoroughly by stirring on a magnetic stirrer. Then drug was added and the resulting dispersion was added manually drop wise with a 22 gauge needle into calcium chloride solution containing 10% (v/v) acetic acid by stirring with a magnetic stirrer. A gelation time of 15 minute was allowed to complete the curing reaction and produce spherical and rigid microbeads. The beads were collected by decantation, washed with distilled water and dried at room temperature.

**Table 2**

| Batch code | Drug : polymer | Polymer Conc (%w/w) | Sodium alginate: HPMC | Polymer:caco$_3$ (%w/w) | Curing time |
|---|---|---|---|---|---|
| **10A** | 1:1 | 4 % | 2:1 | 1:0.25 | 15 |
| **10B** | 1:1 | 4 % | 2:1 | 1:0.50 | 15 |
| **10C** | 1:1 | 4 % | 2:1 | 1:0.75 | 15 |

**Table 3. Formulation of Ranitidine HCl floating beads with sodium alginate, Pectin**

| Batch code | Drug : polymer | Polymer Conc (%w/w) | Sodium alginate : Pectin | Polymer:caco$_3$ (%w/w) | Curing time |
|---|---|---|---|---|---|
| **1A** | 1:1 | 4 % | 4:0 | 1:0.25 | 15 |
| **1B** | 1:1 | 4 % | 4:0 | 1:0.50 | 15 |
| **1C** | 1:1 | 4 % | 4:0 | 1:0.75 | 15 |
| **2A** | 1:1 | 4 % | 3.5:0.5 | 1:0.25 | 15 |
| **2B** | 1:1 | 4 % | 3.5:0.5 | 1:0.50 | 15 |
| **2C** | 1:1 | 4 % | 3.5:0.5 | 1:0.75 | 15 |
| **3A** | 1:1 | 4 % | 3:1 | 1:0.25 | 15 |
| **3B** | 1:1 | 4 % | 3:1 | 1:0.50 | 15 |
| **3C** | 1:1 | 4 % | 3:1 | 1:0.75 | 15 |
| **4A** | 1:1 | 4 % | 2.5:1.5 | 1:0.25 | 15 |
| **4B** | 1:1 | 4 % | 2.5:1.5 | 1:0.50 | 15 |
| **4C** | 1:1 | 4 % | 2.5:1.5 | 1:0.75 | 15 |
| **5A** | 1:1 | 4 % | 2:2 | 1:0.25 | 15 |
| **5B** | 1:1 | 4 % | 2:2 | 1:0.50 | 15 |
| **5C** | 1:1 | 4 % | 2:2 | 1:0.75 | 15 |
| **6A** | 1:1 | 4 % | 1.5:2.5 | 1:0.25 | 15 |
| **6B** | 1:1 | 4 % | 1.5:2.5 | 1:0.50 | 15 |
| **6C** | 1:1 | 4 % | 1.5:2.5 | 1:0.75 | 15 |

**HPMC Evaluation and Characterization of Beads:**

**Study of size and morphology of floating beads:**

The diameter of beads was determined by screw gauge [21, 22]. For this purpose, 20 dried beads were randomly selected from each batch and the mean diameter was determined by screw gauge. The least count of screw gauge was 0.005 mm. Color and shape of dried beads of each batch was noted.

**Floating time of floating beads:**

The floating bead samples (n=10) were placed in a beaker filled with 50 ml of 0.1 N HCl solution. Temperature was maintained at $37^{0C}$. The floating time of beads was observed for 24 hrs. The preparation was considered to have buoyancy in the test solution only when all the beads floated in it[21].

**Determination of drug content of floating beads:**

50 mg of beads were weighed and crushed in a pastel mortar and the crushed material was dissolved in 25 ml of water. Volume of this solution was made up to 50 ml with washings of mortar. This solution was shaken with the help of wrist action shaking machine for 5 hrs and then kept for 24 hrs. Then it was filtered. The filtrate was assayed by spectrophotometricaly at 313 nm. The drug content and the encapsulation efficiency were determined.

**Swelling studies of floating beads:**

Beads were studied for swelling characteristics. Sample from drug-loaded beads were taken, weighed and placed in wire basket of USP dissolution apparatus II. The basket containing beads was put in a beaker containing 100 ml of 0.1 N HCl (pH 1.2) maintained at $37^0$C. The beads were periodically removed at predetermined intervals and weighed. Then the swelling ratio was calculated as per the following formula:

Swelling ratio = weight of wet beads/weight of dried beads

**Drug release studies of floating beads:**

The dissolution of Ranitidine HCl floating beads was studied using USP Type II dissolution apparatus containing 900 ml of 0.1 N HCl (pH 1.2) maintained at $37\pm0.5^0$C and stirred at 50 rpm. Samples were collected periodically

and replaced with a fresh dissolution medium. These samples were analyzed for the drug present in them with help of UV spectrophotometer.

**FT-IR spectroscopy:**

Individual beads were crushed with pestle in an agate mortar. The crushed material was mixed with potassium bromide (Merck IR spectroscopy grade) in 1:100 proportion and dried at 40°C. The mixture was compressed to a 12mmsemitransparent disk by applying a pressure of 10 tons (Digilab press, Randolph, MA, USA) for 2 min. The FTIR spectra over the wavelength range 4000–400 cm−1 were recorded using a FTIR spectrometer (Digilab Excalibur, Randolph, MA, USA).

**Scanning Electron Microscopy (SEM):**

Non- effervescent layered and final coated beads were mounted onto the stages after coating with gold under vacuum. The surface morphology for checking the uniform coating of the units was observed under SEM.

**Study of drug release kinetics:**

To study the release kinetics, the data obtained from in vitro drug release studies were plotted in various kinetic models:

1. Zero order rate kinetics : Cumulative percentage of drug released vs. time
2. First order rate kinetics : Log cumulative percentage of drug remaining vs time
3. Higuchi Model : Cumulative percentage of drug released vs. square root of time

The plots were drawn using Microsoft excel 2007 and the regression equations were obtained for each plot. The linearity of the plots was obtained from the value of regression coefficient (R). The model with the highest linearity (R value approaches unity) was chosen as the best fit kinetic model.

**Zero order kinetics**

A zero order release can be predicted by using the equation:

$$\mathbf{Q_t = Q_0 - K_0 t} \qquad \textbf{Eqn.20}$$

Where,

$Q_0$ initial amount of drug present in solution (most cases $Q_0 = 0$)

$Q_t$ is the amount of drug release at time t

$K_0$ is the zero order release rate constant

A graph of cumulative percentage of drug released vs time would yield a straight line with a slope equal to $k_0$.

**First order kinetics**

The first order describes the release from system where the release rate is concentration dependent. It can be described by following equation:

$$\mathbf{\ln Q = \ln Q_o - K_1 t} \qquad \textbf{Eqn.21}$$

Where,

$K_1$ is first order release rate constant

**Higuchi model kinetics**

The drug release can be predicted by the following equation:

$$\mathbf{Q = Kt^{1/2}} \qquad \textbf{Eqn.22}$$

Where,

K is Higuchi dissolution constant

T is the time in hours

The model predicts that the drug release from the dosage form is directly proportional the square root of time.

**Stability Studies:**

The stability studies for beads were done by keeping the sample beads from optimized batches at room temperature for 45 days. The beads were filled in capsules and these capsules were packed in vials. The vials were sealed and stored at room temperature only because the polymer used in preparation of beads i.e. sodium alginate is not stable at higher temperature. The selected batches for stability study were batch 3 A-C and 4 A-C. The samples were put for 45 days. In the end of one month the beads were evaluated for different parameters like morphology, floating time, swelling ratios and drug release studies. Methods followed to evaluate these parameters were similar as followed previously.

## 4. Conclusion

- Floating Drug Delivery System offers a simple and practical approach to achieve increased gastric residence and to modify drug release profiles essential for sustained, site specific and localized drug action.

- The GFDDS of Ranitidine HCl were developed by using different ratio of polymers by ionotropic gelation technique. Sodium alginate, pectin and HPMC were used as the polymers. Calcium carbonate was used for attainment of floating property.
- All the prepared beads were found to be sufficiently good without agglomeration, deformation and sticking.
- The drug content was uniform and well within the accepted limits with low values of standard deviation indicating uniform distribution of drug within the GFDDS.
- IR spectroscopic studies indicated that the drug is compatible with polymer and co-excipients.
- The drug-polymer ratio, type of polymers and floating providing agents were found to influence the release of drug and floating characteristics from the prepared floating beads of Ranitidine HCl.
- The prepared GFDDS of Ranitidine HCl showed excellent in-vitro floating properties. As the concentration of $CaCO_3$ increased in the beads the floating time increases and the floating lag time decreases. The floating lag time varied considerably batch to batch due to the difference in polymer and $CaCO_3$ concentration. All the GFDDS have showed a floating time of more than 24 hours.
- The in-vitro dissolution profiles of all the prepared GFDDS formulations of Ranitidine HCl were found to extend the drug release over a period of more than 14 hours and the drug release increased with decrease in sodium alginate concentration and increase in pectin ratio.
- Release of Ranitidine HCl from most of the GFDDS formulations was found to follow zero order kinetics (0.92 to 0.95) and derived correlation coefficient '$R^2$' (0.98) indicated good fit of Higuchi model suggesting that diffusion is the predominant mechanism controlling the drug release.
- Among the various GFDDS formulations studied, formulation 3C containing drug-polymer ratio (1:1) prepared with pectin showed promising results releasing ≈ 88% of the drug in 14 hours with a floating lag time of 1 sec and floating time of more than 24 hours.
- Finally, it may be concluded that this novel drug delivery system i.e GFDDS offers a valuable dosage form which delivers the drug at a controlled rate and at a specific site. The GFDDS of Ranitidine HCl provides a better option for increasing the bio availability and reliability for peptic and duodenal ulcers by allowing a better control of fluctuations observed with conventional dosage forms.

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