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Research Article

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Design, development and in vitro evaluation of gastro retentive alginate floating beads for ranitidine hydrochloride

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ABSTRACT

This study aims to encapsulate Ranitidine hydrochloride within floating alginate Hydroxy Propyl Methylcellulose beads as an oral Sustained release delivery system using ionotropic gelation technique. Ranitidine hydrochloride (RHCL) 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 half life 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. To optimize drug entrapment efficiency and dissolution behavior of the prepared beads, different parameters of drug: polymer ratio, polymer mixture ratio, and gelling agent concentration were involved. The prepared beads were investigated with respect to their buoyancy, encapsulation efficiency, and dissolution behavior in the media 0.1 N HCl (pH 1.2).The release kinetics and mechanism of the drug from the prepared beads was investigated. All prepared Ranitidine hydrochloride beads remained floating on 0.1 N HCl medium over 12 hours. Besides, high yield beads of 71.01- 87.30% was obtained. Encapsulation efficiencies were in the range of 33.10 % -79.04 %, and were found to increase as a function of increasing drug: polymer mixture ratio and the gelling agent concentrations. The obtained results suggest that Formulation of RHCl as a sustained release dosage form can also minimize the loss of drug in comparison to conventional tablets.

Key words: Ranitidine hydrochloride, Alginate Floating Beads, Sustained Drug Release

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INTRODUCTION

One of the most feasible approaches for achieving a prolonged and predictable drug delivery in gastro intestinal tract (GIT) is to control gastric resistance time i.e. gastro retentive drug delivery system, which will provide us with new and important therapeutic options, which utilize several approaches intra gastric floating system, high density system, mucoadhesive system, magnetic system, unflodable, extendable or expandable and super porous biodegradable hydrogel systems. From the formulation and technology point of view, the floating drug delivery system is considerably easy and logical approaches in development of gastro retentive drug delivery system [1, 2]. Floating drug delivery system is an approach to prolong gastric residence time, there by targeting site-specific drug release in the upper gastro intestinal tract [GIT] for local or systemic effects[1,3]. FDDS have a bulk density lower than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying time for prolonged time. As a result GRT is increased fluctuations plasma drug concentration can be better controlled [4]. This drug delivery system not only prolongs GI residence time but also maximise the drug reaching its absorption site in solution and hence ready for absorption [3]. The design of gastro retentive drug delivery systems depends upon physicochemical properties, dose and purpose of controlling the drug release, constraining pathophysiological factors. In present study the prime objective is to develop a newer floating drug delivery system of Ranitidine HCL as a model drug to prolong gastric retention with low frequency of administration for better patient compliance [5, 6].

EXPERIMENTAL SECTION

Ranitidine Hydrochloride and HPMC are gift samples obtained from Glukem pharmaceuticals, Hyderabad, Sodium alginate obtained from Finar chemicals pvt.ltd; Mumbai, Calcium carbonate supplied by Loba chemie pvt Ltd; Mumbai, Calcium chloride and Acetic acid supplied from Universal lab pvt ltd. Mumbai.

Ionotropic Gelation Method

336 mg of Ranitidine HCl was dissolved in 5mL distilled water. The solution was dispersed in 30 mL sodium alginate solution (3% v/v) containing HPMC (alginate: HPMC=9: 1, w/w). Then, gas forming agent such as CaCO3 was added to the solution with levels from 0.25:1 to 1:1 (gas-forming agent/alginate, w/w). The mixture was then degassed under bath sonicator. The resulting solution was dropped through a 26 G Syringe needle into 1 % (w/v) CaCl2 solution containing 10% (v/v) acetic acid. The solution containing suspend beads was stirred with a magnetic stir bar for 10 min to improve the mechanical strength of the beads and allowed to complete the reaction to produce gas. Since the carbonate salts are insoluble at neutral pH, the divalent ions were only released in the presence of acid, thereby preventing premature gelatin. The fully formed beads were collected, washed with ethanol and distilled water.

EVALUATION:

Density:

The density of different formulations is calculated by using the following formula

$$\text{Density} = \frac{\text{Weight of dry beads}}{4/3\ \pi\ r^3}$$

Buoyancy:

10mg of Beads were taken and introduced into the dissolution medium. The time taken to reach the upper one third of the dissolution vessel (buoyancy lag time) and the time taken to float on the surface of the medium (duration of buoyancy) were measured simultaneously as a part of dissolution studies.

Drug entrapment efficiency:

Accurately weighed sample of beads (10mg) was crushed in a mortar and added to 10 ml of phosphate buffer P^H 7.4. This mixture was centrifuged at 4200 rpm for 30 minutes, filtered and analysed spectrophotometrically against buffer as blank λ max 226.7nm.

$$\text{Encapsulation efficiency}(\%) = \frac{AQ}{TQ} \times 100$$

Where,

AQ is the actual drug content of the beads

TQ is the theoretical quantity of drug present in the beads.

Drug loading content:

Accurately weighed sample of beads (10mg) was crushed in a mortar and added to 10 ml of phosphate buffer P^H 7.4. This mixture was centrifuged at 4200 rpm for 30 minutes, filtered and analysed spectrophotometrically against buffer as blank at λ max 226.7nm.

% Drug loading = Amount of drug in bead / Amount of beads taken × 100

Swelling studies:

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 (P^H 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

Scanning electron microscopy:

Beads and their cross-sections were coated with a thin gold palladium layer by a sputter - coater unit. The surface topography was analyzed by a scanning electron microscope (SEM).

FT-IR spectroscopy analysis:
The sample preparation was done by grinding a quantity of the sample with potassium bromide to remove scattering effects from large crystals. The powder mixture was crushed in a mechanical die press to form a translucent pellet, through which the beam of the spectrometer can pass and the spectra was taken.

In vitro Dissolution Studies:
In vitro dissolution studies were performed for all the formulation combinations in dissolution apparatus. An accurately weighed sample (50 mg) of floating alginate bead formulations was dropped into 900 ml of HCl buffer P^H 1.2 maintained at a temperature of 37ºC ± 0.5ºC and stirred at a speed of 50 rpm. At different time intervals, a 10-mL aliquot of the sample was withdrawn and the volume was replaced with an equivalent amount of plain dissolution medium and kept at 37ºC. The collected samples were filtered and analyzed at λ max 226.7nm using a UV-visible spectrophotometer against HCl buffer P^H 1.2 taken as blank.

RESULTS AND DISCUSSION

Table1.Optimization of Formulation

Formulation Code	Polymer ratio(Sodium alginate:HPMC)9:1(w/w)	Polymer: Calcium Carbonate
RHF1	3%	1: 0
RHF2	3%	1:0.25
RHF3	3%	1:0.50
RHF4	3%	1:0.75
RHF5	3%	1:1
RHF6	3%	1:0.25
RHF7	3%	1:0.50
RHF8	4%	1:0.75
RHF9	4%	1:1

Table.2 Buoyancy and of various Ranitidine Hydrochloride formulations

Formulation codes	Floating property	Duration of buoyancy
RHF1	-	--
RHF2	+/+	+/+
RHF3	+/-	+/-
RHF4	+/-	+/-
RHF5	+/-	+/-
RHF6	+/+	+/+
RHF7	+/-	+/-
RHF8	+/-	+/-
RHF9	+/-	+/-

+/- Partial floating, ++ Complete floating

Table.3. Density, swelling ratio, DEE%, % Drug Release of various Ranitidine Hydrochloride formulations

Formulation Codes	Density	Swelling Ratio	Drug Entrapment Efficiency%	% Drug Release
RHF1	0.079	3.832	37	41.08
RHF2	0.006	4.201	81.10	83.72
RHF3	0.053	4.570	78.44	71.01
RHF4	0.046	5.705	72.36	62.11
RHF5	0.052	4.641	65.12	53.02
RHF6	0.003	4.424	86.2	87.30
RHF7	0.044	5.189	72.36	71.20
RHF8	0.031	7.733	73.44	61.09
RHF9	0.029	19.92	69.25	51.04

Table.4.Release kinetics of drug release from Ranitidine Hydrochloride floating beads

Kinetics	RH1	RH2	RH3	RH4	RH5	RH6	RH7	RH8	RH9
Zero order	0.9571	0.9642	0.9030	0.9843	0.9771	0.7686	0.9456	0.7720	0.9506
First order	0.9784	0.9835	0.9923	0.9614	0.9259	0.9586	0.9907	0.9573	0.9749
Higuchi	0.9766	0.9665	0.9856	0.9633	0.9381	0.9872	0.9894	0.9881	0.9814
Korsmeyer	0.9920	0.9752	0.9540	0.9946	0.9837	0.9883	0.9912	0.9933	0.9897
Hixson	0.9882	0.9858	0.9840	0.9834	0.9543	0.9145	0.9878	0.9161	0.9843

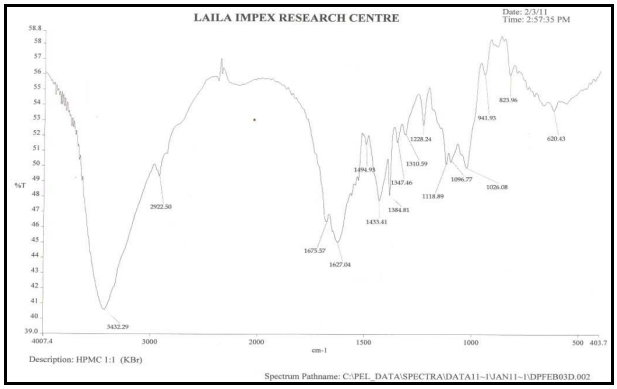

Figure 1. FT-IR Data of Pure Drug –Ranitidine Hcl

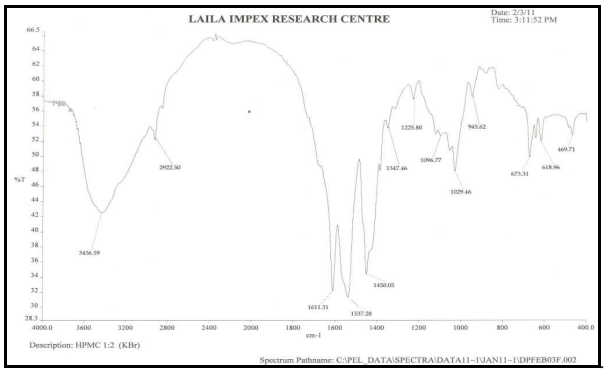

Figure 2. FT-IR Data of Drug+HPMC

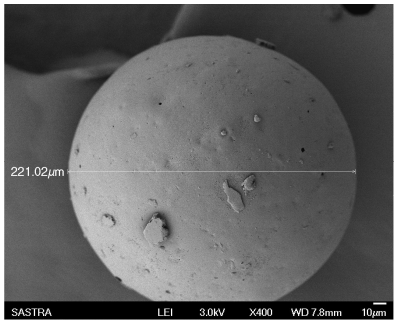

Figure 3.SEM image of RH6 (400X)

In the present study nine different batches were formulated by varying the concentration of polymer and gas forming agents. The physical characterization, drug content and *in vitro* release studies were studied. The bead size was determined by vernier calipers. The mean size of the formulated beads was in the range of 0.1 to 0.5 mm.

In vitro drug release studies were performed with USP type 2 dissolution apparatus using simulated gastric fluid (pH 1.2) at periodic time intervals. The percentage release of Ranitidine HCl from the formulation RHF1 was found to be 41.08% as the gas forming agent was not added to the formulation. The percentage release of Ranitidine Hydrochloride from the RHF2 was found to be 83.72% as it contains (1: 0.25) alginate and gas forming agent. The formulations from RHFl to RHF5 were prepared with alginate solution (3%, w/v) containing HPMC (alginate: HPMC=9: 1, w/w) .The formulations from RHF6 to RHF9 were prepared with alginate solution (4%, w/v) containing HPMC (alginate: HPMC=9: 1, w/w). The dissolution data (from the values of 1 to 7 hours drug release) of all batches were fitted to first-order, Higuchi, zero-order and Korsmeyer's-Peppas models. The formulations didn't follow zero-order release kinetics. The data obtained are represented in Table 4. When data were treated with Higuchi's equation to learn about the mechanism of drug release, it was observed that the values did not give a good fit for the Higuchi equation. None of the formulations followed Zero-order kinetics, which was confirmed by the poor correlation coefficient values. All formulations best fitted to Korsmeyer and Peppas equation (R^2 =0.9823-0.9981). When n takes value 0.5, it indicates Fickian diffusion controlled drug release and for the value 1.0 indicates case II transport (swelling-controlled drug release). Values of n between 0.5 and 1.0 can be regarded as an indicator

for the non-Fickian (anomalous transport) diffusion. For all formulations, the value of n was in the range 0.6341-0.8602 indicating anomalous transport wherein the drug release mechanism is controlled by both diffusion and polymer relaxation.

CONCLUSION

The percentage release of Ranitidine HCl from the formulation RHF6 was found to be 87.30% as it contains (l: 0.25) alginate and gas forming agent. This result suggests that beads formulated with the decrease in the concentration of the gas forming agent and increase in the polymer ratio results in the sustained release of the drug. Since the *in vitro* release of the formulations RHF2 and RHF6 were found to be delayed than the remaining formulations prepared with different ratios of polymer and gas forming agent. The percentage drug entrapment and drug content of the formulated beads were found to be satisfactory by this method. From the study it was concluded that the gastro retentive drug delivery system designed as floating beads could be suitable drug delivery system for Ranitidine HCl.

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