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Stomach-specific Drug Delivery of Famotidine using Floating Alginate beads

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ABSTRACT: The purpose of present research work was to prepare calcium alginate beads containing water-soluble drug Famotidine. A multiple-unit-type oral floating dosage form of famotidine was developed to prolong gastric residence time, target peptic ulcer and increase drug bioavailability. The floating bead formulations were prepared by dispersing famotidine together with calcium carbonate into a mixture of sodium alginate and hydroxypropyl methylcellulose solution and then dripping the dispersion into a solution of calcium chloride. Calcium alginate beads were formed, as alginate undergoes ionotropic gelation by calcium ions and carbon dioxide develops from the reaction of carbonate salts with acid. The evolving gas permeated through the alginate matrix, leaving gas bubbles or pores, which provided the beads buoyancy. The prepared beads were evaluated for percent drug loading, drug entrapment efficiency, buoyancy and in vitro release. The formulations were optimized for different weight ratios of gas-forming agent and sodium alginate.
Keywords: Famotidine, floating dosage form, calcium alginate beads, gastric residence time, buoyancy.

INTRODUCTION

Gastric emptying is a complex process that is highly variable and makes the *in vivo* performance of drug delivery systems uncertain. To overcome this physiological problem, several drug delivery systems with prolonged gastric retention time have been investigated.[1,3] Attempts are being made to develop a controlled drug delivery system that can provide constant plasma drug concentration levels for longer durations, thereby reducing the dosing frequency and minimizing fluctuations in plasma drug concentration.[4] Lately, a wide variety of both natural and synthetic hydrophilic polyionic systems like alginates have been investigated for preparation of multiple-unit floating dosage forms (FDFs).[5] Hydroxypropyl Methylcellulose (HPMC) has been reported to enhance the sustained-release properties of alginate by providing a denser inner matrix. Also, the preparative methodology of alginate beads involves the use of aqueous solvents, avoiding exposure of ingredients to high temperatures and toxic organic solvents. The present study was to prepare a stomach-specific multiple-unit FDF of famotidine to reduce its unwanted side effects at other sites by localized and sustained delivery to gastric ulcers. Famotidine is incompletely absorbed. The bioavailability of oral doses is 40 to 45 %. The apparent volume of distribution following i.v. administration of famotidine to healthy subjects ranges from 1.14-1.42 L/kg and is unchanged in patients with renal failure or in patients with compensated or decompensated hepatic cirrhosis. Plasma levels after multiple doses are similar to those after single doses. 15 to 20 % of famotidine in plasma is protein bound. Famotidine does not readily enter the CSF. Famotidine undergoes minimal first-pass metabolism. In patients with severe renal insufficiency, i.e., creatinine clearance less than 10 mL/min, elimination half-life of famotidine may exceed 20 hours. It has elimination half-life of 2.5 to 3.5 hours. It is eliminated by renal (65 to 70 %) & metabolic (30 to 35 %) routes. All pharmacokinetic parameters of famotidine are summarized in below table**.** [6,7]

MATERIALS AND METHODS

Materials

Famotidine was obtained as a gift sample from Lincoln Pharmaceutical Limited, Ahmedabad, India. HPMC, calcium carbonate, sodium alginate were obtained from S.D.Fine chemicals, Mumbai, India. All other reagents and chemicals were of analytical grade.

Preparation and Evaluation of Floating Beads of famotidine

Exactly 0.2 g of famotidine was dissolved in 10 ml of distilled water. This solution was dispersed in 15 ml of 2.0 %w/v Alginate solution containing HPMC K-15M Alginate: HPMC = 9:1 wt/wt). Then, the gas-forming agent Calcium Carbonate ($CaCO_3$) was added to the solution in weight ratios ranging from 0:1 to 1:1 ($CaCO_3$: Alginate wt/wt). The resulting solution was dropped through a 22-G syringe needle into 30 ml of Calcium Chloride solution (5% w/v). The beads were allowed to remain in the same solution for 15 minutes, to improve their mechanical strength. Table 1 lists the formulation variables for different formulations of famotidine-loaded floating beads.[8,9]

Evaluation of Floating Beads

The prepared beads were evaluated for percent drug loading and drug entrapment efficiency. An accurately weighed sample of beads (10 mg) was crushed in a mortar and added to 10 mL of Sorenson's phosphate buffer pH 7.4. This mixture was centrifuged at 4200 rpm for 30 minutes, filtered, and analyzed spectrophotometrically at max 266 nm against buffer as blank. Blank beads were treated similarly. The percent drug loading was calculated by dividing the amount of drug in the sampled beads by the weight of beads. The particle size and the size distribution of beads were determined in the dry state using the optical microscopy method. The mean surface diameter was calculated arithmetically.

In vitro Dissolution Studies

In vitro dissolution studies were performed for all the formulation combinations in hexaplicate using US Pharmacopeia XXIII Dissolution Apparatus II (paddle type). An accurately weighed sample (40 mg) of floating alginate bead formulations F_1 to F_5 (containing 16-18 mg of active drug) was dropped into 900 mL of HCl buffer pH 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 kept at 37ºC. The collected samples were filtered and analyzed at max 266 nm using a UV-visible spectrophotometer against HCl buffer pH 1.2 taken as blank.

Floating Properties

The time between the introduction of the FDF into the medium and its buoyancy to the upper one third of the dissolution vessel (buoyancy lag time) and the time for which the formulation constantly floated on the surface of the medium (duration of buoyancy) were measured simultaneously as a part of dissolution studies.[10]

RESULTS

Drug Loading and Drug Entrapment Efficiency

The percent drug loading of various formulations ranged between 59.5% and 72%. The entrapment efficiency for various formulations was found to vary between 44.62% and 53.88% (Table 1). It was observed that an increase in the ratio of $CaCO_3$: Alginate resulted in a decrease in the entrapment efficiency of famotidine in floating beads.

Particle Size Analysis

The mean particle size of 5 formulations was between 1.41 ± 0.07 and 1.81 ± 0.09 mm. It was observed that an increase in the proportion of $CaCO_3$ (0:1 to 1:1) led to an increase in the size of beads.

Table 1: Formulation variables and Evaluation parameters of various Famotidine Floating Bead Formulations

Formulation Code	$CaCO_3$: Na Alginate (%w/w)	Drug Loading	% Drug Entrapment Efficiency	% Drug Release	Mean Particle Size	Duration of Floating
F_1	0:1	71.85	53.88	68.42	1.41±0.07	---
F_2	0.25:1	67.25	50.43	71.46	1.45±0.09	---
F_3	0.5:1	65.5	49.12	93.12	1.52±0.08	21.5
F_4	0.75:1	61.5	46.12	95.32	1.69±0.06	24
F_5	1:1	59.5	44.62	97.30	1.81±0.08	24

Floating Properties

The floating ability of the prepared beads was evaluated (Table 1). The beads without $CaCO_3$ (F_1) sank immediately in 0.1 N HCl, while beads containing $CaCO_3$ (F_3-F_5) demonstrated instantaneous and excellent floating ability. Thus, floating ability was found to be directly related to the gas content of the polymer matrix.

F_5 was found to be best batch in terms of in vitro drug release with 97% release after 24 hrs as well as floating time that is 24 hrs (Table 1). F_3 – F_5 showed better release than other two batches. So it could be concluded that floating beads were more efficient to give sustained drug release.

In -vitro Dissolution Studies

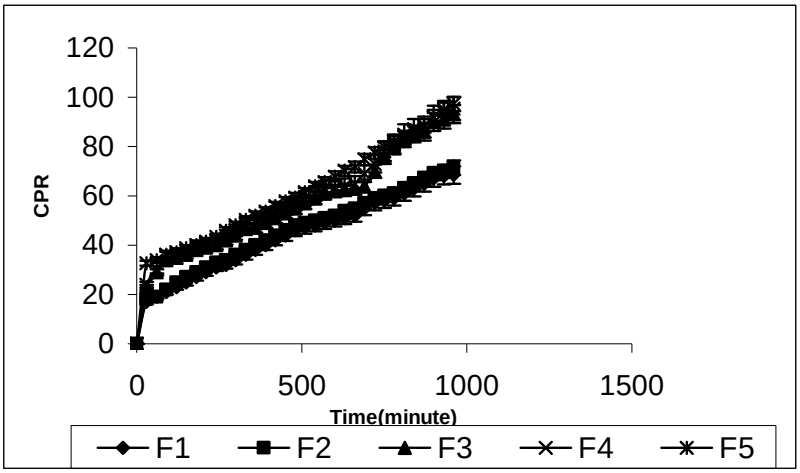

Figure 1: Release Profile of Different batches (F1-F5) of Famotidine Beads

DISCUSSION

In the research work, multiple-unit floating beads of famotidine were formulated to provide sustained release of drug with a view to providing an effective and safe therapy for stomach ulcer with a reduced frequency of dose with prolonged therapeutic effect. The formulation N_5 exhibited the optimum sustained release of famotidine, with excellent floating properties. Therefore, the floating-type gastroretentive dosage form of famotidine would be better for treating gastric ulcers.

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