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Buoyant Microspheres of Famotidine: An Approachable Dosage Form for Gastric Treatment

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ABSTRACT

The present study involves the preparation and evaluation of buoyant microspheres using famotidine as a model drug for prolongation of gastric retention time. The microspheres were prepared by the solvent evaporation method using different polymers i.e., acrycoat S100 and cellulose acetate. The size or average diameter (d_{avg}) characterized by optical microscopic method and surface morphology (internal texture) was recognized by the scanning electron microscopic method, which showed that fabricated microspheres were spherical with a smooth surface. The presence of pores was detected; this indicated leaching of the drug during the dissolution without gelation of polymeric surface. Effects of the stirring rate during preparation and polymer concentration on the size of microspheres and drug release were also observed by in vitro drug release kinetic studies. The prepared microspheres exhibited prolonged drug release (18 h). The cumulative release of famotidine significantly decreased with increasing polymer concentration ($P < 0.05$). The increased density of the polymer matrix at higher concentrations resulted in an increased diffusional path length. This may decrease the overall drug release from the polymer matrix. Furthermore, smaller microspheres are formed at a lower polymer concentration and have a larger surface area exposed to dissolution medium, giving rise to faster drug release that remained buoyant for more than 12 h. The mean particle size increased and the drug release rate decreased at higher polymer concentrations. No significant effect of the stirring rate during preparation on drug release was observed. In vitro studies demonstrated diffusion-controlled drug release from the microspheres.

Key words: Buoyant microspheres, famotidine, gastric treatment

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INTRODUCTION

Buoyant microspheres were used to increase the gastric residence time of dosage forms. The multiple unit system has been developed to identify the merit over a single unit dosage form. Such dosage forms are better because they reduce the inter-subject variability in absorption and lower probability of dose dumping.[1] Many polymeric solution systems that have been used to prepare floating microspheres are polycarbonate/dichloromethane[2,3] cellulose acetate butyrate/eudragit RL100 mixtures in acetone[4] and eudragit S100/i-propanol.[5] Famotidine was used as a model drug and was widely used for treating gastric and duodenal ulceration.[6] It is an anti-histaminic drug, that has been widely used in treating gastric and duodenal ulceration and also in the treatment of zollinger ellison syndrome and reflux esophagitis. It is poorly absorbed from the lower gastrointestinal tract and has a short elimination half life (3 h). The objective of this study was to develop floating microspheres of famotidine in order to achieve an extended retention in the upper gastrointestinal tract, which may result in enhanced absorption and thereby improved bioavailability. The prepared microspheres were evaluated for particle size,

buoyancy percentage, incorporation efficiency, and *in vitro* release study.

MATERIALS AND METHODS

Famotidine was obtained as a gift sample from Intas Pharmaceutical, Ahmedabad. Polyvinyl alcohol was obtained from S.D. Fine Chemicals Ltd., Mumbai. Dichloromethane, Acrycoat S100, Cellulose acetate, and Tween 80 were obtained from Central Drug House (P) Ltd., Delhi. All other chemicals or reagents used were of analytical grade.

Experimental methods

Preparation of buoyant microspheres

Microspheres were prepared by the solvent evaporation technique as employed by many of the researchers. Famotidine and polymers such as acrycoat S100 or cellulose acetate were dissolved in a mixture of solvent system [Table 1] at room temperature. This was poured into 150 mL of 0.1 M acidic solution containing polyvinyl alcohol and was maintained at 30–40°C and subsequently stirred at agitation speed [Table 1] for 2 h to allow the volatile solvent to evaporate completely. The formed microspheres were collected by filtration using a nylon cloth, washed repeatedly with distilled water, and dried in a vacuum or 1 h at room temperature and subsequently stored in a desiccator over fused Calcium chloride.

Table 1: Different formulations of buoyant microspheres

Code	Drug: Polymer ratio	Organic solvent system		Polyvinyl alcohol (%w/v)
C1*	1:1	Ethyl acetate: Acetone	1:1	0.05
C2*	1:2	Ethyl acetate: Acetone	1:1	0.05
C3*	1:3	Ethyl acetate: Acetone	1:1	0.05
C4**	1:2	Ethyl acetate: Acetone	1:1	0.05
C5***	1:2	Ethyl acetate: Acetone	1:1	0.05
A1*	1:1	Dichloromethane: Ethanol	1:1	2.0
A2*	1:2	Dichloromethane: Ethanol	1:1	2.0
A3*	1:3	Dichloromethane: Ethanol	1:1	2.0

Stirring rate = * 300 rpm, ** 400 rpm, *** 500 rpm

Table 2: Angle of Repose, Carr's Index, and Hausner's Ratio as an indication of powder flow properties

Angle of Repose	Carr's Index	Hausner's ratio	Type of Flow
>20°	5–15%	-	Excellent
20–30	12–16%	<1.25	Good
30–40°	18–21%	-	Fair to passable
–	23–35%	>1.25	Poor
–	33–38%	1.25–1.5	Very poor
>40°	>40%	-	Extremely poor

Characterization of microspheres

Size and shape of microspheres: The size distribution in terms of average diameter (d_{avg}) of microspheres was determined using the optical microscopic method (Olympus NWF 10x, Educational Scientific Stores, India). Scanning electron microscopy (SEM) was performed to characterize the surface morphology of formed microspheres (Philips-XL-20, The Netherlands).[2]

Flow properties: Flow properties were determined in terms of Carr's index (Ic), Hausner's ratio (H_R), and Angle of repose (θ) by using following equations [Table 2]:[4]

$$H_R = \varrho_t / \varrho_b \qquad I_c = \varrho_{t-} \varrho_b / \varrho_t \qquad \tan\theta = 2H / D$$

Where ϱ_t = tapped density, ϱ_b = bulk density, H= height of the heap, and D= diameter of heap

Incorporation efficiency (IE): To determine the incorporation efficiency, microspheres (100 mg) were taken, thoroughly crushed by triturated in pestal mortar, and suspended in a minimal amount of dichloromethane for dissolving coat shell of microspheres. The suspension was suitably diluted with water and filtered to separate shell fragments. The drug content was analyzed after suitable dilution spectrophotometrically at 265 nm (Thermospectronic, UV 1-103909, and England). The amount of drug incorporation in microspheres was calculated by the following formula:[7]

IE = (amount of drug actually present/theoretical drug load expected) x 100

Buoyancy percentage: An *in vitro* buoyancy study was conducted by spreading microspheres (0.3 g) over the surface of a USP XXIV dissolution apparatus (Type II) (DA-6DR USP standards Veego-Scientific, Mumbai) filled with 900 ml 0.1 M acidic solution (HCl) containing 0.02% Tween 80 as a dispersing medium. The medium was agitated with a paddle rotating at a speed of 100 rpm for 12 h. After each time interval, the floated microspheres were collected, dried, and weighed. Buoyancy percentage was calculated using the following formula:[7]

% buoyancy of microspheres = (weight of buoyant microspheres/initial weight of buoyant microspheres) x 100

In vitro release: A USP basket apparatus has been used to study *in vitro* drug release from prepared buoyant microspheres. In the present study, drug release was studied using a modified USP XXIV dissolution apparatus

Table 3: Various parameters of characterization of formulations

Code	Mean particle size (μm)[a]	Angle of Repose[a] (θ)	Carr's Index[a] (%)	Hausner's Ratio[a]	Incorporation efficiency (%)[b]	Buoyancy percentage[b]
C1	375.1±1.818	21.390+0.671	13.253+0.624	1.152+0.013	86.15±0.044	70.6±2.1
C2	378.7±2.914	23.410+0.035	14.285+0.345	1.66+0.023	85.32±0.011	69.2±3.3
C3	389.3±1.984	22.820+0.553	13.496+0.413	1.156+0.072	84.85±0.012	62.6±3.6
C4	372.2±1.154	25.390+0.308	13.812+0.823	1.160+0.062	84.23±0.025	61.25±4.1
C5	368.3±2.128	29.810+0.071	12.972+0.316	1.149+0.012	83.56±0.035	63.17±3.6
A1	380.8±2.164	22.520+0.351	12.359+0.749	1.166+0.039	83.15±0.032	62.2±2.1
A2	383.6±1.854	23.460+0.421	10.054+0.613	1.141+0.013	83.51±0.034	58.1±1.8
A3	390.6±1.931	24.310+0.312	11.053+0.931	1.148+0.027	81.35±0.016	60.6±1.9

[a]Mean ± SD, n = 10. [b]Mean ± SD, n = 3.

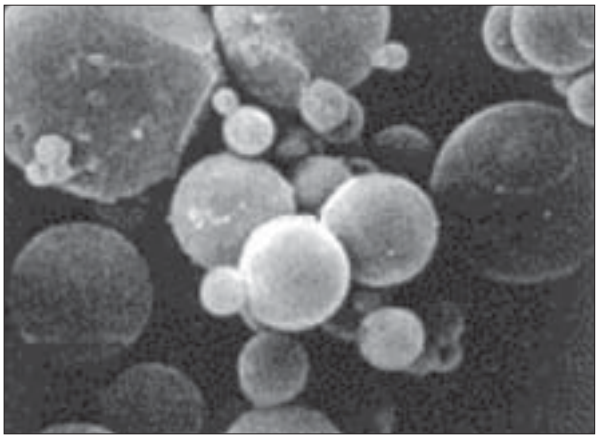

Figure 1: Surface morphology of buoyant microspheres before *in vitro* release by scanning electron microscopic photographs (the parameters of the scanning electron microscopy were acceleration voltage of 20 kV, chamber pressure of 0.6 mm Hg, and original magnification X 800)

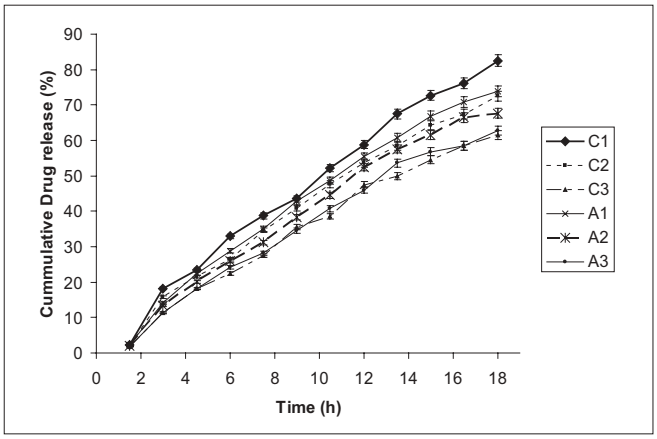

Figure 2: The effect of cellulose acetate (batch C1-C3) and acrycoat S100 (batch A1-A3) polymeric concentration on the *in vitro* release of famotidine (bars represent mean ± SD; n=3, codes in Table 1)

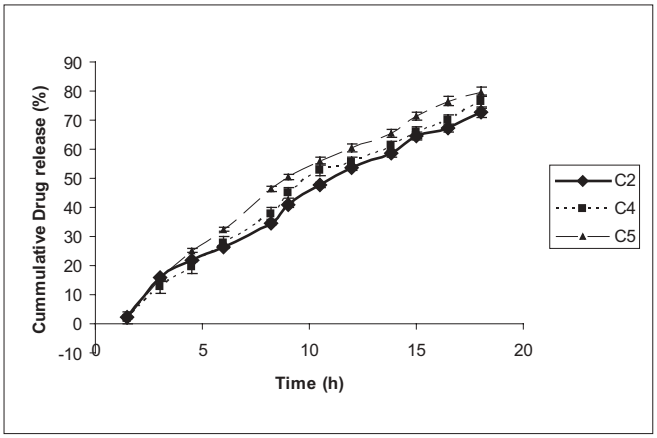

Figure 3: The effect of the stirring rate during preparation of microspheres on the *in vitro* release of famotidine (bars represent mean ± SD; n=3, codes in Table 1)

Type I (basket mesh # 120, equals 125 μm) (DA-6DR USP standards Veego-Scientific, Mumbai) at 100 rpm in distilled water or in 0.1 mol L^{-1} hydrochloric acid (pH 1.2) as dissolution fluids (900 ml) maintained at 37 ± 0.5 °C separately. Withdrawn samples (10 ml) were analyzed spectrophotometrically as stated above. The volume was replenished with the same amount of fresh dissolution fluid each time to maintain the sink condition. All experiments were performed in triplicate.[7] Linear regression was used to analyze the *in vitro* release mechanism.

RESULTS AND DISCUSSION

Buoyant microspheres were prepared using the solvent evaporation method using various proportions of drug and polymer such as cellulose acetate (batch C1-C5) and acrycoat S100 (batch A1-A3) by variation stirring rate for determination of the microspheric characteristics [Table 1]. It was found that cellulose acetate containing microspheres showed a desirable high-drug content, good flow properties, buoyancy, and adequate release characteristics; hence formulations prepared by such polymers are suitable for the development of gastric retention dosage forms. The surface morphology and internal texture were observed by scanning electron microscopic photographs, which showed that the fabricated microspheres were spherical with a smooth surface [Figure 1]. The presence of pores was detected on a microspheric surface, this indicated leaching of the drug during the dissolution without gelation of the polymeric surface.

Microspheres were prepared using a gradually increasing polymer concentration in combination with a fixed concentration of drug to assess the effect of polymer concentration on the size of microspheres. The mean particle size or average diameter (d_{avg}) of the microspheres significantly increased with increasing cellulose acetate concentration ($P < 0.05$) and was in the range 368.2±2.128 to 389.3±1.984 μm [Table 3]. Cellulose acetate polymer containing microspheres were smaller in size and have a smoother surface than acrycoat S 100 polymer coated microspheres; microspheres prepared by a higher stirring rate showed smaller size particles and lower drug content but the size of the microspheres reduced, thus, changing flow properties of the microspheres which was not seen in other formulations [when co-relate between Tables 1 and 3]. Those particles or microspheres having a smaller size showed good flow properties [Table 3]. All formulations floated for more than 12 h over the surface of the dissolution medium without any apparent gelation. The cumulative release of famotidine significantly decreased with increasing polymer concentration ($P < 0.05$; Figure 2). Furthermore, smaller microspheres were formed at a lower polymer concentration with a higher stirring rate having a larger surface area exposed to dissolution medium, giving rise to faster drug release [Figure 3]. The data obtained for *in vitro* release were fitted into equations for the zero-order, first-order, and Higuchi release models. The *in vitro* drug release showed the highest regression coefficient values for Higuchi's model, indicating diffusion to be the predominant mechanism of drug release.

CONCLUSION

Buoyant microspheres of famotidine were prepared using the solvent diffusion-evaporation method. The nature of polymers and their concentration influenced the physical and floating behavior of prepared microspheres. *In vitro* release data obtained from buoyant microspheres showed excellent flow property, good buoyancy, and prolonged drug release. The prepared microspheres had a different size and the incorporation efficiency of the drug could be obtained by varying the formulation variables such as polymeric concentration and stirring rate. Such formulation variables can change microspheric characteristics. Drug release was based on the diffusion type of release mechanism. Thus, the prepared buoyant microspheres may prove to be potential candidates for multiple-unit delivery devices adaptable to any intragastric condition. Further, their potential to improve famotidine bioavailability in animal modeling needs to be investigated in further studies for *in vitro* and *in vivo* co-relation.

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