

Formulation and Evaluation of Floating Microspheres of Famotidine

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ABSTRACT : The purpose of this research was to prepare a floating drug delivery system of famotidine. In the present study, preparation of famotidine floating microspheres, evaluation of Floating Drug Delivery System (FDDS) in vitro, prediction of the release, and optimization of stirring speed and polymers ratio to match target release profile was investigated. Floating microspheres were prepared by solvent evaporation (Oil-in-water emulsion) technique using hydroxylpropyl methylcellulose (HPMC) and Ethylcellulose (EC) as the rate controlling polymers. Particle size analysis, drug entrapment efficiency, surface topography, buoyancy percentage and release studies were performed. Results showed that the polymer ratio and stirring speed affected the size, incorporation efficiency and drug release of microspheres (> 12 h), floating time (> 12 hr) and the best results were obtained at the ratio of HPMC:EC (1:6). The mean particle size of prepared floating microspheres increased but the drug release rate from the microspheres decreased as the polymer concentration increased. The developed floating microspheres of famotidine may be used in clinic for prolonged drug release in stomach for at least 12 hrs, thereby improving the bioavailability and patient compliance.

Keywords: Floating drug delivery system (FDDS), HPMC, Ethyl cellulose, famotidine, *in-vitro* release.

INTRODUCTION

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms.¹

Several approaches are currently used to prolong gastric retention time. These include floating drug delivery systems, also known as hydrodynamically balanced systems, swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems, and other delayed gastric emptying devices.²

Floating drug delivery system (FDDS) promises to be a potential approach for gastric retention. The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion,

flotation, sedimentation, expansion, modified shape systems, or by the simultaneous administration of pharmacological agents that delay gastric emptying.¹

Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. Hollow microspheres are in strict sense, spherical empty particles without core. These microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs. Floating microspheres have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs the increasing sophistication of delivery technology will ensure the development of increasing number of gastro-retentive drug delivery systems to optimize the

delivery of molecules that exhibit absorption window, low bioavailability, and extensive first pass metabolism.^{3,4}

Famotidine is a histamine H₂-receptor antagonist. It is widely prescribed in gastric ulcers, duodenal ulcers, Zollinger-Ellison syndrome and gastroesophageal reflux disease. In the management of benign gastric and duodenal ulceration the dose is 40 mg daily by mouth at bedtime, for 4 to 8 weeks. In gastroesophageal reflux disease the recommended dose is 20 mg by mouth twice daily for 6 to 12 weeks; where gastroesophageal reflux disease is associated with esophageal ulceration, the recommended dosage is 40 mg twice daily for a similar period. For the short term symptomatic relief of heartburn or non-ulcer dyspepsia a dose of 10 mg up to twice daily is suggested. In the Zollinger-Ellison syndrome the initial dose by mouth is 20 mg every 6 hours, increased as necessary; dose up to 80 mg daily have been employed. The low bioavailability (40-45%) and short biological half life (2.5-4.0 hours) of famotidine following oral administration favors development of a sustained release formulation.^{5,6}

In the present investigation floating microsphere of famotidine were prepared by solvent evaporation (Oil-in-water emulsion) using two different polymer hydroxypropylmethyl cellulose (HPMC) and ethyl cellulose (EC). The aim of the work was to evaluate microspheres for size, *in-vitro* release, buoyancy and incorporation efficiency. The effect of various formulation variables on the size and drug release was also investigated.

MATERIALS AND METHODS

MATERIAL

Famotidine was obtained as a gift sample from Zydus Cadila Healthcare (India). Dichloromethane (DCM), dimethylformamide (DMF), hydroxypropylmethyl cellulose (HPMC), ethyl cellulose (EC) and Tween 80 were obtained from Sigma (India). All other chemicals/reagents used were of analytical grade, available commercially and used as such without further processing. A UV/Vis spectrophotometer (Systronics, Double beam UV-VIS Spectrophotometer: 2201) was used for drug analysis.

PREPARATION OF MICROSPHERES

Microspheres were prepared by solvent evaporation (Oil-in-water emulsion) technique. Famotidine, hydroxypropyl methylcellulose (HPMC), and ethyl cellulose (EC) (1:1) were dissolved in a mixture of dimethylformamide and dichloromethane (1:1) at room temperature. This was poured into 250 ml water containing 0.02% Tween 80 maintained at a

temperature of 30-40 °C and subsequently stirred at ranging agitation speed for 20 min to allow the volatile solvent to evaporate. The microsphere formed were filtered, washed with water and dried in vacuum.

CHARACTERIZATION OF MICROSPHERES

Microsphere Image Analysis

Scanning electron microscopy (SEM) was performed to characterize the surface of formed microspheres. Microspheres were mounted directly onto the sample stub and coated with gold film under reduced pressure. This film acts as a conducting medium on which a stream of electron was allowed to flow and then photograph was taken with SEM.

Determination of Entrapment Efficiency

To determine the incorporation efficiency, 40 mg of microsphere were taken, thoroughly triturated and suspended in a minimal amount of dimethylformamide. The suspension was filtered to separate shell fragments. Drug contents were analyzed spectrophotometrically at 265 nm.^{7,8}

$$\text{Drug entrapment efficiency} = \frac{\text{Experimental drug content}}{\text{Theoretical drug content}} \times 100$$

Buoyancy percentage:

Microparticles (0.3g) were spread over the surface of a USP XXIV dissolution apparatus (type II) filled with 900 ml 0.1 mol- HCl containing 0.01% Tween 80. The medium was agitated with a paddle rotating at 100 rpm for 12 hrs. The floating and the settled portion of microspheres were recovered separately. The microspheres were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the microspheres that remained floating and the total mass of the microspheres.^{9,10}

$$\% \text{ Buoyancy} =$$

$$\frac{\text{Microsphere remained floating}}{\text{Total mass of microspheres}} \times 100$$

In Vitro Release of Famotidine from Microspheres

The United States Pharmacopoeia basket-type dissolution rate test apparatus was used for all the *in vitro* release studies. A weighed quantity of the microspheres was suspended in 900 mL of 0.1 mol HCL of pH 1.2. The dissolution medium was stirred at 100 rpm and maintained at constant temperature (37±0.5 °C). At preset time intervals 5 mL aliquots were withdrawn and replaced by an equal volume of fresh pre-warmed dissolution medium maintaining sink condition throughout the experiment. After suitable dilution, the samples were analyzed for drug quantification at 265 nm using Systronics, Double beam UV-VIS Spectrophotometer: 2201. The

concentrations of famotidine in samples were calculated using regression equation ($y = 0.0118x$, $R^2 = 0.9995$) of the calibration curve of famotidine in 0.1 N HCl of pH 1.2.¹¹

Mechanism of release

The mechanism of release was determined by fitting the release data to the various kinetic equations such as zero-order, first-order, Higuchi, and Korsmeyer-Peppas and finding the R^2 values of the release profile corresponding to each model.^{12, 13}

RESULTS AND DISCUSSIONS

Particle size analysis

The particle size of floating microspheres varied somewhat among the formulation due to variation in the composition of formulations. The effects of stirring speed and polymer to polymer ratio on the particle size of microspheres are shown in Table 1 and Table 2. Formulation A7 showed relatively higher percentage of large size and formulation A1 showed relatively small size floating microspheres because as viscosity of the medium increases at a higher polymer concentration resulting in enhanced interfacial tension. Shearing efficiency is also diminished at higher viscosities. This results in the formation of larger particles. As stirring speed increases from 300 rpm to 1000rpm particle size decrease from 282.11 μm to 147.36 μm due to agitation speed break up the bulk of the polymer into finer droplets.

The size and surface morphology of floating microspheres were examined by scanning electron microscopy as shown in figures 1 illustrating the microphotographs of formulation A6. The floating microspheres were spherical with no visible major surface irregularity.

Drug entrapment efficiency

Drug entrapment efficiency was found to be optimum (63.47 %) at the stirring speed of 500 rpm. As the stirring speed reduced to 300 rpm or increased to 1000 rpm there was significant decrease in entrapment efficiency shown in Table 1.

The entrapment efficiency was found to be 57.34% to 85.03% for formulation A1 to A6 but there is no significant difference between batch A6 and A7. Drug entrapment efficiency was increased with increasing polymer concentration in floating microspheres. This may be due to low solubility of famotidine in water which facilitates the diffusion of a part of entrapped drug to surrounding medium during preparation of floating microspheres. The drug entrapment efficiency of different batches of floating microspheres was found to about 85.03 % w/w, results are given in Table 2. Among the different polymer-drug ratios

investigated, 1:6 polymer- drug ratio had the optimum capacity for drug encapsulation.

The Buoyancy Percentage

The buoyancy percentage for all batches was almost above 70%, which was studied for 12 h. Average buoyancy in percentage was found to be 71.04% to 89.36%. The highest percentage was obtained with formulation A6. In general with increase in the amount of polymer (Ethyl Cellulose), there was an increase in the buoyancy percentage. From the table 2, it was concluded that on increasing ethyl cellulose concentration incorporation efficiency and % buoyancy increase continuously.

In-vitro dissolution study

Ethyl cellulose is low permeable and water insoluble polymer. Floating microspheres showed sustained release of the drug in acidic environment and the drug release was found to be approximately linear. Approximately 15% of the drug was released initially. Furthermore, the drug release from the floating microspheres matrix was controlled by the polymer. As the ethyl cellulose was increased, the release of drug was decreased significantly this may be due to increased density of the polymer matrix at higher concentrations results in an increased diffusional pathlength. 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.(figure-2)

Mechanism of release

The data obtained for *in-vitro* release were fitted into equations for the zero-order, first- order and higuchi release models. The interpretation of data was based on the value of the resulting regression coefficients. The *in-vitro* drug release showed the highest regression coefficient values for higuchi model, indicating diffusion to be the predominant mechanism of drug release.(Table-3)

CONCLUSION

In-vitro data obtained for floating microspheres of famotidine showed good incorporation efficiency, good buoyancy and prolonged drug release. Microspheres of different size and drug content could be obtained by varying the formulation variables. From the results it can be concluded that the drug release from the floating microspheres matrix was controlled by the polymer proportion. Prepared formulation showed best appropriate balance between buoyancy and drug release rate.

Table 1- Optimization of stirring speed with regards to average particle size and average percent drug entrapment

| Batch | Resolution Per Minute | Mean particle size (μm) | Drug Entrapment Efficiency |
|----------|-----------------------|--------------------------------------|----------------------------------|
| A | 300 | 282.11 \pm 0.74 | 57.83 \pm 1.28 |
| B | 500 | 222.116\pm2.42 | 63.47\pm0.37 |
| C | 1000 | 147.36 \pm 1.32 | 38.97 \pm 0.95 |

Table 2- Optimization of polymer ratio with regards to average particle size and average percent drug entrapment

| S. No | Batch code | HPMC:EC | Mean particle size (μm) | Entrapment efficiency% | Buoyancy (%) | Cumulative % release after 12 hours |
|-------|------------|---------|--------------------------------------|------------------------|-----------------|-------------------------------------|
| 1 | A1 | 1:1 | 222.116 \pm 2.42 | 57.34 \pm 1.78 | 71.04 \pm 2.2 | 98.47 |
| 2 | A2 | 1:2 | 247.313 \pm 1.15 | 60.65 \pm 0.987 | 75.30 \pm 1.6 | 95.04 |
| 3 | A3 | 1:3 | 280.031 \pm 2.50 | 67.16 \pm 0.768 | 79.53 \pm 0.5 | 92.57 |
| 4 | A4 | 1:4 | 347.842 \pm 0.95 | 72.45 \pm 0.234 | 82.26 \pm 3.1 | 88.19 |
| 5 | A5 | 1:5 | 366.129 \pm 19.11 | 78.84 \pm 1.34 | 87.52 \pm 0.9 | 84.45 |
| 6 | A6 | 1:6 | 462.777 \pm 0.39 | 85.03 \pm 3.09 | 89.36 \pm 2.2 | 81.24 |
| 7 | A7 | 1:7 | 499.982 \pm 0.37 | 86.13 \pm 1.43 | 88.87 \pm 2.1 | 76.49 |

Mean \pm S.D., n=3**Table 3: Study of drug release kinetics of optimized batch A6**

| Batch code | Zero order equation | | First order equation | | Higuchi model | | Korsmeyer–Peppas | |
|------------|---------------------|-------------------------------------|----------------------|-------------------------------------|----------------|-------------------------------------|------------------|--------|
| | R ² | k ₀ (day ⁻¹) | R ² | k ₁ (day ⁻¹) | R ² | k _H (day ⁻¹) | R ² | n |
| A6 | 0.7536 | 0.2225 | 0.9247 | 0.0016 | 0.9764 | 4.2997 | 0.9683 | 0.4867 |

**Fig. 1 Surface morphology of floating microspheres by scanning electron microscopy**

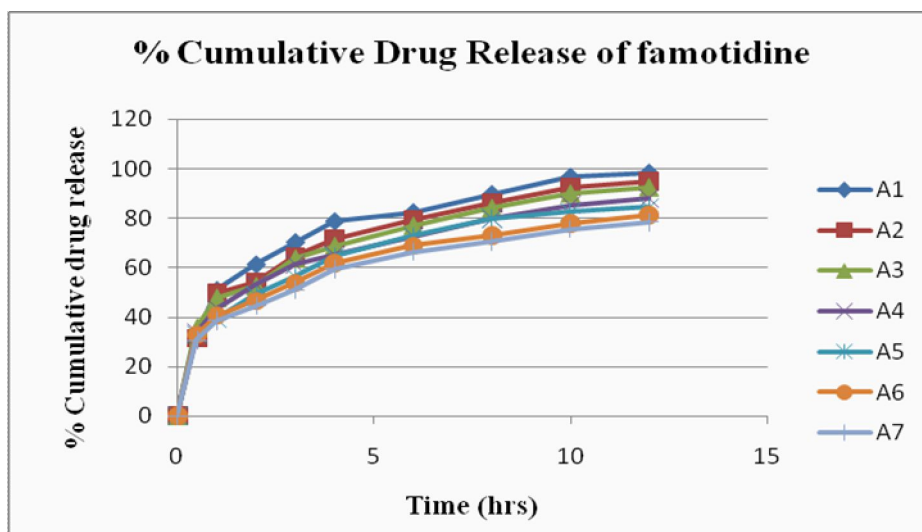


Fig. 2 In-vitro release of famotidine floating microspheres

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