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Optimization of Methods for the Preparation of Famotidine Floating Microspheres

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ABSTRACT

The objective of present study was development and optimization of floating microspheres of famotidine. The floating microspheres can be prepared for the improvement of absorption and bioavailability of famotidine by retaining the system in the stomach for prolonged period of time. The FDDS of famotidine were prepared by different techniques, i.e. polymer phase-separation method, multiple emulsions–water–in-oil-in-water method, oil-in-water emulsion method by using ethyl cellulose and HPMC polymers in same concentration (1:1). Microspheres were evaluated for particle size, drug loading entrapment efficiency and in-vitro drug release. The results obtained from in-vitro dissolution studies were fitted into various kinetic models. The drug release kinetics was best expressed by Higuchi model.

Keywords: Floating drug delivery system (FDDS), HPMC, Ethyl cellulose, Famotidine.

INTRODUCTION

One of the most viable approaches for achieving a prolonged and predictable drug delivery in the gastrointestinal tract is to control the gastric residence time (GRT), i.e. gastro retentive dosage form 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, polymeric bioadhesive systems, swelling and expanding systems, high-density systems, modified-shape systems, and other delayed gastric emptying devices. Floating drug delivery system (FDDS) is an oral dosage form (capsule or tablet) designed to prolong the residence time of the dosage form within the GIT. [2, 7]

Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach and involve the mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract.[6-8] Floating microspheres have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs (aspirin, griseofulvin, p-nitroaniline, ibuprofen, terfinadine and tranilast) [3, 11-15].

Famotidine is a histamine H2-receptor antagonist. It is widely prescribed in gastric ulcers, duodenal ulcers, Zollinger-Ellison syndrome and gastroesophageal reflux disease (dose is 20 mg by mouth twice daily for 6 to 12 weeks). 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. [4, 10]

The present investigation deals with floating microspheres of famotidine, prepared by different techniques using hydroxypropylmethyl cellulose (HPMC) and ethyl cellulose (EC). The aim of the work was to optimize the methods for preparation of microspheres and their evaluation with regard to size, drug loading, incorporation efficiency and *in-vitro* drug release.

MATERIALS AND METHODS

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.

Preparation of microspheres

1. Polymer phase-separation method: In this method famotidine and HPMC, ethyl cellulose was dissolved in dichloromethane and dimethylformamide (1:1) at room temperature to form polymeric solution, then the polymeric solution was added slowly to the tween 80 with constant stirring using a magnetic stirrer at a rate of 500 rpm for 45 min. The finely dispersed droplets of the polymer-drug were filtered, washed and dried.

2. Multiple emulsions – Water-in-oil-in-Water: In this method, firstly the famotidine was dissolved in mixture of water and dimethyformamide (DMF) which contained Tween 80 (0.02%), then hydroxypropyl methylcellulose (HPMC), and ethyl cellulose (EC) (1:1) were dissolved in dichloromethane (DCM) and stirred to form primary emulsion. The prepared primary emulsion was then added to a large volume of water containing PVA (1% w/v) to form multiple emulsions. The double emulsion was then stirred to evaporate the solvent. Microspheres were collected, washed and dried.

3. Oil-in-water emulsion: Microspheres were prepared by solvent evaporation technique in which drug (famotidine) and polymers hydroxypropyl methylcellulose (HPMC), and ethyl cellulose (EC) in ratio of 1:1 were dissolved in a mixture of dimethylformamide and dichloromethane (1:1) at room temperature. This drug-polymer solution was slowly poured into 250 ml water containing 0.02% Tween 80 maintained at a temperature of 30-40 ◦C and

subsequently stirred at 500 rpm for 1 hr to allow the evaporation of volatile solvent. The prepared microsphere were filtered, washed with water and dried in vacuum. [12]

Characterization of prepared microspheres

Microsphere image analysis

Scanning electron microscopy was performed to characterize the surface of formed microspheres using SEM, Philips-XL-20. Microspheres were mounted directly onto the sample stub and coated with platinum film.

Entrapment efficiency & drug loading

Entrapment efficiency and drug loading was determined by taking weighed quantity of microspheres equivalent to 40 mg drug, thoroughly triturated and dissolved in a minimal amount of dimethylformamide. The resulting solution was filtered, suitably diluted and analyzed spectrophotometrically at 265 nm by using the equations given below.

(1) Drug loading (%) = weight of drug/ weight of powdered microspheres x 100

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

***In-vitro* release of famotidine from microspheres**

The *in-vitro* release studies were performed in USP (XXIV) Dissolution Apparatus Type I in 900 ml of 0.1M HCl of pH 1.2. A weighed quantity of the microspheres was placed into the baskets (tied using muslin cloth) and dissolution medium was stirred at 100 rpm and maintained at constant temperature (37±0.5 ^{O}C). At preset time intervals, 5 ml aliquots were withdrawn and replaced by an equal volume of fresh pre-warmed dissolution medium thereby 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.

Kinetics of drug release

In order to investigate the mechanism of famotidine release from microspheres, the release data was analyzed with the following mathematical models, zero order (Eq. (3)), Higuchi (Eq. (4)), first order (Eq. (5)).

$$Q = k_1 t \quad (3)$$

$$Q = k_2(t)0.5 \quad (4)$$

$$Q = 100(1 - e^{-k_3 t}) \quad (5)$$

where Q is the percentage release at time t. k_1, k_2 and k_3 are the rate constants of zero order, Higuchi, and first order model, respectively.

In addition to these basic release models, there are several other models as well. One of them is Peppas and Korsmeyer (Eq. (6)).

$$Mt / M\alpha = K_p t^n \qquad (6)$$

where Mt / Mα is the fraction of the drug release at time t, K_p is the rate constant and n is the release exponent. The n value is used to characterize different release mechanisms and is calculated from the slope of the plot of log of fraction of drug released (Mt / Mα) vs log of time (t). [16, 17]

RESULTS AND DISCUSSION

The particle size of floating microspheres varied somewhat among the formulation due to variation in the method of preparation of various formulations (Fig. 1). Particle size (225.109±0.72 µm) was found to be satisfied when prepared by o/w emulsion method (Table I). Microspheres prepared by o/w emulsion method showing lesser size than other methods. This range of particle size can be accredited to the effect of stirring time, stirring speed and rate of solvent evaporation during preparation of microspheres.

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

Drug entrapment efficiency was found to be optimum (61.37±0.24 %) when prepared by oil-in-water emulsion method at the stirring speed of 500 rpm and ratio of polymer (HPMC:EC) was 1:1. It can be due to the drug is fully dispersed in the polymer phase by continuous stirring for a longer period. Drug content of microspheres was found to be optimum (33±0.75) in formulation M-3.

Table I: Effect of method of preparation on the particle size, entrapment efficiency

Batch No.	Method	Mean Particle Size (µm)	Drug Entrapment (%)	Drug Loading (%)
M-1	Polymer phase-separation methods	497.842±0.95	35±0.34	11±0.56
M-2	Multiple emulsion (water-in-oil-in-water)	389.982±0.37	45±0.95	22±0.87
M-3	Solvent evaporation (Oil-in-water emulsion)	225.109±0.72	61.37±0.24	33±0.75

The formulation M-3 prepared by o/w emulsion method, has potential to deliver famotidine in a controlled manner in a regular fashion over extended period of time in comparison to all other

formulations. The *in-vitro* release of floating microspheres showed 97.36% release of the drug after 12 hrs in acidic environment, due to small particle size of formulation M-3, provide large surface area for dissolution shown in Fig. 2.

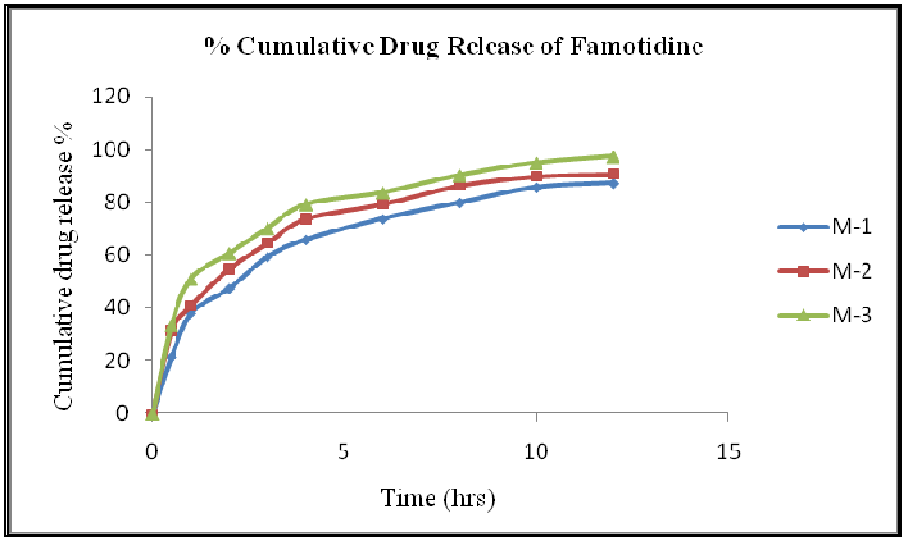

Fig. 2: *In-vitro* Release of Famotidine Microspheres

The *in-vitro* release profiles were fitted into various kinetic models in order to find out the mechanism of drug release of optimized formulation (M-3). The rate constants were calculated from the slope of the respective plots. High correlation (R^2=0.9435) was observed in the Higuchi plot rather than first-order (R^2=0.3162) and zero-order (R^2=0.7162) models. The drug release was proportional to square root of time, indicating that the drug release from microspheres was diffusion controlled. The data obtained was also fit into Korsmeyer-Peppas model in order to find out n value, which describes the drug release mechanism. The n value of the optimized formulation (M-3) was above 0.5, indicating that the mechanism of the drug release was anomalous (Table II).

Table II: *In-vitro* release kinetic parameters of famotidine loaded microspheres (Batch M-3)

Batch No	Kinetic Model							
	Zero Order		First Order		Higuchi Model		Korsemeyer Peppas Model	
M-3	R^2	K_o	R^2	K_1	R^2	K_h	R^2	K_n
	0.7162	6.2302	0.3162	0.0803	0.9435	24.884	0.906	0.6663

CONCLUSION

Selection of appropriate method for preparation of microspheres must be taken in to consideration for designing the best microsphere formulation. Data obtained for floating microspheres of famotidine showed good incorporation efficiency, optimum particle size and controlled release of drug from microspheres as they are prepared by oil-in-water emulsion method. The release kinetics followed the Higuchi model. From the above study it could be concluded that method of preparation have great effect on better physical properties and drug release profile of microspheres.

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