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Research Article

Formulation Development and Evaluation of Floating Microsphere of Famotidine for the Treatment of Peptic Ulcer

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ABSTRACT

The purpose of this research was to prepare a floating drug delivery system 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. Floating microspheres of famotidine were prepared using different polymers like ethyl cellulose, hydroxy propyl methyl cellulose by solvent diffusion-evaporation method. The microspheres had smooth surfaces with free-flowing and good-packing properties. The yield of the microspheres was up to $73.32 \pm 0.14\%$ and ethyl cellulose microspheres entrapped the maximum amount of the drug. Scanning electron microscopy confirmed their hollow structures with sizes in 331.6 nm. The prepared microspheres exhibited prolonged drug release and Percentage buoyancy was found to 73.25 ± 0.23 . The formulated batches were evaluated for percentage yield, particle size measurement, flow properties, percent entrapment efficiency, swelling studies. The formulations were subjected to stability studies and In-vitro release and release kinetics data was subjected to different dissolution models. It was concluded that developed floating microspheres of famotidine offers a suitable and practical approach for prolonged release of drug over an extended period of time and thus oral bioavailability, efficacy and patient compliance is improved.

Keywords: Famotidine, Solvent diffusion evaporation method, Ethyl cellulose, Hydroxyl propyl methyl cellulose

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INTRODUCTION

Oral route of administration is the most convenient and widely used method of drug administration and the development of stomach specific oral controlled-release drug delivery systems is a challenging job due to the variation of pH in different segments of the gastrointestinal tract, the fluctuation in gastric emptying time and the difficulty of localizing an oral delivery system in a selected region of the gastrointestinal tract. Rapid gastrointestinal transit can prevent the absorption of complete drug in the absorption zone and reduce the efficacy of the administered dose since the majority of drugs are absorbed in stomach or the upper part of small intestine^{1, 2}. To overcome the above discussed issues, many types of oral controlled drug delivery systems having prolonged gastric residence times have been reported such as: floating drug dosage systems (FDDS)³⁻⁷, swelling or expanding system⁸, mucoadhesive systems^{9,10} modified-shape systems¹¹, high-density systems and other delayed gastric emptying devices¹². FDDS have lower density than gastric fluids and thus remain buoyant in the stomach fluid without affecting the gastric emptying for a prolonged period

of time. While the system is floating in the gastric fluid, the drug is released slowly from the system at a desired rate. Materials used for FDDS include carbon dioxide gas-forming agents (carbonate or bicarbonate compounds)^{8,13}, highly swellable hydrocolloids and light mineral oils^{14,15}. Multiple unit systems and floating systems prepared by solvent evaporation methods have also been developed^{12, 16-20}. However, it has been shown that products based on a multiple unit system comprising many small units have advantages over single-unit preparations such as matrix tablets²¹. The gastric emptying of multiple unit dosage forms occur gradually, in a more consistent manner, with less individual variation^{2,22}. Multiple unit dosage forms also have the potential to distribute widely over a large area in the stomach and small intestine, thus yielding a more predictable drug release by suppressing the effect of many variables in the gastrointestinal environment. As multiple unit dosage forms consist of many small units, less risk of dosage dumping is expected²³. Famotidine, a competitive histamine H₂-receptor antagonist is used to treat gastrointestinal disorders such as gastric or duodenal ulcer, gastroesophageal reflux disease, and pathological

hypersecretory conditions. Famotidine inhibits many of the isoenzymes of the hepatic CYP450 enzyme system. Other actions of famotidine include an increase in gastric bacterial flora such as nitrate-reducing organisms²⁴. Famotidine is widely used as the treatment of peptic ulcer disease and gastroesophageal reflux disease. Famotidine binds competitively to H₂- receptors located on the basolateral membrane of the parietal cell, blocking histamine affects. This competitive inhibition results in reduced basal and nocturnal gastric acid secretion and a reduction in gastric volume, acidity, and amount of gastric acid released in response to stimuli including food, caffeine, insulin, betazole and pentagastrin²⁵. Floating microspheres are one of the multiparticulate delivery system and are prepared to obtain prolonged or controlled drug delivery to improve bioavailability and to target drug to specific sites. Microspheres can also offer advantages like limiting fluctuation within therapeutic range, reducing site effects, decreasing dosing frequency and improving patient compliance²⁶.

MATERIAL AND METHODS

Material

Famotidine was a gift sample from Pharmaceuticals Company. Dichloromethane, ethanol and isopropyl alcohol were purchased from E. Merck (India) Ltd., Mumbai. Ethyl cellulose, hydroxyl propyl methyl cellulose was purchased from Loba Chem. Pvt. Ltd, Mumbai. Double distilled water was prepared freshly and used whenever required. All the chemicals used in this work were of analytical grade.

Methods

Determination of absorption maxima

A solution of containing the concentration 10µg/ml was prepared in 0.1N HCl. UV spectrum was taken using Double beam UV/VIS spectrophotometer (Labindia-3000+). The solution was scanned in the range of 200-400nm.

Preparation calibration curve

Accurately weighed 10 mg of drug was dissolved in 10 ml of 0.1N HCl solution in 10 ml of volumetric flask. The resulted solution 1000µg/ml and from this solution 1 ml pipette out and transfer into 10 ml volumetric flask and volume make up with 0.1N HCl solution. Prepare suitable dilution to make it to a concentration range of 5-25µg/ml. The spectrum of this solution was run in 200-400 nm range in U.V. spectrophotometer (Labindia-3000+). Linearity of standard curve was assessed from the square of correlation coefficient (r²) which determined by least-square linear regression analysis.

Preparation of floating microsphere of Famotidine

Floating microspheres loaded with famotidine were prepared using solvent diffusion-evaporation method using HPMC and EC in different ratio like 1:0.5, 1:0.75, 1:1, 1:1.5, 1:1.75, 1:2 w/w. Drug and polymer in proportion of drug and polymers were dissolved in 1:2 mixture of solvent system of ethanol and dichloromethane. This clear solution was poured slowly in a thin stream into the aqueous solution of 1% polyvinyl alcohol. The emulsion was continuously stirred for 3 hrs at a speed of 500 rpm at 27±2°C. The floating microspheres were collected by decantation, while the non-floating microspheres were discarded. The microspheres were dried overnight at 40±2°C and stored in desiccator. The compositions of the formulations were shown in Table 1.

Table 1 Formulations of the floating microspheres prepared

Sr. No	Formulation Code	Famotidine (mg)	HPMC (mg)	EC (mg)
1.	F1	40	100	50
2.	F2	40	100	75
3.	F3	40	100	100
4.	F4	40	100	125
5.	F5	40	100	150
6.	F6	40	100	175
7.	F7	40	100	150
8.	F8	40	100	200

Evaluation of microspheres

Microscopic observation of prepared microsphere

An optical microscope (cippon, Japan) with a camera attachment (Minolta) was used to observe the shape of the prepared microsphere formulation.

Percentage yield

The prepared microspheres with a size range of 1µm to 1000µm were collected and weighed from different formulations. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microspheres.

$$\% \text{ Yield} = \frac{\text{Actual weight of product}}{\text{Total weight of drug and polymer}} \times 100$$

Drug entrapment

The various formulations of the floating microspheres were subjected for drug content. 10 mg of floating microspheres from all batches were accurately weighed and crushed. The powder of microspheres were dissolved in 10 ml 0.1 N HCl and centrifuge at 1000 rpm. This supernatant solution is than filtered through whatmann filter paper No. 44. After filtration, from this solution 0.1 ml was taken out and diluted up to 10 ml with 0.1 N HCl. The percentage drug entrapment was calculated using calibration curve method

Floating behavior

Ten milligrams of the floating microspheres were placed in 0.1 N HCl (100 ml). The mixture was stirred at 100 rpm in a magnetic stirrer. After 10 h, the layer of buoyant microsphere was pipetted and separated by filtration.

Particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in desiccators until a constant weight was obtained. Both the fractions of microspheres were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles.

$$\text{Percent buoyancy} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Measurement of mean particle size

The mean size of the microspheres was determined by Photo Correlation Spectroscopy (PCS) on a submicron particle size analyzer (Malvern Instruments) at a scattering angle of 90°. A sample (0.5mg) of the microspheres suspended in 5 ml of distilled water was used for the measurement

Determination of zeta potential

The zeta potential of the drug-loaded microspheres was measured on a zeta sizer (Malvern Instruments) by determining the electrophoretic mobility in a micro electrophoresis flow cell. All the samples were measured in water at 25°C in triplicate.

In-vitro release studies

The drug release rate from floating microspheres was carried out using the USP type II (Electro Lab.) dissolution paddle assembly. A weighed amount of floating microspheres equivalent to 100 mg drug were dispersed in 900 ml of 0.1 N HCl (pH=1.2) maintained at 37 ± 0.5°C and stirred at 55rpm. One ml sample was withdrawn at predetermined intervals and filtered and equal volume of dissolution medium was replaced in the vessel after each withdrawal to maintain sink condition. The collected samples analyzed spectrophotometrically at 266 nm to determine the concentration of drug present in the dissolution medium^{27,28}.

Drug release kinetic data analysis

Several kinetic models have been proposed to describe the release characteristics of a drug from matrix. The following three equations are commonly used, because of their simplicity and applicability. Equation 1, the zero-order model equation (Plotted as cumulative percentage of drug released vs time); Equation 2, Higuchi's square-root equation (Plotted as cumulative percentage of drug released vs square root of time); and Equation 3, the Korsmeyer-Peppas equation (Plotted as Log cumulative percentage of drug released vs Log time).

To study the release kinetics of Famotidine from the Floating microspheres the release data was fitted to these three equations

Zero order equation

When a graph of the cumulative percentage of the drug released from the matrix against time is plotted, zero order release is linear in such a plot, indicating that the release rate is independent of concentration.

$$Q_t = k_0 \cdot t \quad \text{..... (1)}$$

Where Q_t is the percentage of drug released at time t and k_0 is the release rate constant;

First order equation

$$\ln(100 - Q_t) = \ln 100 - k_1 \cdot t \quad \text{..... (2)}$$

Where k_1 is the release rate constant;

Higuchi's equation (Wagner, 1969):-

$$Q_t = k_H \cdot t^{1/2} \quad \text{..... (3)}$$

Where k_H is the Higuchi release rate constant

Korsmeyer-Peppas

The curves plotted may have different slopes, and hence it becomes difficult to exactly pin-point which curve follows perfect zero order release kinetics. Therefore, to confirm the kinetics of drug release, data were also analyzed using Korsmeyer's equation.

$$Q_t / Q_\infty = k_{KP} \cdot t^n$$

Where Q_t / Q_∞ is the fraction of drug released at time t , k_{KP} constant comprising the structural and geometric characteristics of the device and n is the release exponent.

The slope of the linear curve gives the 'n' value. Peppas stated that the above equation could adequately describe the release of solutes from slabs, spheres, cylinders and discs, regardless of the release mechanism. The value of 'n' gives an indication of the release mechanism. When $n = 1$, the release rate is independent of time (typical zero order release / case II transport); $n = 0.5$ for Fickian release (diffusion/ case I transport); and when $0.5 < n < 1$, anomalous (non-Fickian or coupled diffusion/ relaxation) are implicated. Lastly, when $n > 1.0$ super case II transport is apparent. 'n' is the slope value of $\log M_t / M_\infty$ versus \log time curve²⁹⁻³¹.

Stability studies for optimized formulation

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light and to establish a re-test period for the drug substance or a shelf life for drug product and recommended storage conditions. In general, a drug substance should be evaluated under storage condition (with appropriate tolerances) that test its thermal stability and if applicable, its sensitivity to moisture. Three types of storage conditions are used i.e. long term, Accelerated and where appropriate, Intermediate.

RESULTS AND DISCUSSION

The λ_{\max} of famotidine was found to be 266 nm by using U.V. spectrophotometer (Labindia-3000+) in linearity range 5-25 µg/ml Fig.1, 2. The floating microspheres of famotidine were prepared by solvent diffusion-evaporation method. Percentage yield of different formulation was determined by weighing the microspheres after drying. The percentage yield of different formulation was in range of 63.23±0.25 to 73.32±0.14 % Table 2. The maximum percentage yield was found in formulation F5, 73.32±0.14 as compare to all formulation. The drug entrapment efficacies of different formulations were in range of 62.23±0.41 to 76.65±0.58 %w/w. The maximum percentage drug entrapment was found in formulation F5 (76.65±0.58% w/w) Table 3. To assess the floating properties, the microspheres were placed in 0.1N hydrochloric acid. The microspheres floated for prolonged time over the surface of the dissolution medium without any apparent gelation. Buoyancy percentage of the microspheres was in the range of 55.56±0.41 to 73.25±0.23. The nature of the polymer influenced the floating behaviour of the microspheres Table 4. The maximum percentage yield, drug entrapment, percentage buoyancy and floating lag time was found to be formulation F5 in floating microsphere. The optimized formulation of F5 both batches subjected to further studies. The mean size of the microspheres was determined by photo correlation spectroscopy (PCS) on a submicron particle size analyzer (Horiba Instruments) at a

scattering angle of 90°.The results of measurement of mean particle size of optimized formulation F5 of floating microsphere was found to be 331.6 nm Fig. 3. Results of zeta potential of optimized formulation F4 of floating microsphere was found -32.8 mV Fig. 4.

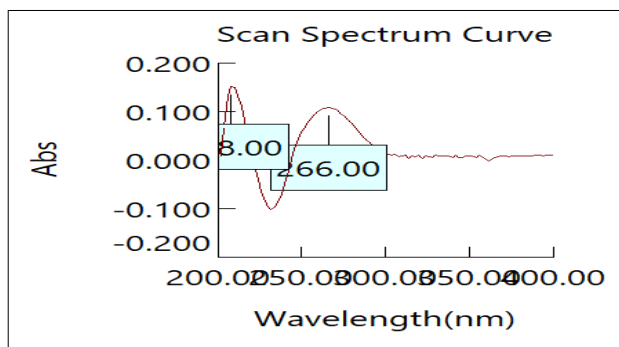


Figure 1 U.V. Spectra of Pure Drug (Famotidine)

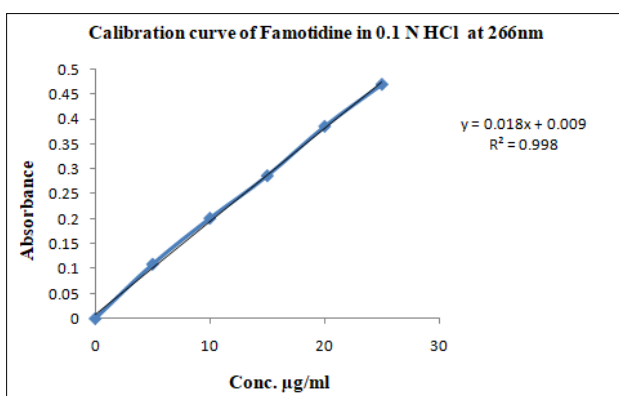


Figure 2 Calibration Curve of Famotidine in 0.1 N HCl at 266 nm

Table 2 Percentage Yield for Different Formulation

Formulation	Percentage Yield*
F1	65.58±0.45
F2	68.89±0.65
F3	63.23±0.25
F4	68.89±0.32
F5	73.32±0.14
F6	69.98±0.18
F7	68.78±0.74
F8	65.65±0.65

Table 3 Drug Entrapment for Different Formulations

Formulation	Drug entrapment (% w/w) of prepared microsphere
F1	65.76±0.45
F2	69.98±0.23
F3	71.12±0.36
F4	65.56±0.56
F5	76.65±0.58
F6	69.98±0.74
F7	65.41±0.65
F8	62.23±0.41

*Average of three determination (n=3)

Table 4 Percentage Buoyancy and Floating Lag Time of Floating Microsphere

Formulation	Floating Lag Time (Sec.)	Percentage Buoyancy
F1	69±3	62.23±0.45
F2	78±4	60.25±0.65
F3	65±5	61.25±0.58
F4	98±6	65.58±0.41
F5	32±4	73.25±0.23
F6	49±2	62.23±0.25
F7	88±5	55.56±0.41
F8	98±6	65.45±0.32

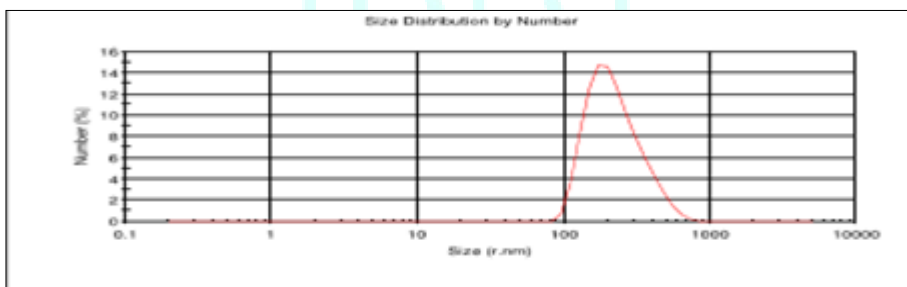


Figure 3 Particle Size Data of Optimized Microsphere Formulation F5

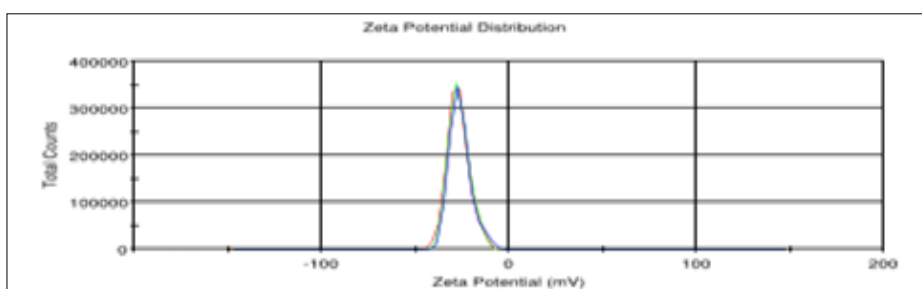


Figure 4 Zeta Potential Data of Floating Microsphere F5

The drug release from floating microspheres was found to be 99.89% at the end of 12 h for F2 Table 5 & Fig. 5. The *In vitro* drug release data of the optimized formulation was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetic equation, in order to determine the mechanism of drug release. When the regression coefficient values were compared, it was observed that an 'r' value of microsphere was maximum zero order i.e 0.989 hence indicating drug releases from

formulations was found to follow zero order for floating microsphere. Table 6 and Fig.6 & 7. According to ICH guidelines, 3 months accelerated stability study at 40±2°C and 75±5% RH optimized formulations (F5) was carried out. It showed negligible change over time for parameters like appearance, drug content, dissolution and assay etc., No significant difference observed in the drug content between initial and formulations stored at 40±2°C & 75±5% RH for 3 months.

Table 5 Release Study Data of Formulation F1-F8

Time (hr)	% of Drug Release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	33.25	30.25	29.98	25.65	20.23	18.23	15.65	13.23	10.23
1	45.65	43.23	40.56	35.56	30.45	25.65	20.23	19.56	15.56
2	55.65	49.98	45.65	40.23	38.89	35.65	30.25	25.65	23.32
4	69.98	65.56	60.23	55.65	49.98	45.56	40.25	39.98	35.45
6	89.98	90.25	85.65	69.98	60.23	55.56	52.23	45.56	40.23
8	95.65	99.98	92.32	77.65	75.65	70.23	64.45	55.56	50.41
10			99.85	96.65	85.59	82.23	80.23	63.23	60.36
12					97.85	89.98	85.56	75.65	73.321

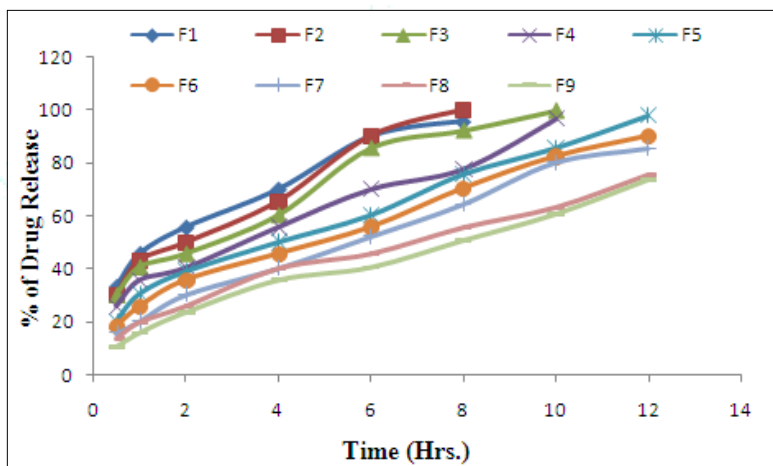


Figure 5 Graph of Release Study of Formulation F1-F8

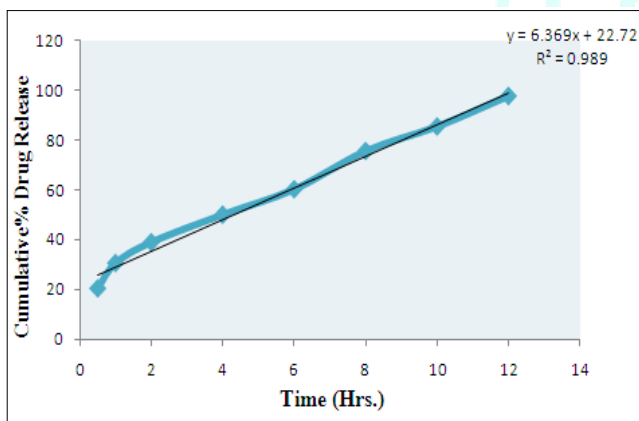


Figure 6 Zero Order Release Kinetics of Optimized Formulation F5

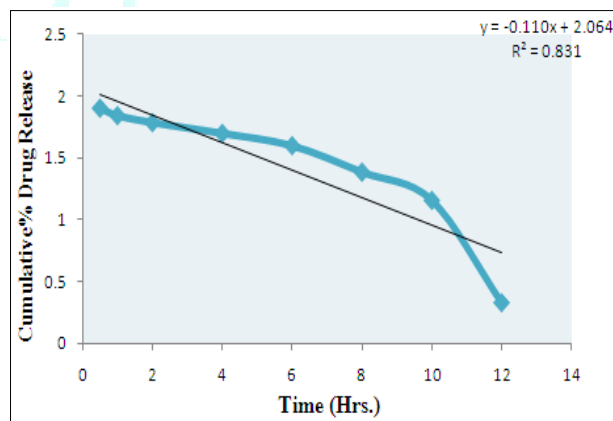


Figure 7 First Order Release Kinetics Optimized Formulation F5

Table 6 Comparative Study of Regression Coefficient for Selection of Optimized Formulation F-5

Release Kinetics	Zero order	First order
r ²	0.989	0.831

CONCLUSION

Floating microspheres of famotidine can be successfully prepared from sodium alginate by ionic gelation in combination with HPMC and EC for the purpose of gastroretentive drug delivery. On the basis of drug release, percentage yield, drug entrapment, percentage buoyancy and floating lag time F5 could be considered as promising formulations. Thus, the prepared floating microspheres may prove to be potential candidates for multiple-unit delivery devices adaptable to any intragastric condition.

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