

## Mucoadhesive Microspheres of Famotidine for Gastro Retentive Drug Delivery

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### Abstract

Famotidine, a histamine H<sub>2</sub> receptor antagonist is absorbed only in the initial part of gastro intestinal (GI) tract and has less bioavailability. Hence the drug was formulated as gastro-retentive drug delivery systems in the form of mucoadhesive microspheres to prolong its residence time in the stomach and improve its absorption. The microspheres of famotidine were prepared by emulsification-ionic gelation technique using mucoadhesive polymers such as Sodium Alginate, Carbopol 934P and HPMC in different ratios. All the formulations were subjected to particle size and shape analysis, drug content, *in vitro* mucoadhesion evaluation and *in vitro* drug release studies. Encapsulation efficiency was found to be in the range of 75.95 – 86.76 %. Formulations containing Carbopol 934P showed mucoadhesion for a period of more than 8h. Drug release decreased with increase in mucoadhesive polymer content in the microspheres. Among the formulations, for two different polymer combinations, F<sub>2</sub> and F<sub>4</sub> showed maximum drug release in a sustained fashion at the end of 7 h and 8h respectively with superior mucoadhesion. The rate of drug release follows zero order kinetics. Stability studies for a period of 8 weeks did not show appreciable changes with respect to particle size and drug content.

### Key words:

Famotidine; Gastroretentive; Sodium Alginate; Microspheres; Mucoadhesion

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### INTRODUCTION

Gastro retentive drug delivery systems are primarily controlled release drug delivery systems, which gets retained in the stomach for longer period of time, thus helping in the absorption of drug for the

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intended duration of time. These dosage forms are known to extend the absorption phase of the drug in the proximal part of the small intestine where narrow absorption window drugs are preferentially absorbed due to the large surface area, in comparison to the colon; or because of the enhanced solubility of the drug in the stomach as opposed to more distal parts of the gastrointestinal tract. Several strategies have been proposed to modify the GI transit of oral pharmaceutical formulations. One such approach is to design a formulation, which can adhere to the lining of the stomach, thus retaining the drug at the target absorption site for a prolonged period of time [1]. Mucoadhesive microspheres exhibit a prolonged residence time at the site of application or absorption, facilitate an intimate contact with the underlying absorption surface, and thus contribute to improved and / or better performance of drug [2]. Famotidine is a histamine H<sub>2</sub> receptor antagonist. It produces competitive blockade at histamine H<sub>2</sub> receptors. It has been used in the treatment of gastric ulcers, duodenal ulcers, Zollinger-Ellison syndrome and gastroesophageal reflux disease. Famotidine may be given by mouth in a dose of 20-40 mg daily. The half-life of Famotidine in healthy subjects is about 3 h and has only 40-45 % absolute bioavailability after oral administration due to incomplete absorption [3]. These aspects make the drug suitable for sustained drug delivery; moreover its formulation into gastroretentive dosage forms may improve its absorption from the proximal small intestine due to prolongation of residence time in the stomach. It has been reported that oral treatment of gastric disorders with an H<sub>2</sub>-receptor antagonist like famotidine promotes local delivery of these drugs to the receptor of the parietal cell wall. Local delivery also increases the stomach wall receptor site bioavailability and increases the efficacy of drugs to reduce acid secretion. This principle may be applied for improving systemic as well as local delivery of famotidine, which would efficiently

reduce gastric acid secretion [4]. Hence, the present work was undertaken to formulate and evaluate mucoadhesive microspheres of Famotidine for gastric retention with a view to prolong drug release and improve bioavailability and therefore efficacy by retaining it in the stomach for a longer period.

#### MATERIALS AND METHODS

Famotidine was a gift sample from Vasavaa Pharmaceuticals Pvt Ltd., Hyderabad. Carbopol 934P and Hydroxy Propyl Methyl Cellulose (HPMC 50 cps) was procured from CDH laboratory. Sodium alginate was obtained from Genuine Chemical Co, Mumbai.

#### Preparation of mucoadhesive microspheres:

Mucoadhesive microspheres containing Famotidine were prepared using emulsification – ionic gelation technique. Sodium alginate (1.0 g) was dissolved in 12 ml distilled water and the mucoadhesive polymer (1.0 g) was dissolved in 20 ml distilled water separately. The two above polymer solutions were mixed thoroughly to form a homogeneous polymer solution. The drug, famotidine (0.5 g) was added to the polymer solution and mixed homogeneously to get a smooth viscous dispersion. The resulting dispersion was then added in a thin stream to about 100 ml light liquid paraffin contained in a 500 ml beaker, stirring with 1000 rpm for 15 min to emulsify the added dispersion as fine droplets. Calcium chloride (10 % w/v) solution (40 ml) was then added slowly while stirring for ionic gelation (or curing) reaction. Stirring was continued for 1 h to complete the curing reaction and to produce spherical microspheres. The mixture was then centrifuged and the microspheres thus separated were washed repeatedly with ethanol. The microspheres were dried at 45 ° C for 4 h and kept in desiccators for one day [3, 4, 5, 6].

The different formulations were prepared using sodium alginate and the mucoadhesive polymers viz. Carbopol 934P and HPMC 50 cps, in the ratio 1:1,

1:1.5 and 1:2 while keeping the amount of drug (0.5 g) constant. The composition of different formulations is represented in Table 1.

**Table 1:** Composition of mucoadhesive microspheres

Formulation code	Amount of Famotidine (g)	Amount of sodium alginate (g)	Amount of mucoadhesive polymer* (g)
F1	0.5	1.0	1.0
F2	0.5	1.0	1.5
F3	0.5	1.0	2.0
F4	0.5	1.0	1.0
F5	0.5	1.0	1.5
F6	0.5	1.0	2.0

\* F<sub>1</sub>, F<sub>2</sub> and F<sub>3</sub> contain HPMC 50 cps as mucoadhesive polymer

F<sub>4</sub>, F<sub>5</sub> and F<sub>6</sub> contain Carbopol 934P as mucoadhesive polymer

### Evaluation of mucoadhesive microspheres:

#### Size and shape analysis

The size and shape of the microspheres were evaluated using optical microscopy. The particle sizes of 50 microspheres were determined randomly using 14.44 μm as calibration factor<sup>5, 7, 8</sup>. The average particle size of microspheres can be given by the following formula

$$\text{Average Size} = \frac{\sum nd}{\sum n}$$

Where, **n** is the number of microspheres and **d** is the size of microsphere.

#### Determination of Drug content and Entrapment efficiency

The drug content was measured by extracting 100 mg of the ground microspheres using 0.1 N HCl. The dispersion was sonicated for 15 minutes and filtered. After appropriate dilution with 0.1 N HCl, the absorbance was taken in UV/ Visible

spectrophotometer at 264 nm. The percentage drug content was calculated using the formula,

$$\text{Drug content (\%)} = \frac{\text{Weight of drug in mucoadhesive microspheres}}{\text{Weight of mucoadhesive microspheres}}$$

Drug entrapment efficiency represents the proportion of the initial amount of drug, which has been incorporated into the microspheres. It was calculated using the formula [4, 5, 8, 9]

$$\text{Entrapment efficiency (\%)} = \frac{\text{Calculated drug content}}{\text{Theoretical drug content}} \times 100$$

### In vitro evaluation of mucoadhesion

A freshly cut piece, 4 X 2 cm of sheep stomach mucosa obtained from local abattoir within 1 h of killing the animal was cleaned by washing with isotonic saline solution. The mucosa was affixed such that its mucosal surface is exposed to a glass slide which is placed at an angle of 40 ° relative to the horizontal plane. A weighed amount of microspheres (20 mg) was placed on the affixed mucosal surface. A reservoir containing 0.1N HCl warmed at 37 ° C was placed at certain height above the mucosa. By means of flow regulator on a rubber tube, the warmed 0.1N HCl was peristaltically pumped at a rate of 15 ml/min over the tissue. The duration for complete washing of microspheres from sheep stomach mucosa was determined [10] In the case of those formulations in which complete wash off (after 8h and 30 min) was not obtained, the microspheres remaining on the mucosa were scrapped off, dried and weighed.

### In vitro drug release studies

The drug release rate from mucoadhesive microspheres was carried out using USP dissolution apparatus I. A weight of mucoadhesive microspheres corresponding to 40 mg drug was filled into a capsule and placed in the basket. Dissolution media was 900 ml of 0.1N HCl maintained at 37 ± 0.5 °C and stirred at 100 rpm. 5 ml sample was withdrawn at suitable time intervals for 9 h and 5 ml fresh dissolution

medium was replaced after each withdrawal. These samples were analyzed for the drug spectrophotometrically at 264 nm [6, 9].

### Stability Studies

Stability studies for the formulations were carried out as per ICH guidelines. Selected formulations were stored at, room temperature (25-30°C) and accelerated temperature (45°C) for 8 weeks. The formulations were periodically evaluated for particle size and drug content.

### RESULTS AND DISCUSSION

The average size of mucoadhesive microspheres prepared from the combination of Sodium alginate and HPMC was found to be in the range of 83.75 – 128.45 µm, where as average size of mucoadhesive microspheres prepared from the combination of Sodium alginate and Carbopol 934P was found to be in the range of 86.64 – 127.07 µm. Microscopic observation reveals that most of the microspheres were almost spherical in shape. The comparative average particle size of all formulations is represented in Fig.1.

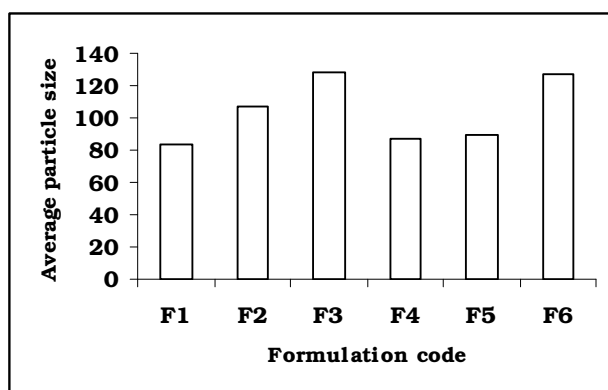


Fig. 1. Comparative average particle size of microspheres from all formulations.

The percentage yield was found to be considerably less for alginate - HPMC microspheres, where as for alginate – Carbopol microspheres it was found to be in the range of 91.6 – 94.2 %. The drug content was closely related to theoretical drug content and ranged

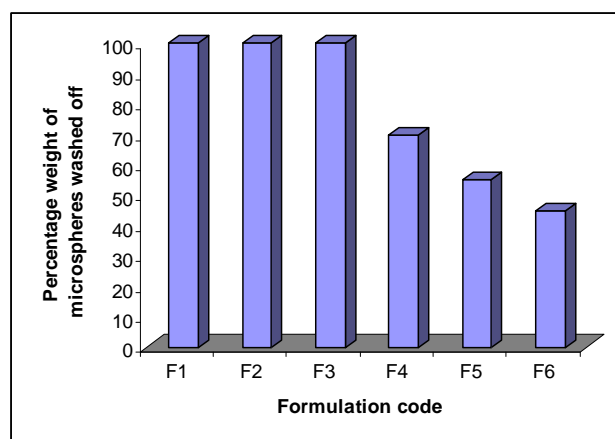
from 12.28 – 15.39 % (theoretical 14.28 – 20.0 %). Drug encapsulation efficiency was found to be in the range of 75.95 – 86.76 %. Results of all these parameters are tabulated in Table 2.

**Table 2.** Results of percentage yield, drug content and entrapment efficiency of different formulations.

Formulation code	Yield* (%)	Drug content (%)*		Encapsulation efficiency (%)*
		Theoretical	Practical	
F <sub>1</sub>	88.36	20.00	15.39	76.95
F <sub>2</sub>	73.26	16.67	12.77	76.60
F <sub>3</sub>	62.80	14.28	12.28	85.99
F <sub>4</sub>	92.00	20.00	15.19	75.95
F <sub>5</sub>	91.60	16.67	12.96	77.74
F <sub>6</sub>	94.20	14.28	12.39	86.76

\*Average of three determinations

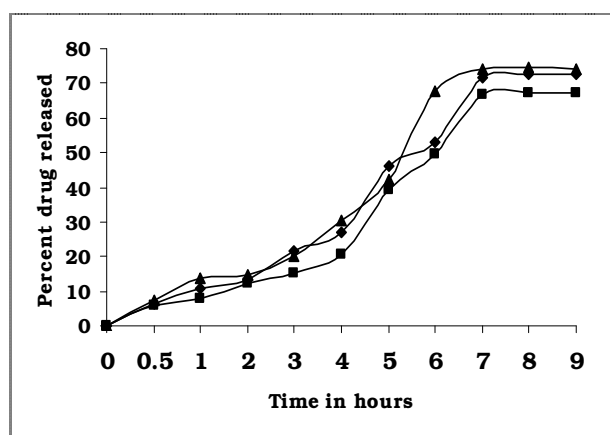
From the *in vitro* evaluation of mucoadhesion, it was observed that as the concentration of mucoadhesive polymer increases the adhesion property also increased. Formulation F<sub>2</sub> and F<sub>3</sub> took more than 5.5 h for 100% of the microspheres to be washed off completely from the mucosa with F<sub>1</sub> taking more than 4.5 h. On the other hand, F<sub>4</sub>, F<sub>5</sub> and F<sub>6</sub> showed a longer mucoadhesion period with more than 30 % of the microspheres remaining even after 8.5 h. The longest mucoadhesion time showed by F<sub>6</sub> is probably due to its greater content of the highly mucoadhesive polymer, carbopol 934 P as illustrated in Fig. 2.



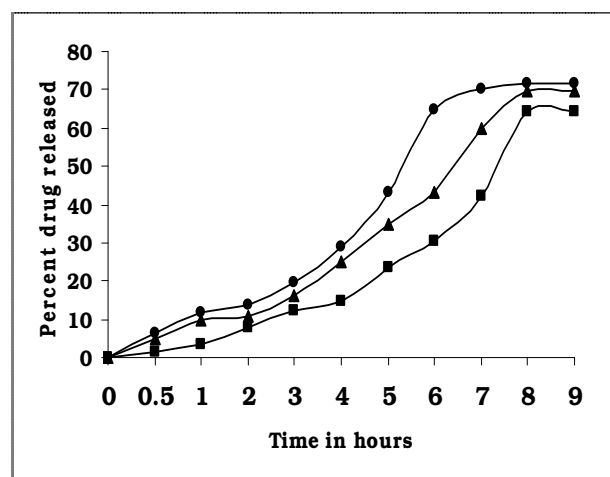
**Fig. 2.** Comparison of percentage weight of microspheres of different formulations washed off from mucosa after 8.5 h

*In vitro* release studies demonstrated 73.91 %, 72.62 % and 67.16 % drug release from F<sub>1</sub>, F<sub>2</sub> and F<sub>3</sub>

respectively in 0.1N HCl dissolution medium, where as formulations F<sub>4</sub>, F<sub>5</sub> and F<sub>6</sub> showed 71.73 %, 69.55 % and 64.52 % drug release respectively. It was found that there was decrease in drug release with increase in mucoadhesive polymer content. This could be attributed to the greater degree of swelling upon hydration with greater mucoadhesive polymer content in the microspheres which leads to increase in the diffusional path length that slows down drug release. This effect was particularly significant among the carbopol formulations, i.e. F<sub>4</sub>, F<sub>5</sub> and F<sub>6</sub>. The *in vitro* drug release profiles are shown in Figs. 3 and 4.



**Fig. 3:** *In vitro* release profile of famotidine from mucoadhesive microspheres of formulations, F<sub>1</sub> (-●-), F<sub>2</sub> (-▲-) and F<sub>3</sub> (-■-).



**Fig. 4:** *In vitro* release profile of famotidine from mucoadhesive microspheres from formulations, F<sub>4</sub> (-●-), F<sub>5</sub> (-▲-) and F<sub>6</sub> (-■-).

The drug release data was subjected to kinetic analysis for both zero order and first order kinetic studies. The regression values obtained indicated

that the drug release pattern from the formulated microspheres was closer to zero order kinetics than first order. This could probably be due to the fact that mucoadhesive microspheres are adhesive micro matrix systems, which consists of drug and mucoadhesive polymers. In this system, the drug is homogenously dispersed through out the polymer matrix which acts as rate controlling element and release of drug is thus controlled by its diffusion throughout the rate controlling polymer matrix. *In vitro* drug release follows zero order kinetics for all the formulations. The correlation coefficient values ( $r^2$ ) for all formulations are given in Table 3.

**Table 3:** Correlation co-efficient ( $r^2$ ) values for all formulations.

Formulation code	Zero order	First order
F1	0.9445	0.9114
F2	0.9669	0.9317
F3	0.9509	0.9187
F4	0.9523	0.9288
F5	0.9706	0.9216
F6	0.9259	0.8477

The stability studies for the formulations carried at various conditions of temperature and humidity shows no significant change in results with respect to particle size and drug content at the end of period of 8 weeks.

### CONCLUSION

Mucoadhesive microspheres of famotidine can be successfully prepared from sodium alginate by ionic gelation in combination with either HPMC or carbopol 934 P for the purpose of gastroretentive drug delivery. On the basis of drug release and mucoadhesive properties, F<sub>2</sub> and F<sub>4</sub> could be considered as promising formulations.

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