An Elsevier Indexed Journal ISSN-2230-7346

Journal of Global Trends in Pharmaceutical Sciences

PREPARATION AND EVALUATION OF FAMOTIDINE MUCOADHESIVE MICROSPHERES

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ARTICLEINFO

Articlehistory:

Received: 28 April 2016
Revised: 10 May 2016
Accepted: 18 May 2016

Keywords:

Sustained release,
Famotidine,
Mucoadhesive microspheres,
ionic gelation technique,
In-Vitro wash-off test

ABSTRACT

Bioavailability is an important quality attribute of pharmaceutical dosage forms. Bioavailability is generally improved by gastro-retentive drug delivery systems. Mucoadhesive dosage forms occupy prominent part of these novel drug delivery systems. Famotidine mucoadhesive microspheres were prepared by orifice-ionic gelation technique employing sodium carboxymethylcellulose and oats powder as mucoadhesive polymers. Seven formulae were designed and all the prapared microspheres were subjected to flowability, particle size, percent yield, encapsulation efficiency, *in-vitro* wash off test, *in-vitro* dissolution study. Encapsulation efficiency was present in the range of 85.4% to 89.8%. Microspheres containing oats powder exhibited better mucoadhesive property compared to those containing sod CMC. However, in microspheres containing oats powder the drug release was completed within 8-10 hours without sustaining the drug release upto 12 hours. The optimised formulation F_7 containing combination of sod CMC and oats powder showed the best results for mucoadhesion and sustained release upto 12 hours. Oats powder was found to be a promising mucoadhesive polymer in the present work. The drug release from all the prepared microspheres followed first order kinetics and diffusion mechanism.

INTRODUCTION:

Mucoadhesive microspheres[1-5]are promising drug carrier systems used not only for sustained release but also for improved bioavailability. Mucoadhesive systems utilize the property of bioadhesion[6], which is a phenomenon in which two materials at least one of which is biological in nature are held together by means of interfacial forces.

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Microspheres are small spherical particles (typically 1 µm to 1000 µm), sometimes referred to as microparticles. The microspheres can be made up of either natural or synthetic polymers[7]. Bhabani S Nayak*et al.* prepared and chracterized Famotidine microcapsules[8] employing carbopol 934 and HPMC, carbopol and methyl cellulose, carbopol and guar gum combinations.

Koland Marina*et al.* formulated mucoadhesive microspheres of Famotidine for gastroretentive drug delivery. The microspheres of Famotidine were prepared by emulsification – ionic gelation technique using mucoadhesive polymers such as sodium alginate, carbopol 934 and HPMC in different ratios[9]. Famotidine is

used for the treatment of gastric and duodenal ulcers and Zollinger-Ellison syndrome. Famotidine is readily but incompletely absorbed after oral administration. Oral bioavailability of Famotidine[10] is about 40-50%. The half-life of Famotidine in healthy subjects is about 3 h. The present work was envisaged to reduce the dosing frequency and improve oral bioavailability by designing and evaluating sustained release mucoadhesive microspheres of Famotidine for effective control of gastric ulcers. In the present investigation a total of 7 formulae were designed and developed. The formulae contain sodium alginate as coating agent and oats powder and Sodium CMC as mucoadhesive agents. Oats powder was tried as a new mucoadhesive agent in the present study.

MATERIALS AND METHODS:

MATERIALS:

Famotidine (Yarrow chem products), Sodium alginate (Yarrow chem products),Oats powder (Local Market,Quaker), Sodium CMC (Qualigens), Calcium chloride (Fisher Scientific), Hydrochloric acid (Qualigens) were purchased from the respective suppliers as indicated.

METHODS:

A) Preparation of Famotidine mucoadhesive microspheres:

Microspheres were prepared by using sodium alginate as coat material and Sod. CMC and oats powder as mucoadhesive polymers. The technique used for this process is orifice-ionic gelation method. The detailed procedure for formulation-1 is given below. Materials for 25 doses were taken in this procedure. The drug: coat polymer: mucoadhesive polymer were present in the ratios of 1:1:0.5, 1:1:1, 1:1:1.5 in different formulations.1gm of sodium alginate and 0.5gm of sodium CMC were taken in a clean and dry mortar. About 50 ml of water was added slowly in small quantities and triturated until a good pourable mucilage was obtained. To this polymer dispersion 1gm of Famotidine and 1.5 gm of lactose were added and triturated thoroughly to get smooth viscous dispersion. By using syringe with needle no.18 gauge the dispersion was addeddropwise into 100 ml of 10% w/v calcium chloride solution. These liquid droplets were retained in the solution for 30 minutes to complete reaction and to get rigidity. These microspheres were separated by decantation and thoroughly washed with distilled water and petroleum ether and dried for 12 hours at 50^{o}c in the oven. After completion of drying, the microspheres were collected, weighed and labelled properly. They were stored in the desiccator for further use. All the other formulations were prepared in similar procedure by taking the materials as given in table 1. Lactose was included as a diluent to maintain constant weight of granules, which contain equal amount of drug. 160 mg of microspheres contain 40 mg (one dose) of Famotidine.

B) Evaluation of mucoadhesive microspheres:

1) Flow properties

a) Angle of repose

A funnel was fixed to a stand at certain height from the surface. 5 gm of microspheres were passed from the funnel, so that they form a pile. The height and the radius of the heap was measured and angle of repose[11] was calculated by

$$\theta = \tan^{-1}(h/r)$$

Where, θ = angle of repose, h = height, r = radius

b) Bulk density and tapped density

Accurately weighed 5 gm microspheres were transferred to a graduated cylinder to measure bulk volume. The measuring cylinder was tapped for 200 times and tapped volume was measured. Then the bulk density and tapped density were calculated by

Bulk density (ρ_b)=

Weight of microspheres (g)/ Bulk volume (v_b)(ml)

Tapped density (ρ_t) =
Weight of microspheres (g)/ Tapped volume (v_t)(ml)

c) Carr's index =

Tapped density – Bulk density/ tapped density X100

d) Hausner's ratio = Tapped density/ Bulk density

2) Particle size measurement

To determine the particle size of mucoadhesive microspheres, 100 microspheres from each formulation were measured using an optical micro-

scope at a magnificance of 50x (Eye piece magnification=10x and objective magnification=5x) with an ocular micrometer which was calibrated using a stage micrometer (Erma, Tokyo). The average size of microspheres can be given by the following formula.

$$\text{Average size} = \frac{\Sigma nd}{\Sigma n}$$

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

3) Percentage Yield

The microspheres were evaluated for percentage yield. The yield was calculated as per the equation given below.

Percentage Yield=Weight of microspheres recovered-Weight (drug + polymer)x 100

4) Encapsulation efficiency

100 mg of drug equivalent microspheres were taken in a mortar and crushed into a fine powder. 2 to 3 drops of glacial acetic acid was added and transferred into 100 ml volumetric flask and the volume was made up to 100 ml with 0.1 N HCL to get 1000 µg/ml. From this solution, 10 ml was taken in 100 ml volumetric flask and the volume was made up to 100 ml with 0.1 N HCl to get 100 µg/ml and the solution was filtered and from the filterate 1ml was taken in 10 ml volumetric flask and the volume was made up to 10ml with 0.1 N HCl to get 10 µg/ml and absorbance was measured at λ_{max} of 265nm. Encapsulation efficiency was calculated by the following formula.

Estimation of Encapsulation efficiency=

Estimated drug content/ Theoretical drug content x 100

5) *In vitro* wash–off test

The mucoadhesive property of the microspheres was evaluated by an *in vitro* adhesion testing method known as wash-off method[12]. A piece of goat intestinal mucus (2x2cm) was mounted onto glass slide with elastic bands. Glass slide was connected with a suitable support. About 50 microspheres were spread onto each wet tissue specimen, and there after the support was hung onto the arm of a USP tablet disintegration test machine (Veego). The disintegration machine containing tissue specimen was started to move up and down in 0.1 N HCL at 37^{o}C taken in a beaker. At the end of 8 hours the machine was stopped and the number of microspheres still adhering onto the tissue was counted.

% Mucoadhesion =No.of microspheres remains/No.of applied microspheresx100

6) *In vitro* dissolution test

The release of Famotidine from the prepared microspheres was studied using USP-Type II basket apparatus. Drug release test was carried out in 900ml of 0.1 N HCl (pH=1.2) medium maintained at 37 ± 0.5^{o} C temperature at 50 rpm. 160 mg of microspheres equivalent to 40 mg (one dose) of Famotidine were taken for the test. Three trials were carried out for each formulation. 5ml of samples were withdrawn at regular time intervals and the test was carried upto 12 hours. The samples were analysed at λ_{max} of 265 nm by UV spectrophotometer (ELICO- SL 159). Different graphs were constructed from the obtained data[8].

RESULTS ANDDISCUSSION:

The present work was ultimately aimed at reducing the dosing frequency and improving oral bioavailability by designing and evaluating sustained release mucoadhesive microspheres of Famotidine for effective control of gastric ulcers.Sodium alginate was used in combination with the mucoadhesive polymers in the ratios of 1:0.5, 1:1 and 1:1.5. All the formulations produced discrete microspheres of uniform size and almost spherical shape. The relevant evaluation tests were performed for the microspheres and all the obtained data was given in the form of mean ± standard deviation.The microspheres prepared were evaluated for flow properties, the results were shown in table 2.

The results indicated that the microspheres prepared exhibited excellent flow properties. The results of particle size, percentyield and encapsulation efficiency data were shown in tables 3. The size of the microspheres was present in the range of 1067-1124 µm. The encapsulation efficiency was present in the range of 85.4% to 89.3%. The percent yield values were present in the range of 89.2 ±3.46 to 95.6 ±4.35.

Table 1: Composition of Famotidine mucoadhesive microspheres

Ingredients (gm)	**F_1**	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**
Famotidine	1	1	1	1	1	1	1
Sodium Alginate	1	1	1	1	1	1	1
Sodium CMC	0.5	1	1.5				0.5
Oats Powder				0.5	1	1.5	0.5
Lactose	1.5	1	0.5	1.5	1	0.5	1
Purified Water (ml)	50	50	50	50	50	50	50

Table 2: Flow properties of Famotidine microspheres

	Evaluation parameters (Mean ± SD)				
	Angle of repose (θ)	**Bulk Density (g/ml)**	**Tapped density (g/ml)**	**Carr's Index (%)**	**Hausner's ratio**
F_1	11.12±0.12	0.62±0.018	0.64±0.018	4.46±0.16	1.04±0.012
F_2	11.34±0.12	0.69±0.016	0.73±0.020	5.56±0.14	1.05±0.019
F_3	11.85±0.18	0.62±0.018	0.69±0.016	8.98±0.18	1.09±0.013
F_4	13.49±0.19	0.66±0.017	0.71±0.018	6.75±0.15	1.07±0.013
F_5	14.03±0.20	0.55±0.015	0.62±0.018	10.61±0.20	1.11±0.019
F_6	15.64±0.15	0.56±0.015	0.64±0.018	12.75±0.36	1.14±0.018
F_7	16.17±0.16	0.55±0.015	0.63±0.017	11.42±0.40	1.12±0.017

Table 3: Particle size of Famotidine microspheres

Formulation	**Pparticle size (µm)**	**Percentage Yield (%)**	**Encapsulation efficiency (%)**
F_1	1124 ±22	89.2 ±3.46	85.6 ±2.56
F_2	1117 ±19	94.2 ±2.57	87.4 ±3.42
F_3	1096 ±18	94.2 ±4.44	89.3 ±2.42
F_4	1101 ± 21	91.2 ±2.49	88.2 ±2.46
F_5	1088 ±20	93.2 ±2.08	89.8 ±1.26
F_6	1067 ±24	92.7 ±1.89	86.2 ±2.24
F_7	1094 ±19	95.6 ±4.35	85.4 ±2.32

Table 4: *In - vitro* wash off test (Mean ± SD)

Formulation	**Mucoadhesion (%)**
F_1	82 ±2.46
F_2	86 ±1.15
F_3	87 ±1.28
F_4	92 ±3.46
F_5	94 ±1.18
F_6	94 ±1.26
F_7	94 ±1.48

Table 5: Correlation coefficient values of drug release kinetic data fitted to various models

Formulation	Zero order	First order	Higuchi
F_1	0.930	0.991	0.978
F_2	0.940	0.993	0.983
F_3	0.910	0.981	0.967
F_4	0.761	0.814	0.858
F_5	0.831	0.892	0.909
F_6	0.862	0.960	0.983
F_7	0.900	0.989	0.989

Figure 1: Drug release profiles of Famotidine mucoadhesive microspheres

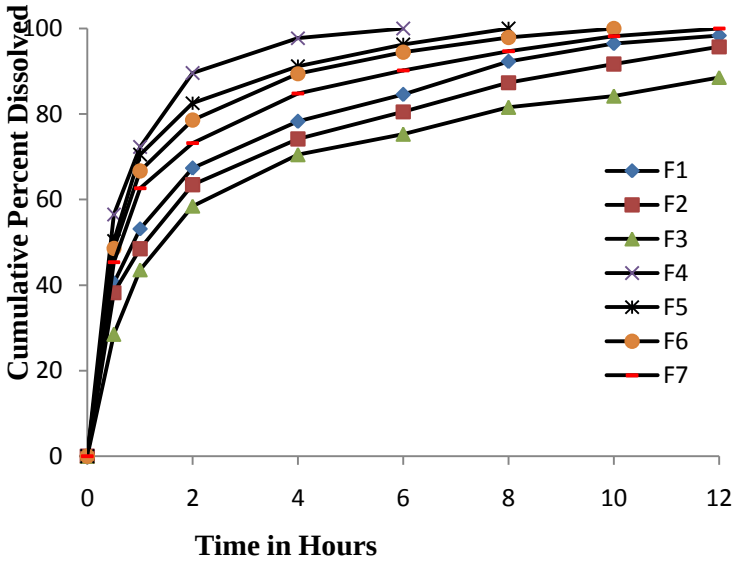


Figure 2: First order plots of Famotidine mucoadhesive microspheres

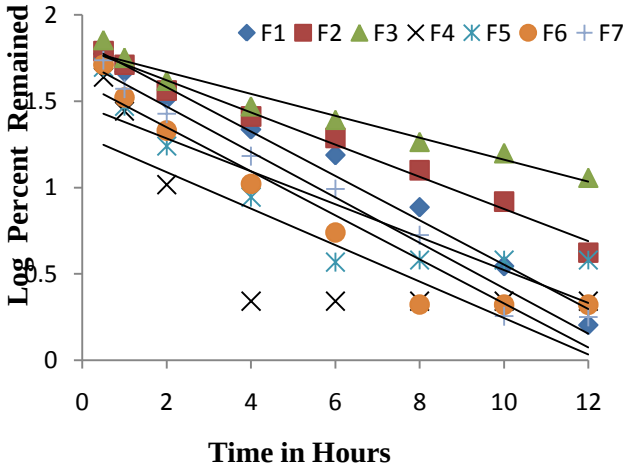
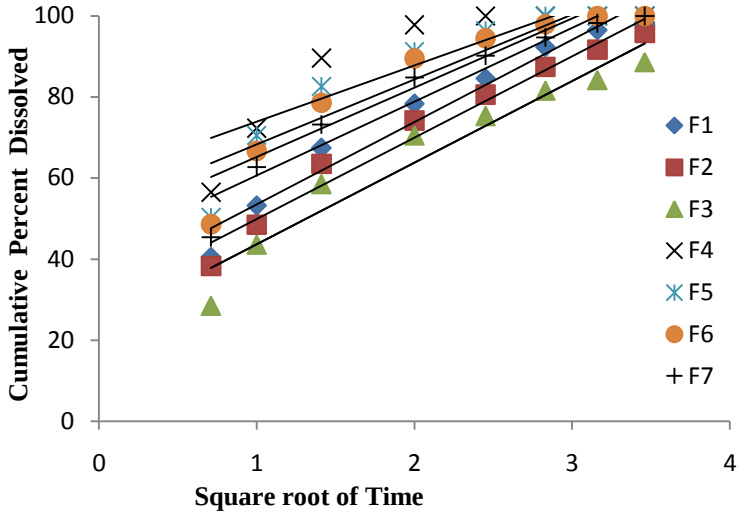


Figure 3: Higuchi plots of Famotidine mucoadhesive microspheres



Mucoadhesion strength was determined by *in vitro* wash off test. Formulations F_4-F_6 containing the oats powder (table 4) showed superior mucoadhesion strength compared to F_1-F_3 formulations containing sodium CMC. As the viscosity of the polymer increases, swelling increases and mucoadhesion depends on the swelling of the gum. This improves the consolidation step that increases the mobility of the molecule and facilitates the interpretation with mucus layer, thus mucoadhesion increases.

The polymer dissolves in presence of water. As the hydrophilicity of the polymer increases, the interaction between water and hydrogel will increase too, this facilitates water diffusion and leads to greater swelling.The results of *in vitro* drug release studies were shown in figures 1, 2 and 3. Microspheres prepared using different ratios of sodium alginate and mucoadhesive polymer showed drug release for a period of 8 -12 hours respectively. In formulations F_4-F_6 the total amount of the drug was dissolved within 8-10 hours. In F_3 only 88.60% of the drug was dissolved within 12 hours. Although formulation F_1 showed 98.42% drug dissolved in 12 hours, its mucoadhesive strength was low and present around 82%. The drug release retardation was higher in case of formulations containing sodium CMC compared to those containing oats powder. However the mucoadhesion strength was lower for sodium CMC polymer. Hence formulation F_7 was developed containing sodium CMC and oats powder in combination. Formulation F_7 showed drug release upto 12 hours and superior mucoadhesive property also.

Hence Formulation F_7 was considered as the best formulation in this study. To ascertain the kinetics and mechanism of drug release, the dissolution data was analysed by first order and Higuchi equations and corresponding (figures 2 and 3) graphs were plotted. The drug release kinetics followed first order as the correlation coefficient values obtained were higher as shown in table 5. Drug release followed Higuchi diffusion mechanism.

CONCLUSIONS:

Ionic- gelation method was found to be a suitable method for the preparation of Famotidine mucoadhesive microspheres in the laboratory. The Famotidine microspheres prepared with mucoadhesive polymers such as sodium CMC and oats powder were distinct, free flowing and almost spherical in shape.

Sodium CMC showed more release retardation and oats powder showed better mucoadhesive property. Formulation F_7 containing both sodium CMC and oats powder was found to be the best formulation. It was found that an increase in concentration of mucoadhesive polymer increases the mucoadhesion strength. Drug release mechanism of all the formulations followed Higuchi diffusion and the drug release kinetics followed first order. Oats powder was found to be a promising mucoadhesive polymer.

ACKNOWLEDGEMENTS:

The authors are grateful to the chairman and principal of Yalamarty pharmacy college for providing facilities to carry the research work.

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How to cite this article:

G.ChandraSekhara Rao, P.LavanyaKumari, R.Sowjanya, P.H.V.S.Amar, Preparation and evaluation of famotidine mucoadhesive microspheres, 7 (2): 3084 – 3090 (2016)