Indian Journal of Research in Pharmacy and Biotechnology
Volume 5, Issue 3, 2017
Journal homepage: http://www.ijrpb.com

ISSN:
2321-5674 (Print)
2320-3471 (Online)

Research article

Indexed in CAS and CABI
Impact factor:0.64

Formulation and evaluation of mucoadhesive microspheres for gastro retentive delivery of Famotidine hydrochloride

K.Divya*, B.Sailaja, K.Y.Guru Swamy, G.Mahesh, V.Ravi Kumar, B.Renuka, B.Nagendra Babu
Department Of Pharmaceutics, St.Marys Group Of Institutions, Chebrole, Guntur (A.P).
***Corresponding author: K.Divya, Department of Pharmaceutics, St.Marys Group Of Institutions, Chebrole, Guntur (A.P).**

Keywords:
Mucoadhesive microspheres, Famotidine, Gastro retentive Drug Delivery

Article Info:
Received: 22-03-2017
Revised: 02-04-2017
Accepted: 19-04-2017

ABSTRACT

The purpose of the research was to develop mucoadhesive gastro retentive drug delivery system containing Famotidine hydrochloride. The mucoadhesive microspheres were prepared by using varying concentrations of sodium alginate and egg albumin. The technique used in the preparation of microspheres was Ion gelation and Thermal cross linking method. The polymers are biodegradable. In-vitro drug release studies were conducted along with other physical parameters like particle size determination, surface morphology, mucoadhesion and drug entrapment efficiency.

1. INTRODUCTION

Bio adhesion can be defined as a phenomenon of interfacial molecular attractive forces amongst the surfaces of the biological substrate and the natural or synthetic polymers ,which allows the polymer to adhere to the biological substrate is a mucosal layer then the phenomena is known as muco adhesion. Bio adhesive polymeric systems have been used since long time in the development of products for various biomedical applications which include denture adhesives and surgical glue. The adhesion of bacteria to the human gut may be attributed to the interaction of lectin like structure (present on the cell surface of bacteria) and mucin (present the biological tissues). In general, various biopolymer show the bio adhesive properties and have been utilized for various therapeutics the common principle underlying this drug administration route is the adhesion of dosage form to the mucous layer until the polymer dissolves or the mucin replaces itself .benefits for this route of drug improved bioavailability.

Benefits for this route of drug Administration are prolonged: drug delivery, targeted therapy and often improved bioavailability. The bio adhesion is the state in which two materials, (at least one of which is biological in nature are held together for an extended period of time by interfacial forces .the term bio-adhesion implies attachment of drug carrier system to specific biological location .this biological surface can be epithelial tissue or the mucous coat on the surface of tissue.

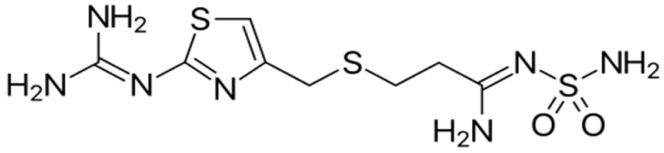

Figure.1.Chemical structure of Famotidine

Famotidine is a potent histamine H2-receptor antagonist widely used in the treatment and prevention of peptic ulcer disease. After intravenous administration the plasma famotidine concentration-time profile exhibits a biexponential decay, with a distribution half-life of about 0.18 to 0.5h and an elimination half-life of about 2 to 4h. The volume of distribution of the drug at steady-state ranges from 1.0 to 1.3 L/kg; plasma protein binding is low (15 to 22%). Famotidine is 70% eliminated unchanged into urine after intravenous administration.

2. MATERIALS AND METHODS

Sodium alginate, Egg albumin, Paraffin (light), Calcium chloride, Tweens 80 purchased from S.D. Fine Chemicals. All the chemicals and reagents used were of analytical grade.

Formulation of microspheres: Microspheres with drug (famotidine Hydrochloride) are prepared by the Ion Gelation and Thermal Cross Linking Method. F1 – F4 are prepared by Thermal Cross Linking Method. F5 – F6 are prepared by Ion Gelation Method.

Thermal cross linking method: Mucoadhesive microspheres of Famotidine Hydrochloride was prepared by thermal cross linking method. 0.4% of Tweens 80 was added to 100mL of light liquid paraffin and it was heated to 70°C till tweens 80 was completely dissolved. It was cooled to room temperature. Prepare 10%W/V solution of egg albumin and drug solution. Add the solution containing egg albumin and drug (Famotidine) to previously cooled Light Liquid Paraffin. Stir it with mechanical stirrer for 10min and heat it to 95oC for 10-15 min. We can see the formation of microspheres. The beads so prepared were collected by decantation, washed with water. Then it was dried over night to become hard microspheres. The process was applied to 4 different formulations by using varying proportions of egg albumin.

Ion gelation method: Accurately weighed about 10% of sodium alginate 20% of egg albumin and kept aside, then it was dispersed in 100 ml of distilled water by using magnetic stirrer at 40°C. Then after complete dispersion, added accurately 100 mg of Famotidine Hydrochloride then the stirring was continued until complete and uniform dispersion was obtained. Then the Calcium chloride solution was prepared by dispersing the 5gm of Calcium chloride powder in 100 ml of distilled water by heating at 40°C.

***In vitro* wash-off test:** The mucoadhesive property of microspheres was evaluated by an in vitro adhesion testing method known as wash-off method. Freshly excised piece of intestinal mucosa (2×2 cm) from albino rat were mounted onto glass slides (3×1 inch) with cyanoacrylate glue. Two glass slides were connected with a suitable support, about 50 microspheres were spread on to each wet rinsed tissue specimen and immediately thereafter the support was hung onto the arm of a USP tablet disintegrating test machine. When the disintegrating test machine was operated, the tissue specimen was given slowly, regular up and down moment in the test fluid (500 ml pH 1.2 phosphate buffers) maintained at 37ºC. At the end of 30 min, 1h, and hourly intervals up to 8h, the numbers of microspheres adhering to tissue were counted.

Mucoadhesion= (no. of microspheres adhered/no. of microspheres applied) ×100

***In vitro* drug release data and profiles:** The prepared formulation was evaluated for in-vitro release by USP dissolution apparatus 1 at 50 rpm and at 37°C temperature in order to determine 100% drug release. To evaluate microspheres containing famotidine were exposed to 900 ml of HCl (pH 1.2). The samples were collected in pre-determined time intervals. Famotidine concentrations were determined by UV at 265 nm.

Table.1.Formulation table of Famotidine mucoadhesive microspheres

Ingredients (mg)	Formulation codes					
	F1	F2	F3	F4	F5	F6
Drug	100	100	100	100	100	100
Egg albumin	5	10	15	20	20	20
Sodium alginate	-	-	-	-	10	5
Calcium chloride	-	-	-	-	5	5
Light liquid paraffin	100	100	100	100	-	-
Tween 80	0.4	0.4	0.4	0.4	-	-
Purified water	q.s	q.s	q.s	q.s	q.s	q.s

3. RESULTS AND DISCUSSION

The mucoadhesive microspheres of sodium alginate and egg albumin prepared by Ion Gelation and Thermal cross linking method. The polymer sodium alginate was selected to control the release rate and egg albumin as a mucoadhesive polymer. Both are biodegradable and mucoadhesive polymer. The formulation of the present microspheres was based on the solubility behavior of both polymers. Eight Formulations F1-F6 were formulated by varying concentration of sodium alginate and egg albumin, to study effect of release of famotidine from the microspheres and effect of polymer concentration on the size, percentage mucoadhesion, and drug entrapment efficiency. The particle size and surface morphology was determined with the help of optical microscope and Scanning Electron microscope. To investigate the effect of release of famotidine from the microspheres eight batches F1-F6 were prepared. The drug release prolonged to 17 hours in formulation F5.

Product yield: The percentage yield of formulations was in the range of 86.15 ± 0.3 to 95.56 ± 0.31. The product yield was manageable with little loss of drug during the formulation stage.

Estimation of drug Content: The percentage drug content of formulations were in the range of 95.21 ± 0.45 to 98.65 ± 0.31. The low SD and CV value indicates uniform distribution of drug within the various batches of microspheres prepared. The drug content

results suggest a negligible loss of drug during the formulation

Stage.

Encapsulation efficiency: Encapsulation efficiency of all the formulations is presented in the percentage encapsulation efficiency of set-1 formulations were in the range of 83.32 ± 0.11 to 98.16 ± 0.45. The results suggest encapsulation efficiency depend upon concentration of sodium alginate used in the formulation. The encapsulation efficiency is increased progressively with increase in the concentration of sodium alginate. This could be attributed due to formation of larger microspheres with increasing concentration of sodium alginate, thus entrapping more amount of drug.

Morphology and Particle size Determination: The size analysis of microspheres is carried out by optical microscope. The sizes of microspheres were in the range of 20-90 microns. The size of microspheres is depending upon concentration of sodium alginate used in the formulation. The increase in size of microspheres was observed with increase in concentration of sodium alginate. This could be due to increase in viscosity of the polymeric dispersion, which eventually lead to formation of bigger particle during ionic gelation. The results of the particle size of many of the formulations were in the limits and comply with the standards.

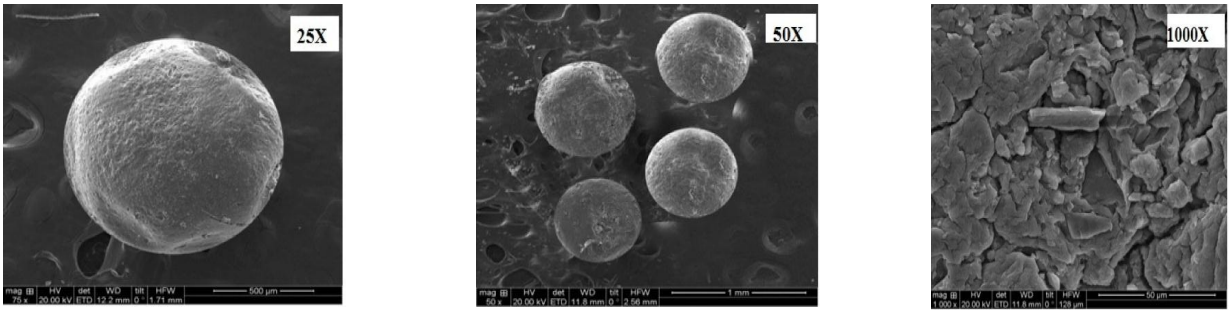

Figure.2.Scanning electron micrographs of F5 formulation

Scanning electron microscopy: Scanning electron microscopy was used to know surface morphology of microspheres. The SEM photographs of F5 revealed that microspheres were spherical, discrete. The outer surface of microspheres was coarse rough texture, with few pores, mild cracks and completely covered with coat materials.

***In vitro* wash off test:** The mucoadhesion is a phenomenon in which two materials, at least one of which is biological are held together by means of interfacial force. *In vitro* mucoadhesion data of mucoadhesive microspheres carried out with everted rat intestinal mucosa in presence of pH 1.2. The percentage of microspheres retained on everted intestinal mucosa after 6 h in set-1 formulations were found in the range of 71-55. The overall results suggest that concentration and type of mucoadhesive polymer does not show much more difference in the mucoadhesive property.

Table.2.Cumulative percentage *in vitro* drug release

Time (h)	Cumulative Percentage Drug Release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
0.25	26.28	22.5	23.8	7.94	1.02	3.06
0.5	35.2	29.23	28.4	17.86	2.52	10.06
1	55.6	47.51	45.14	26.47	11.2	21.4
3	72.5	65.4	58.38	35.73	19.64	35.14
5	85.32	85.92	65.27	51.7	26.24	49.62
7	98.2	89.1	71.24	69.2	46.67	64.12
9	-	97	85.42	82.05	66.42	77.42
11	-	-	97.02	94.2	77.81	88.4
13	-	-	-	96.6	82.4	97.4
15	-	-	-	-	91.42	-
17	-	-	-	-	97.1	-

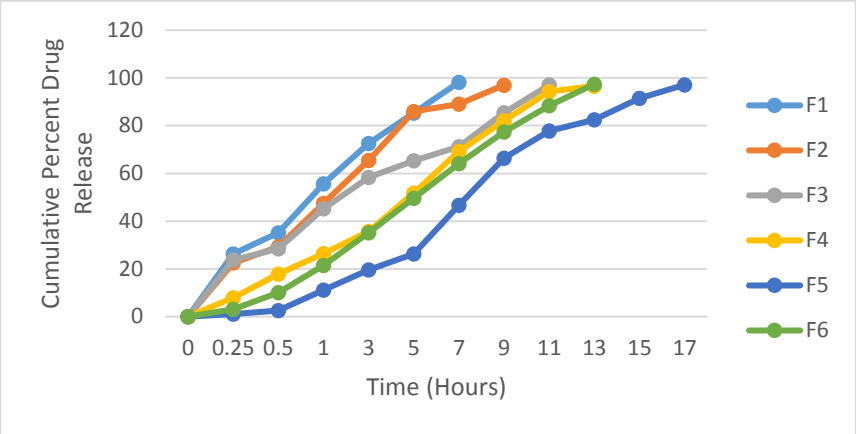

Figure.3. Cumulative percentage *in vitro* drug release

4. CONCULSION

The present study shows that the microspheres prepared polymer sodium alginate and egg albumin both have a significant effect on the mucoadhesion, drug entrapment efficiency and drug release. Egg albumin is hydrophilic polymer has good entrapment efficiency and good mucoadhesion but it releases the drug immediately therefore sodium alginate was used to control the release rate as well as the other factors to match the acceptance criteria. After evaluating all the formulation, the formulation F5 which is containing the higher percentage of egg albumin showed the good entrapment efficiency about 98%, *in vitro* wash off test was found to be about 82% and good drug release profile in 8 hours. Therefore it was selected as the best formulation.

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