Original Article

Novel interpenetrating polymer network mucoadhesive microspheres of locust bean gum and poly(vinyl alcohol) for the delivery of Famotidine

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ABSTRACT

Novel interpenetrating polymer network (IPN) of locust bean gum (LBG) and poly vinyl alcohol (PVA) were prepared and crosslinked with glutaraldehyde (GA) to form mucoadhesive microspheres by emulsion cross-linking method to deliver model anti-ulcer drug, famotidine. Various formulations were prepared by changing the ratio of LBG: PVA, extent of cross-linking in order to optimize the formulation variables on drug encapsulation efficiency and release rate. FTIR spectroscopy was done to confirm the formation of interpenetrating network and the chemical stability of famotidine after penetration of microspheres. Microspheres formed were spherical with smooth surfaces as revealed by SEM and mean particle size as measured by optical microscopy ranged between 10.83±0.75μm to 21.13±0.74μm. Drug entrapment efficiency was ranges between 65.44±2.57% to 84.67±2.58%. Percentage mucoadhesion of the microspheres was found to be in the range between 63.33±2.57% to 86.66±3.65%. Equilibrium and dynamic swelling studies were performed in 0.1N HCl buffer solution of pH 1.2 and diffusion coefficients were calculated by considering the spherical geometry of the matrices. *In vitro* release studies were performed in pH 1.2 media. Release data indicated that a drug release which depends on the extent of cross-linking and the ratio of LBG: PVA present in the microsphere. The release data were fitted to an empirical equation to estimate the transport parameters, which indicated that the release follows Super Case II transport mechanism. Based on the results of *in-vitro* studies it was concluded that these IPN mucoadhesive microspheres provided oral controlled release of famotidine.

1. INTRODUCTION

Oral ingestion is the most convenient and commonly employed route of drug delivery [1]. Though, the low bioavailability and short biological half-life of drug for the oral administration favors the development of a controlled release formulation [2]. Controlled drug delivery systems offer numerous advantages compared to conventional dosage forms such as improved efficiency, reduced toxicity and improved patient compliance and convenience [3]. The gastroretentive drug delivery systems can be retained in the stomach for long time and improve the oral bioavailability of drugs that have an absorption window in a particular region of the gastrointestinal tract [4]. Recently, dosage forms that can precisely control the release rates and target drugs to a specific body site have made an enormous

impact in the formulation and development of novel drug delivery systems. Microspheres form an important part of such novel drug delivery systems [5,6]. Mucoadhesive microspheres offers several advantages such as efficient absorption and enhanced bioavailability of drugs owing to a high surface-to-volume ratio, a much more intimate contact with the mucus layer, and specific targeting of drugs to the absorption site [7]. Mucoadhesive microspheres have the ability to adhere to the stomach wall in rats and thereby remain in the gastrointestinal tract for an extended period. In recent years, considerable attention has been focused on hydrophilic polymers in the design of oral controlled drug delivery systems because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance [8]. These polymeric systems have been the potential candidates to deliver bioactive molecules, particularly in controlled release applications [9, 10]. Such naturally abundant carbohydrate polymer however exhibiting some limitations in their reactivity and processibility, have still been used after being modified by blending, crosslinking etc.

The chemical and physical combination methods and properties of multipolymers have been of great practical and academic interest for the controlled release of drugs because they provide a convenient route for the modification of properties to meet specific needs [11]. Among these methods, interpenetrating polymer network (IPN) structures has received greater attention as they increase the phase stability and enhance the mechanical properties of the final product [12]. Better mechanical properties of IPN make it suitable for microspheres preparation for the controlled delivery of drugs [13]. An IPN is a composite of two polymers, which is obtained when at least one polymer network is synthesized or cross-linked independently in the immediate presence of the other [14,15].

This study presents the development of novel interpenetrating network mucoadhesive microspheres of locust bean gum and PVA for the controlled release of famotidine. Locust bean gum is a high molecular weight branch polysaccharide and is extracted from the seeds of carob tree *Ceratonia siliqua*. It consists of a 1, 4-linked β-D-mannopyranose backbone with branch points from their 6-positions linked to α-D-galactose (1, 6-linked α-D-galactopyranose). This galactomannan occurs as a white to yellow-white powder, odorless and tasteless, but acquires a leguminous taste when boiled in water. It is less soluble in water and needs heating to dissolve. Being non-ionic, it is not affected by pH or ionic strength. It is dispersible in either hot or cold water, forming a sol having a pH between 5.4–7.0, which may be converted to a gel by the addition of small amounts of sodium borate [16]. Its film forming property is used in the textile industry, making it ideal as a sizing and finishing agent, as well as in the pharmaceutical and cosmetics industries for the production of lotions and creams [17]. It also finds its application as excipients for tablets. Moreover, this ingredient is approved for food uses by the US Food and Drug Administration (FDA). Famotidine is a H_2 receptor antagonist with short biological half-life (3.5-4.5h) and low oral bioavailability (40-45%) has been used as a model drug. Famotidine has variable absorption in the gastrointestinal tract and the absorption in the intestine is less due to microbial degradation. Hence, an oral controlled release preparation of famotidine should be preferably placed in the stomach to achieve uniform drug absorption. Poly vinyl alcohol (PVA) is a widely used hydrophilic polymer because of its processability, strength, and pH as well as its temperature stability. Because it is biocompatible and non-toxic, it has a wide variety of pharmaceutical applications [18-20]. Locust bean gum and PVA both have good mucoadhesive property.

2. MATERIALS AND METHODS

Materials

The famotidine was kindly received as a gift sample by M/s Zydus Cadila Health Care Ltd. (Ahmedabad, India). Locust bean gum and poly vinyl alcohol was a gift sample procured from Loba Chemie Pvt. Ltd. (Mumbai, India). Analytical reagent grade samples of glutaraldehyde (25% v/v), soyabean oil, span 80 and acetone were purchased from S.D Fine chemicals (Mumbai, India). Double distilled water was used throughout the work.

Preparation of mucoadhesive microspheres

Locust bean gum and poly vinyl alcohol (LBG-PVA) IPN mucoadhesive microspheres containing famotidine were prepared by the emulsion cross-linking method. PVA was first dissolved in hot water at 80°C. After that, the required amount of locust bean gum was dispersed in the above homogeneous solution and stirred overnight with magnetic stirrer to obtain a thick, viscous, homogeneous polymeric mass. Then, famotidine was dissolved in minimum quantity of methanol in order to make it complete soluble and was added to the above homogeneous polymeric mass. The drug loaded homogeneous polymeric mass was emulsified into 100 ml of soya bean oil containing 1% w/w span-80 to form water-in-oil (w/o) emulsion under constant stirring at 900 rpm speed for 40 minutes using a high-speed mechanical stirrer (LT400A, Yamoto, Japan). To this w/o emulsion, 1 ml of 1N hydrochloric acid and required amount of glutaraldehyde was added slowly by dropwise in order to form hardened microspheres and further stirred for 3 hour. The hardened microspheres were separated by filtration process and washed repeatedly with acetone and distilled water to remove the oil layer as well as excess amount of unreacted surfactant from the prepared emulsion. Finally, the hardened microspheres were washed with 0.1M glycine solution to mask the unreacted glutaraldehyde. At last, the hardened microspheres were dried in an oven at 36°C temperature for 24 hour and then stored in a vacuum desiccators fused with calcium chloride until further use. In total, nine formulations were prepared to study the effect of different formulation variables on the characteristics of IPN microspheres.

Table 1. Formulation codes and different process variables used to prepare IPN mucoadhesive microspheres.

Formulation code	Gum: polymer ratio	Glutaraldehyde (ml)
F1	1:2	3.5
F2	1:3	3.5
F3	1:4	3.5
F4	1:2	4.5
F5	1:3	4.5
F6	1:4	4.5
F7	1:2	5.5
F8	1:3	5.5
F9	1:4	5.5

Fourier transform infrared (FTIR) spectral studies

FTIR spectral measurements were performed using FTIR-8400S spectrophotometer, Shimadzu (Japan) to confirm the formation of IPN structure, presence of cross-linking agent in LBG and PVA and also to find the chemical stability of the drug in the microspheres. FTIR spectra of the pure famotidine, placebo microspheres and drug-loaded microspheres were obtained. Samples were crushed with KBr to get pellets at 600 kg/cm^2 pressure. Spectral scanning was done in the range between 4000–400 cm^{-1}.

Scanning electron microscopy (SEM) analysis

SEM photographs of the IPN microspheres were taken at required magnification at room temperature. Microspheres were mounted onto stubs using double sided adhesive tape and vacuum coated with gold film using a sputter coater. The coated surface was observed under SEM (LEO 435VP model, Cambridge, UK) for surface appearance.

Estimation of percentage yield

The percentage yield of the mucoadhesive microspheres was calculated using the formula [21]:

Percentage yield = (amount of microspheres/amount of drug + amount of polymer) × 100

Estimation of drug entrapment efficiency

The actual amount of famotidine present in the different formulations of locust bean gum and poly(vinyl alcohol) IPN mucoadhesive microspheres were estimated by crushing the swollen microspheres (10 mg) in 100 ml of pH 1.2 (0.1 N HCl) at 50°C temperature to extract the drug from the microspheres in a water bath. The whole system was kept for 24 hours. Then, the whole solution was centrifuged (Remi Equipments Private Limited, Mumbai, India) to remove the suspended polymeric debris and the clear supernatant liquid was taken for the determination of ranitidine content spectrophotometrically by using UV spectrophotometer at a wavelength of 265 nm against appropriate blank. In order to maintain the accuracy, experiments were carried out in triplicate for all the formulations to check its reproducibility. The average drug entrapment efficiency values were considered for data treatment and calculations along with standard deviation values. These data are presented in Table 2.

Entrapment efficiency (%) = (actual drug content/theoretical drug content) × 100

Particle size measurements

Particle size of IPN based formulations were measured using an optical microscope. A standard stage micrometer was used to calibrate the eye-piece micrometer. Dried IPN microspheres were placed in a glass slide and the number of divisions of the calibrated eye piece was counted. A hundred particles were randomly selected from each formulation and the individual particle diameter was calculated based on this formula: 1 eyepiece division = [(no of stage micrometer divisions/no of eyepiece micrometer division) × 10 μm]. For measurement of particle size of different formulations, volume mean diameter (V_d) was recorded [22]. These data are presented in Table 2.

In-vitro mucoadhesion study

The *in-vitro* mucoadhesion test was carried out using small intestine from chicken. A strip of intestinal mucosa was excised and everted using a glass rod. An accurately weighed mucoadhesive microspheres (100 mg) were scattered uniformly on the everted sac from the position of 2 cm above. Then the sac was suspended with the help of thread in a 25ml beaker containing 20 ml of 0.1 N HCl (pH 1.2) to immerse in the solution completely. The sac were incubated at 37⁰C and agitated horizontally. Then, the sac were taken out of the medium after immersion for 1, 2, 3, 4, 5 and 6 h, immediately repositioned as before in a similar tube containing 20ml of fresh media and washings were collected at different time intervals and microspheres were separated by centrifugation followed by drying at 50⁰C. The weight of microspheres washed out was taken and percentage mucoadhesion was calculated by [23]:

% Mucoadhesion= (Wa – W$_1$) / Wa × 100

Where, Wa = weight of microspheres applied; W$_1$ = weight of microspheres leached out

% Equilibrium liquid uptake studies

The pH-dependent equilibrium water uptake of the blank IPN mucoadhesive microspheres were measured by immersing 10 mg samples into 100 ml of the simulated gastric pH conditions using 0.1N HCl buffer solution at pH 1.2. To ensure complete equilibration, microspheres were allowed to swell completely for about 24 hour to attain equilibrium at 37°C temperature. The excess surface adhered liquid droplets of the particles were removed by blotting with soft tissue papers without pressing hard and the swollen microspheres were weighed by using balance. In order to maintain the accuracy level, experiments were carried out in triplicate for all the formulations in order to obtain reproducible results. The average percent equilibrium water uptake values were considered for data treatment and

calculations along with standard deviation values. The percentage equilibrium water uptake was calculated as[24]:

Swelling ratio = (Final weight-Initial weight) / Initial weight × 10

Dynamic swelling studies

Drug release from the cross-linked microspheres depends upon the extent of water penetration into the matrix. Dynamic swelling of the microspheres was carried out in order to understand the molecular transport of water into cross-linked blank mucoadhesive microspheres. Dynamic swelling of the microspheres was measured by the microscopic technique by using an optical microscope. The change in the diameter of only the variable blank microspherical formulations in gastric pH conditions were monitored precisely with an ocular microscope under the plane polarized light at room temperature as a function of time. Experiments were performed in triplicate, but average values were considered for data treatment and calculations by using equation given below. The dynamic swelling study was determined by plotting Dt/Do on Y-axis against time (t) on X-axis.

$$Dt/Do \sim t$$

Where,

Dt is the measured changes in the normalized microsphere diameter at definite time intervals.

Do is the initial diameter of the microspheres.

t is the time.

Differential scanning calorimetric study

DSC analysis was performed on the blank microspheres and drug-loaded microspheres. Initially, the moisture was removed by heating the samples and then, each sample (about 3-7 mg) was accurately weighed into platinum crucible 40 µl aluminium pan in hermetically sealed condition, where alpha alumina powder used as a reference. Thermograms were recorded from 50°C to 300°C at the heating rate of 20°C/min under a constant flow of an inert nitrogen gas atmosphere with the flow rate of 20 ml/min. These analyses were done on Perkin-Elmer instrument (Pyris-1, Osaka, Japan), available at Department of Textile Technology, Indian Institute of Technology, New Delhi, India.

In-vitro drug release study

In-vitro release of famotidine mucoadhesive microspheres were monitored in 0.1 N HCl solution (pH 1.2) at 37°C using programmable dissolution tester (Paddle type, Electrolab, model TDT-08L, USP, Mumbai, India). Microspheres (100 mg) were immersed in 900 ml of the respective medium and stirred at 100 rpm. Aliquots were removed at pre-determined times and were replenished immediately with the same volume of fresh media. The aliquots, following suitable dilution, were assayed spectrophotometrically at 265 nm.

Release kinetics of IPN mucoadhesive microspheres

In order to investigate the mode of drug release (Table 4) from IPN mucoadhesive microspheres, the release data were fitted with the following mathematical models:

Zero-order kinetics equation:

$$Q_t = k_0 \cdot t$$

Where,

Q_t is the amount of drug released at time t

k_0 is the zero-order release rate constant

t is the time

First-order kinetics equation:

$$\ln Q_t = \ln Q_0 - k_1 t$$

Where,

Q_t is the amount of drug released at time t

Q_0 is the initial amount of drug in the solution

k_1 is the first-order release rate constant

Higuchi model kinetics equation:

$$Q_t = k_H \cdot t^{1/2}$$

Where,

Q_t is the amount of drug released at time t

k_H is the Higuchi release rate constant

Korsmeyer-Peppas model kinetics equation:

$$M_t/M_\infty = K_{KP} \cdot t^n$$

Where,

M_t is the fraction of drug released at time t

M_∞ is the fraction of drug released at infinite time

K_{KP} is the Korsmeyer-Peppas release rate constant

n is the release exponent

Hixson-Crowell model kinetics equation:

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC} \cdot t$$

Where,

Q_0 is the initial amount of the drug in the dosage form

Q_t is the remaining amount of drug in the dosage form at time t

K_{HC} is the Hixson-Crowell release rate constant

3. RESULTS

FTIR was used to confirm the formation of the IPN matrix. Figure 1 shows the FTIR spectra of famotidine, placebo microsphere and drug loaded microspheres respectively. Famotidine showed that the principle IR peaks at 1027.99 cm^{-1} resulted from C-N stretching and the peak at 3377.12 cm^{-1} resulted from N-H stretching and the peak at 1533.30 cm^{-1} resulted from N-H bending. In the case of placebo microspheres, a broad band which appeared at 3458.13 cm^{-1} is attributed to the presence of a hydroxyl group that is hydrogen bonded to various degrees and broad peak around 3640.07 cm^{-1}, indicating stretching of hydroxyl groups and peaks at 2894.95 cm^{-1} is attributed to the stretching vibration of –CH$_2$. In the spectra of drug loaded

microspheres, the appearance of peaks at 1056.92 cm^{-1} indicates the presence of a C-O-C group.
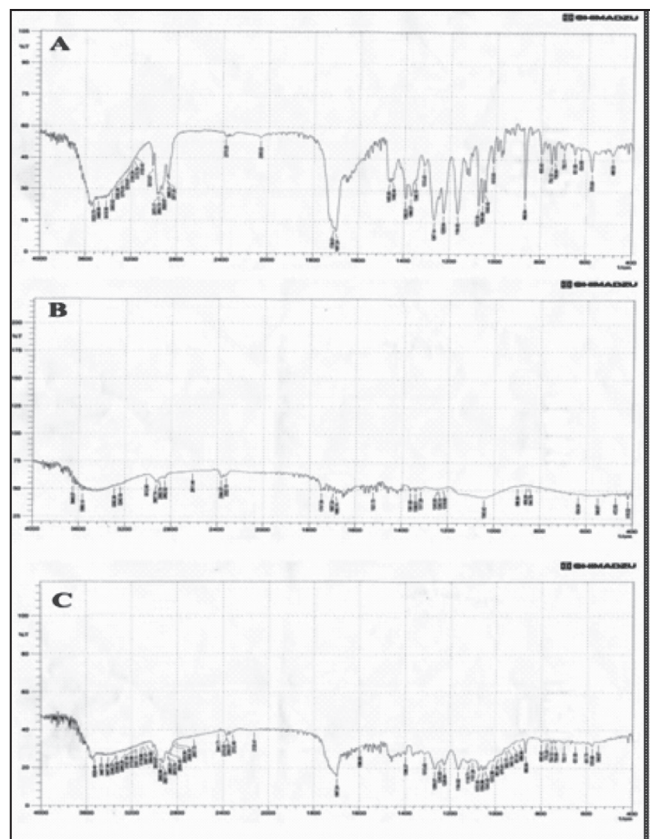

Fig. 1. FTIR spectra of (a) Famotidine (b) Placebo microspheres (c) drug loaded microspheres

In the present study, famotidine loaded IPN mucoadhesive microspheres of LBG and PVA were prepared using glutaraldehyde as a cross-linking agent shown in Table 1. The microspheres obtained were all spherical in nature with smooth surfaces as demonstrated by SEM images shown in Figure 2 and they fell.

in the size range of 10.83±0.75 µm to 21.13±0.74 µm (Table 2). Table 2 also shows that % drug entrapment efficiency (% DEE) of
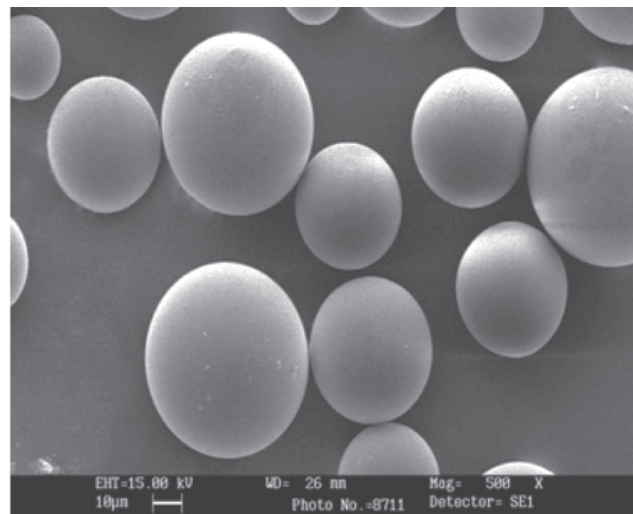
Fig. 2. SEM photograph of IPN mucoadhesive microsphere.

the microparticles prepared using different formulation variables was in the range between 65.44±2.57 % to 84.67±2.58 % and it depends on the GA concentration and the ratio of LBG: PVA

To assess the mucoadhesivity of the IPN microspheres *in-vitro* wash off test was performed for all the formulations for 6 h. Table 2 shows that % mucoadhesion of the microspheres prepared using different formulation variables was in the range between 63.33±2.57 % to 86.66±3.65 % and it also depends on the GA concentration and the ratio of LBG: PVA. Equilibrium water uptake of the cross-linked microspheres exerts an influence on their release rates [25]. The percentage equilibrium water uptake data of the cross-linked microspheres presented in Table 2 shows that as the amount of GA in the matrices increases from 3.5 ml to 5.5 ml, the equilibrium water uptake in pH 1.2 decreases significantly from 266.60±3.21% to 100.50±3.08%.

Table 2. Effect of crosslinking agent, locust bean gum: poly(vinyl alcohol) ratio on particle size, drug entrapment efficiency and percentage equilibrium liquid uptake in pH 1.2 media.

Formulation code	% Yield	% DEE (± SD, n=3)	Volume mean diameter (µm) (± SD, n=3)	% Mucoadhesion (± SD, n=3)	% Equilibrium liquid uptake study in pH 1.2 media
F1	73.75±1.96	65.44±2.57	10.83±0.75	63.33±2.57	266.60±3.21
F2	76.40±2.15	67.81±1.98	11.81±0.65	67.66±1.96	223.20±2.75
F3	81.16±1.68	73.02±1.88	12.90±0.77	71.66±2.35	199.40±2.86
F4	78.25±2.05	76.17±2.56	13.88±0.33	74.66±3.05	191.40±2.92
F5	83.20±1.88	78.29±3.52	14.96±0.57	77.33±2.78	186.30±3.05
F6	85.33±1.57	80.87±2.98	15.75±0.65	80.33±3.45	151.60±3.12
F7	82.75±2.16	82.31±1.28	19.85±0.76	82.66±1.69	132.90±2.65
F8	85.60±1.78	83.13±3.67	20.85±0.66	84.66±2.68	119.60±2.76
F9	91.33±1.57	84.67±2.58	21.13±0.74	86.66±3.65	100.50±3.08

The dynamic swelling studies were performed by monitoring the changes in the microsphere diameter, D_t, as a function of time with the help of an optical microscope with a micrometer. Table 3 displays the mean values of normalized diameter, D_t/D_o, (where, D_o is initial diameter of the microsphere and D_t is the diameter of the microsphere at time t) as a function of time (t) in simulated gastric fluid (0.1N HCl) at pH 1.2. Figure 4 shows the plot of normalized diameter (D_t/D_o) versus time (t) for different ratios of LBG: PVA in the matrix. It is observed that the normalized diameter of F4 (LBG: PVA= 1:2) was greater than F6 (LBG: PVA= 1:4) in simulated gastric fluid at pH 1.2 media. From the Figure 5, it is evident that the normalized diameter values decreases with an increasing amount of cross-linking agent.

Table 3. Results of dynamic swelling study of all formulations in 0.1N HCl buffer solution at pH 1.2 media.

| Time (min)	Average diameter values (µm) of dynamic swelling study report								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	1	1	1	1	1	1	1	1	1
30	1.050	1.044	1.038	1.044	1.031	1.026	1.016	1.013	1.006
60	1.100	1.085	1.076	1.074	1.058	1.046	1.033	1.023	1.018
90	1.150	1.133	1.124	1.117	1.095	1.063	1.050	1.033	1.025
120	1.200	1.175	1.166	1.151	1.128	1.078	1.066	1.045	1.041
150	1.250	1.210	1.201	1.185	1.155	1.102	1.083	1.064	1.047
180	1.300	1.223	1.213	1.193	1.161	1.108	1.100	1.068	1.053
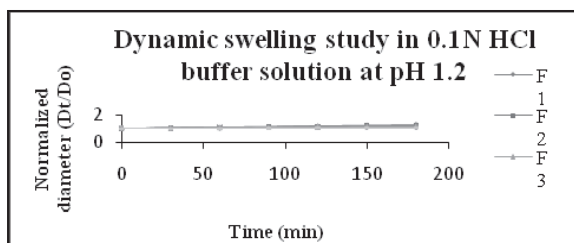
Fig. 3. Dynamic swelling studies for all formulations in 0.1N HCl buffer solution at pH 1.2.
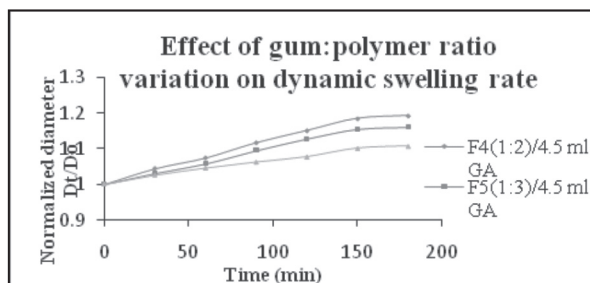

Fig. 4. Effect of gum: polymer ratio while cross-linking density constant in 0.1N HCl buffer solution at pH 1.2.
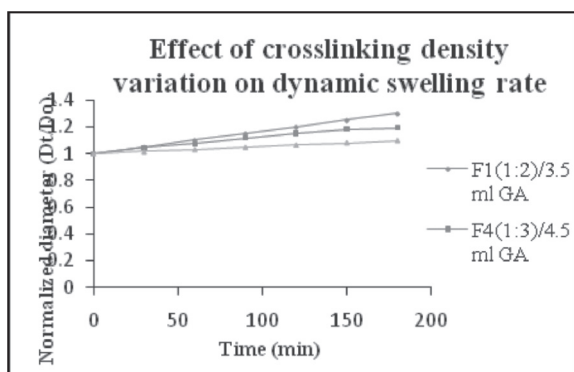

Fig. 5. Effect of crosslinking density while gum: polymer ratio constant in 0.1N HCl buffer solution at pH1.2.

DSC thermograms of blank microspheres and drug-loaded microspheres were displayed in Figure 6 and Figure 7. DSC thermogram of pure famotidine showed a sharp endothermic peaks at 169.079ºC (area=192.493 mJ, delta H=192.493 J/g) and a small peak at 176.475ºC (area=130.246 mJ, delta H=130.246 J/g) indicating the crystal melting point and thermal decomposition of the drug respectively. In case of blank microspheres, one sharp endothermic peak was seen at 191.923ºC (area=68.890 mJ, delta H=22.963 J/g) indicating the melting point of PVA, but there was no sharp endothermic peak was observed for locust bean gum indicating the uniform blending of locust bean gum into the drug-polymer mixture.
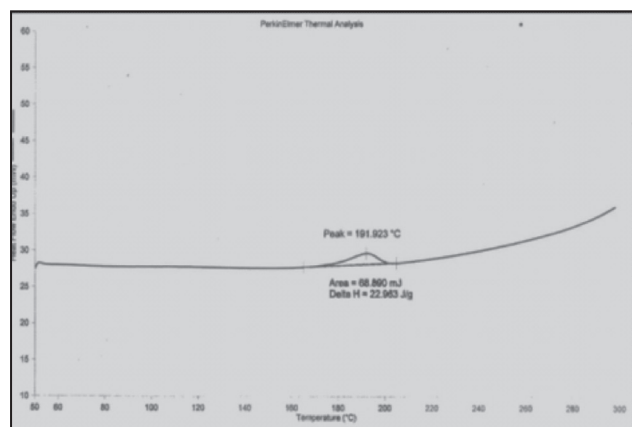

Fig. 6. DSC thermogram tracings of blank microspheres.

In-vitro drug release was performed in pH 1.2 and percentage cumulative release vs time data are presented in Figure 8. The percentage cumulative release vs time for the microspheres prepared with different crosslinking density loaded with famotidine are presented in Figure 9. The formulation F4 showed a higher release rate than F7 and similarly the formulation F1 showed a higher release rate than F4 (i.e. F1 > F4 > F7). The percentage cumulative release vs time for the microspheres

prepared with different ratios of LBG: PVA loaded with famotidine are presented in Figure 10. The cumulative percentage released is higher in the case of F5 than F6, and similarly F4 shows higher release rates than F5 (i.e. F4 > F5 > F6).
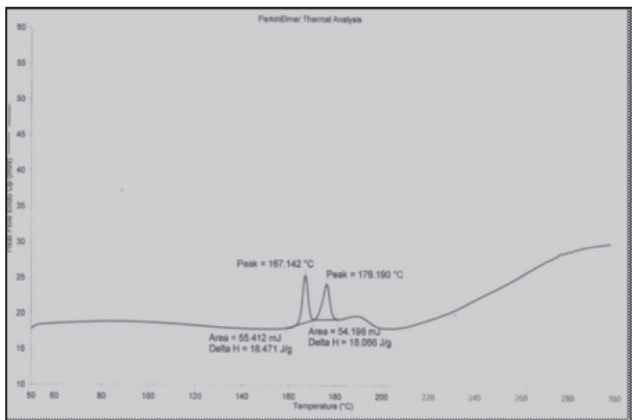

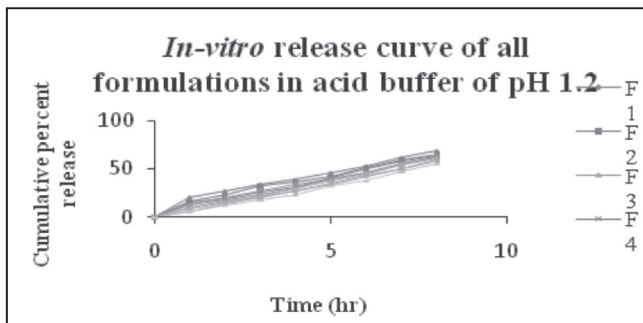**Fig. 7.** DSC thermogram tracings of drug-loaded microspheres.

Fig. 8. Release profiles of drug loaded IPN mucoadhesive microspheres of all formulations in 0.1N HCl buffer solution at pH 1.2.
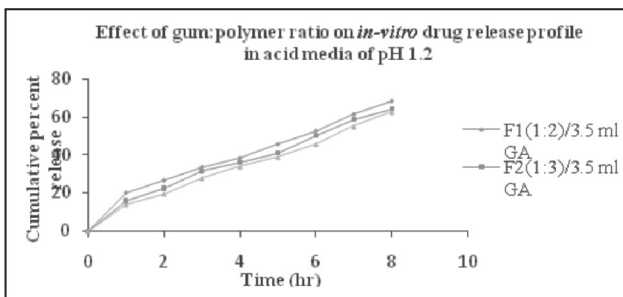

Fig. 9. Effect of gum: polymer ratio variation on *in-vitro* drug release profile in 0.1N HCl buffer solution of pH 1.2.
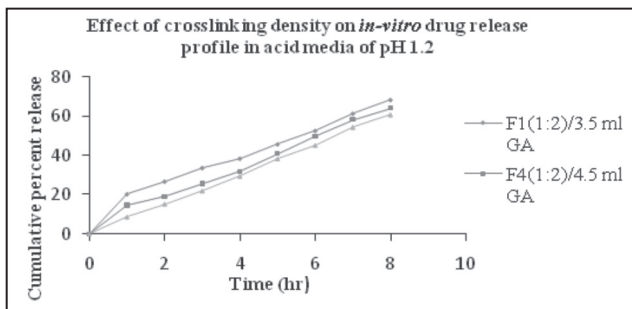

Fig. 10. Effect of crosslinking density variation on *in-vitro* drug release profile in 0.1N HCl buffer solution of pH 1.2.

The *in-vitro* release studies data were fitted into various release equations to explain the kinetics of drug release from these microspheres. The kinetic models used were zero-order, first-order, Higuchi release model, Korsmeyer-Peppas model and Hixson-Crowell model [26]. Co-relation coefficients of formulation F1 to F9 for zero-order, first-order, Higuchi release model, Korsmeyer-Peppas model and Hixson Crowell model were summarized in Table 4 and their release pattern were shown in Figure 11 to Figure 15 respectively. The determination of the corelation coefficient (R^2) value indicated that drug release have followed zero order kinetics for formulation F3 to F7, Hixson-Crowell kinetics for formulation F1 and Korsmeyer-Peppas kinetics for formulation F2, F8 and F9 which predicts the release may be dissolution controlled mechanism from the IPN mucoadhesive microspheres. The 'n' value for F1 to F9 was given in Table 4. The 'n' value could be used to characterize different drug transport mechanisms and was in the range of 0.5851 to 1.1558. This indicates that the release of formulations F1 to F9 follows Super Case-II transport mechanism.

Table 4. Results of drug release kinetics

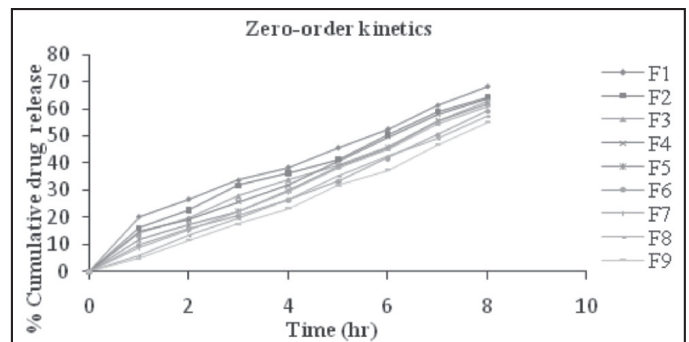| Formulation code	Zero order kinetics	First order kinetics	Higuchi kinetics	Korsemeyer's Peppas kinetics	Diffusional exponent (n)	Hixson-Crowell Kinetics
F1	0.9705	0.9663	0.9709	0.9745	0.5851	0.9800
F2	0.9819	0.9759	0.9621	0.9866	0.6745	0.9853
F3	0.9890	0.9686	0.9473	0.9859	0.7234	0.9807
F4	0.9910	0.9688	0.9294	0.9643	0.7434	0.9791
F5	0.9944	0.9681	0.9147	0.9757	0.8224	0.9790
F6	0.9916	0.9543	0.8952	0.9806	0.8713	0.9681
F7	0.9987	0.9799	0.9097	0.9961	0.9528	0.9889
F8	0.9984	0.9826	0.8965	0.9993	1.0812	0.9907
F9	0.9938	0.9704	0.8746	0.9985	1.1558	0.9812

Fig. 11. Zero-order release kinetics of all formulations (F1 to F9)
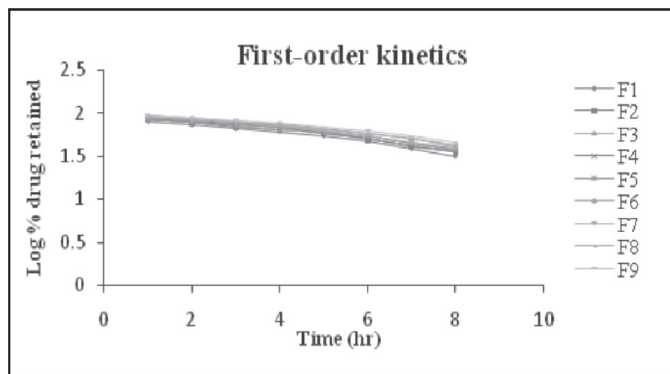
Fig. 12. First-order release kinetics of all formulations (F1 to F9)
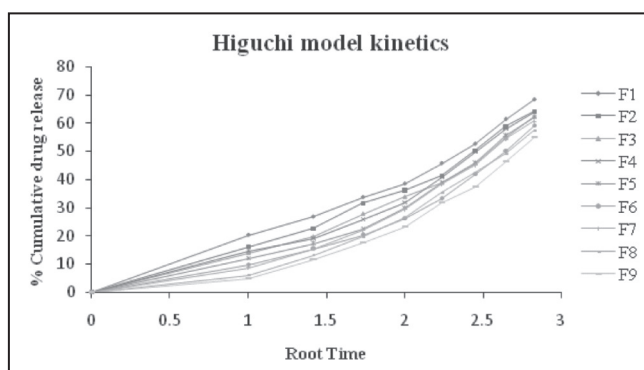

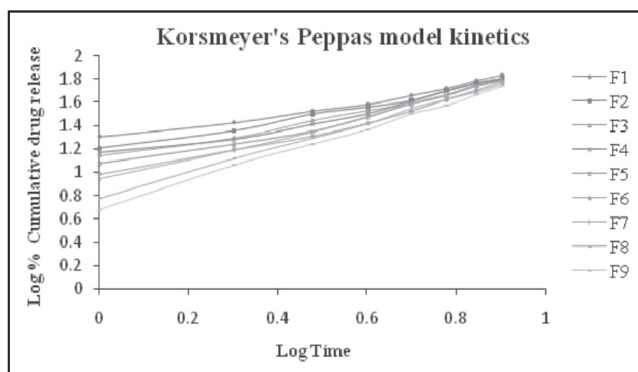**Fig. 13.** Higuchi model kinetics of all formulations (F1 to F9)

Fig. 14. Korsmeyer's Peppas model kinetics of all formulations
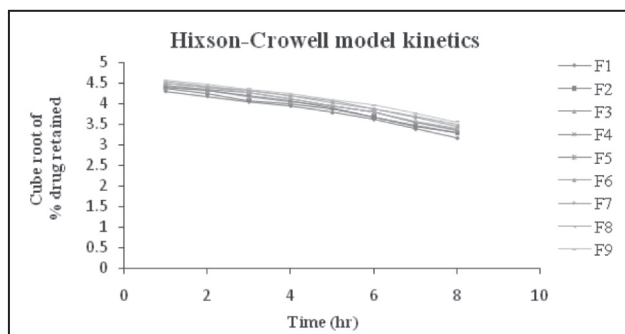(F1 to F9)

Fig. 15. Hixson-Crowell kinetics of all formulations (F1 to F9)

4. DISCUSSION

It was confirmed by FTIR that the entire principal peaks of famotidine are present in IPN microparticles, which confirm the stability of famotidine in IPN microparticles. In the case of placebo microspheres, a broad band with less intensity compared to both LBG and PVA matrices is due to the presence of very few uncross-linked hydroxyl groups that are hydrogen bonded to various degrees. The bands appearing at 1027.99 cm^{-1} are due to the presence of an acetal group, which formed due to the reaction of glutaraldehyde with hydroxyl groups of both PVA and LBG. Thus, FTIR confirms the cross-linking reaction in addition to the formation of an IPN matrix.

In the present study, famotidine loaded IPN mucoadhesive microspheres of LBG and PVA were effectively prepared using glutaraldehyde as a cross-linking agent. An increase in size of microspheres was also observed with the increase in ratio of polymer in the microspheres. This could be due to the fact that at higher amounts of polymer, the viscosity of the polymer solution increased, thus producing bigger droplets during emulsification that were later hardened in the presence of GA. It was indicated that % drug entrapment efficiency (% DEE) of the microparticles was in the range between 65.44±2.57% to 84.67±2.58% and it depends on the GA concentration and the ratio of LBG: PVA. At lower concentrations of GA, a loose network are formed due to insufficient cross-linking, which results in higher leakage of drug from the polymer matrix, whereas at higher GA concentration, a more rigid network was formed which caused retention of more drug particles during microspheres preparation.

Percentage mucoadhesion of the IPN microspheres was successfully performed for all the formulations for 6 h. It was observed that the formulation F9 showed the highest percentage mucoadhesivity 86.66±3.65% due to the presence of higher proportion of LBG: PVA (1:4) and F1 showed the lowest % mucoadhesivity 63.33±2.57% due to lower proportion of LBG: PVA (1:2) therefore, the irregular surface was increased.

The reduction in water uptake capacity is due to the formation of a rigid network structure at the higher concentration of cross-linking. Again it was observed that formulations containing higher amounts of polymer showed lower percentages of equilibrium water uptake than formulations containing small amounts of polymer. Formulation F1 (LBG: PVA=1:2) showed higher water uptake capacity than F2 (LBG: PVA=1:3). Similarly, formulation F2 exhibited greater swelling than formulation F3 (LBG: PVA=1:4) due to the hydrophilic nature of LBG, thereby leading to higher water uptake capacity.

In-vitro drug release study was successfully performed in 0.1N HCl (pH 1.2). This indicates that the release was slower for those formulations in which a higher amount of GA was used compared to those where lower GA was used. This confirms the formation of a denser network structure, which reduces the rate of swelling as well as the rate of drug release from the matrix. It was also found that with increase in the ratio of LBG: PVA, the swelling of the matrix decreases which leads to the slower release of drug from the matrix.

5. CONCLUSION

LBG-PVA based IPN mucoadhesive microspheres were successfully prepared by the emulsion cross-linking method using glutaraldehyde as cross-linking agent for the effective encapsulation and controlled release of famotidine. Mucoadhesive microspheres with spherical shapes were produced with a narrow size distribution ranging from 10.83±0.75 to 21.13±0.74 µm. FTIR was used to confirm the formation of the IPN network. Microspheres were able to provide drug release for an extended period of time (8 h or more) in 0.1 N HCl solution (pH 1.2). The amount of cross-linking agent and the ratio of LBG: PVA influences the drug entrapment efficiency and release of famotidine from microspheres. When prepared with higher extent of GA, the higher level of drug entrapment could be attained in IPN based formulation. The percentage mucoadhesivity was increased with increase in the ratio of LBG: PVA. The release of famotidine depends on the extent of cross-linking of the matrix as well as the ratio of LBG: PVA present in the matrix.

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