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Research Article

NOVEL INTERPENETRATING POLYMER NETWORK MUCOADHESIVE MICROSPHERES OF GUM GHATTI AND POLY(VINYL ALCOHOL) FOR THE DELIVERY OF RANITIDINE HCL

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ABSTRACT

Novel interpenetrating polymer network (IPN) of gum ghatti (Gg) 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, ranitidine HCl. Various formulations were prepared by changing the ratio of Gg:PVA, extent of cross-linking in order to optimize the formulation variables on drug encapsulation efficiency and release rate. Fourier transform infrared (FTIR) spectroscopy was done to confirm the formation of interpenetrating network and the chemical stability of ranitidine HCl after penetration of microspheres. Microspheres formed were spherical with smooth surfaces as revealed by scanning electron microscopy (SEM), and mean particle size as measured by optical microscopy ranged between 17.17±1.33 to 35.48±0.65 µm. Drug encapsulation of up to 87.80% was achieved as measured by UV method. Both equilibrium swelling studies and 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 Gg:PVA present in the microsphere. Based on the results of in vitro studies it was concluded that these IPN mucoadhesive microspheres provided oral controlled release of ranitidine HCl.

Keywords: Interpenetrating polymer network, Gum ghatti, Poly vinyl alcohol, Mucoadhesive microspheres, Ranitidine HCl

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 gum ghatti and PVA for the controlled release of ranitidine HCl. Gum ghatti is a dried gummy exudation obtained from *Anogeissus latifolia* belonging to family combretaceae. It is a high molecular weight polysaccharide which on hydrolysis yields arabinose, galactose, mannose, xylose and glucuronic acid and mainly occurs as a calcium-magnesium salt[16]. Gum ghatti has been widely used as a thickening and stabilizing agent in oral topical formulations. Ranitidine HCl is a H_2 receptor antagonist[17] with short biological half-life (2–3 h) and low oral bioavailability (45-50%) has been used as a model drug. Ranitidine HCl has variable absorption in the gastrointestinal tract and the absorption in the intestine is less due to microbial degradation[18]. Hence, an oral controlled release preparation of ranitidine HCl 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[19,20]. Gum ghatti and PVA both have good mucoadhesive property.

MATERIALS AND METHODS

Materials

The ranitidine HCl was kindly received as a gift sample by M/s Zydus Cadila Health Care Ltd. (Ahmedabad, India). Gum ghatti 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

Gum ghatti and poly vinyl alcohol (Gg-PVA) IPN mucoadhesive microspheres containing ranitidine HCl were prepared by the emulsion cross-linking method. PVA was first dissolved in hot water at 80°C, then, after cooling to ambient temperature, Gg was added (total polymer concentration was 5% w/v) and stirred overnight to get a homogenous solution. Ranitidine HCl (3% w/v of polymer) was dissolved in 1 ml distilled water and then added to the mixture of gum ghatti and PVA and the solution was stirred to get a uniform suspension. This suspension was added to soyabean oil and 1% w/w span 80 and mixed with a stirrer at 1800 rpm for 30 min. Then, glutaraldehyde (GA) and 1 ml 1N H_2SO_4 was added slowly and

stirred for 5 h. After 5 h hardened microspheres were formed and they were separated by filtration and washed with acetone and distilled water to remove the oil as surfactant. Finally the microspheres were washed with 0.1 M glycine solution to mask the untreated glutaraldehyde and distilled water to remove the unreacted glutaraldehyde[21]. Then the prepared microspheres were dried at 50°C for 24 h. In total, nine formulations were prepared to study the effect of different formulation variables on the characteristics of IPN microspheres.

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 Gg and PVA and also to find the chemical stability of the drug in the microspheres. FTIR spectra of the physical mixture, drug-loaded microspheres, and pure ranitidine HCl 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. The working distance of 26 mm was maintained and acceleration voltage used was 15 kV with the secondary electron image (SEI) as a detector.

Estimation of percentage yield

The percentage yield of the mucoadhesive microspheres was calculated using the formula[22]:

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

Estimation of drug entrapment efficiency

The actual amount of ranitidine HCl present in the different formulations of gum ghatti 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 315 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[23]. These data are presented in Table 2.

% Equilibrium liquid uptake studies

The pH-dependent equilibrium swelling of the drug loaded cross-linked microspheres were studied in pH 1.2 (0.1 N HCl) media. Samples of known weight (10 mg) were exposed to 100 ml of the swelling medium and allowed to swell completely for 24 h to attain equilibrium at 37°C. Adhered liquid droplets on the surface of the particles were removed by blotting with tissue paper and the swollen microspheres were weighed on an electronic balance. The percentage equilibrium water uptake was calculated as[24]:

Swelling ratio = (Final weight-Initial weight) / Initial weight × 100

***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 (100mg) 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 37^{0}C 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 50^{0}C. The weight of microspheres washed out was taken and percentage mucoadhesion was calculated by[25]:

% Mucoadhesion= (Wa-W_1) / Wa × 100

Where, Wa = weight of microspheres applied; W_1 = weight of microspheres leached out

***In-vitro* drug release study**

In-vitro release of ranitidine HCl 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 315 nm.

RESULTS AND DISCUSSION

Fourier transform infrared (FTIR) spectral studies

FTIR was used to confirm the formation of the IPN matrix. Figures 1 and 2 compare the FTIR spectra of Gg, PVA and physical mixture and ranitidine HCl, placebo microsphere, drug loaded microspheres respectively. In the case of Gg, a broad band which appeared at 3446.56 cm^{-1} is attributed to the presence of a hydroxyl group that is hydrogen bonded to various degrees. The appearance of peaks at 1247.86 cm^{-1} in the spectra of Gg indicates the presence of a C-O-C group. The FTIR spectra of PVA showed a broad peak around 3448.49 cm^{-1}, indicating stretching of hydroxyl groups and peaks at 2933.53 cm^{-1} is attributed to the stretching vibration of –CH_2. The band at 1076.21 cm^{-1} indicates the C-O stretching vibration. Ranitidine HCl (Figure 2) showed that the principle IR peaks at 1384.79 cm^{-1} resulted from C-N stretching and the peak at 3352.05 cm^{-1} resulted from N-H stretching and the peak at 1612.38 cm^{-1} resulted from N-H bending. All the principal peaks of ranitidine HCl are present in IPN microparticles, which confirm the stability of ranitidine HCl in IPN microparticles. In the case of placebo microspheres, a broad band with less intensity compared to both Gg 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 1161.07 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 Gg. Thus, FTIR confirms the cross-linking reaction in addition to the formation of an IPN matrix.

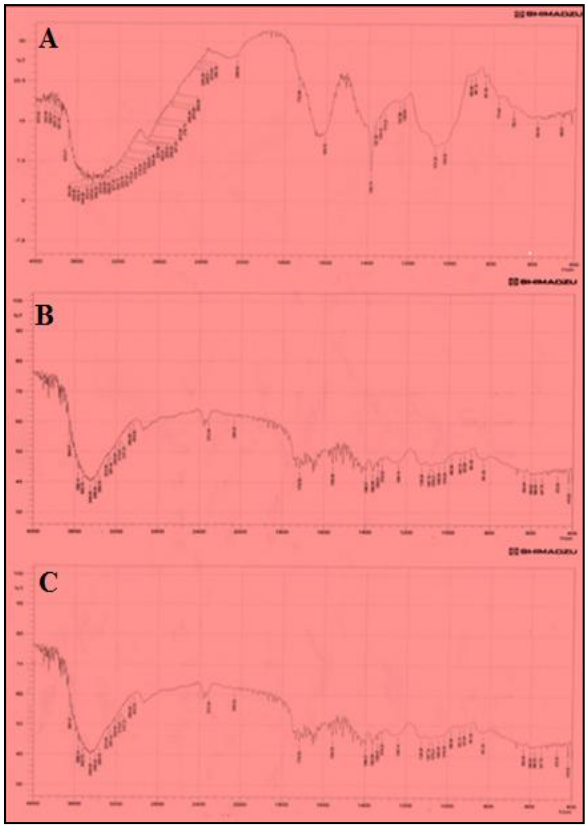

Figure 1: FTIR spectra of (a) gum ghatti (b) PVA (c) physical mixture.

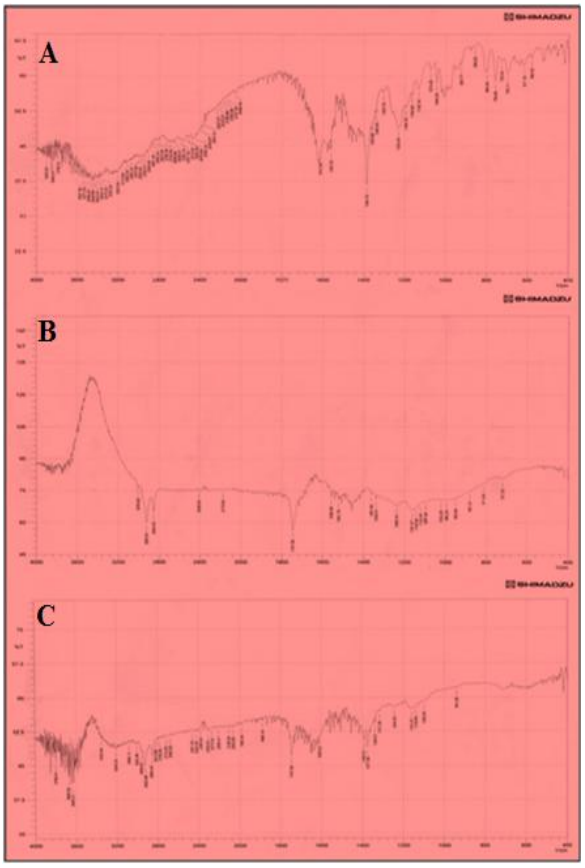

Figure 2: FTIR spectra of (a) ranitidine HCl (b) placebo microsphere (c) drug loaded microsphere.

Formation of mucoadhesive microspheres and drug entrapment efficiency

In the present study, ranitidine HCl loaded IPN mucoadhesive microspheres of Gg and PVA were prepared using glutaraldehyde as a cross-linking agent (Table 1). The microspheres obtained were all spherical in nature with smooth surfaces as demonstrated by SEM images shown in Figure 3 and they fell in the size range of 17.17±1.33 to 35.48±0.65 µm (Table 2). 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. Table 2 shows that % drug entrapment efficiency (% DEE) of the microparticles prepared using different formulation variables was in the range 60.33±0.60 to 87.80±0.19 and it depends on the GA concentration and polymer concentration. 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 is formed which caused retention of more drug particles during microspheres preparation.

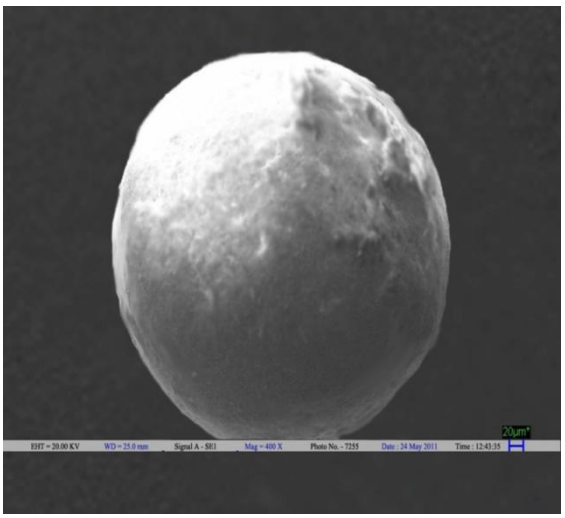

Figure 3: SEM photograph of IPN mucoadhesive microsphere.

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

Formulation code	Gum: polymer ratio	Glutaraldehyde (ml)
F1	1:2	1.5
F2	1:3	1.5
F3	1:4	1.5
F4	1:2	2.5
F5	1:3	2.5
F6	1:4	2.5
F7	1:2	3.5
F8	1:3	3.5
F9	1:4	3.5

***In-vitro* mucoadhesion study**

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 62.66±0.57 to 82.33±0.57 and it also depends on the GA concentration and the ratio of Gg:PVA. It was observed that the formulation F9 showed the highest mucoadhesivity 82.33±0.57% due to the presence of higher proportion of Gg:PVA (1:4) and F1 showed the lowest mucoadhesivity 62.66±0.57 due to lower proportion of Gg:PVA (1:2) therefore, the irregular surface was increased.

Table 2: Effect of crosslinking agent, Gs:PVA ratio on particle size, drug entrapment efficiency (DEE) 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	70.83	60.33±0.60	17.17±1.33	62.66±0.57	210.33
F2	73.33	72.70±0.57	18.52±0.77	67.33±1.52	197.00
F3	80.01	75.26±0.96	20.14±1.16	71.33±0.57	183.66
F4	82.67	75.89±0.26	22.91±1.31	72.66±0.57	176.00
F5	82.78	77.14±0.34	26.82±1.44	73.33±1.52	169.00
F6	83.88	78.84±0.24	30.01±0.80	79.66±1.15	163.33
F7	90.12	80.66±0.57	31.76±0.60	80.33±0.57	152.33
F8	90.67	82.04±0.99	33.10±0.83	81.66±0.57	133.66
F9	91.83	87.80±0.19	35.48±0.65	82.33±0.57	110.00

Equilibrium water uptake studies

Equilibrium water uptake of the cross-linked microspheres exerts an influence on their release rates[26]. 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 (Gg:PVA=1:2) increases from 1.5 ml to 3.5 ml, the equilibrium water uptake in pH 1.2 decreases significantly from 210.66% to 152.33%. 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 (Gg:PVA=1:2) showed higher water uptake capacity than F2 (Gg:PVA=1:3). Similarly, formulation F2 exhibited greater swelling than formulation F3 (Gg:PVA=1:4) due to the hydrophilic nature of Gg, thereby leading to higher water uptake capacity.

***In-vitro* drug release studies**

In-vitro drug release was performed in pH 1.2 and percentage cumulative release vs time data are presented in Figure 4 to investigate the extent of cross-linking density on the *in-vitro* release profiles. 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). 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. The percentage cumulative release vs time for the microspheres prepared with different ratios of Gg:PVA loaded with ranitidine HCl are presented in Figure 5, 6 and 7. 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). This indicates that with increase in the ratio of Gg:PVA, the swelling of the matrix decreases which leads to the slower release of drug from the matrix.

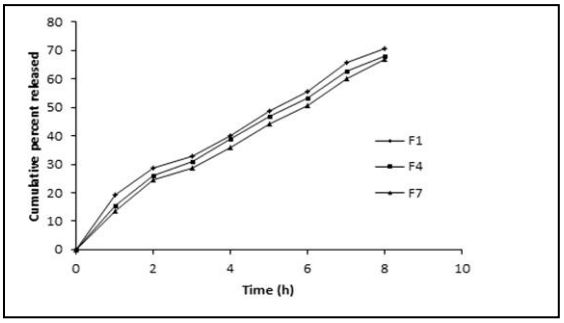

Figure 4: Effect of cross-linking density on *in-vitro* release profiles of formulations F1, F4 and F7 in pH 1.2 media.

CONCLUSION

Gg-PVA 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 ranitidine HCl. Mucoadhesive microspheres with spherical shapes were produced with a narrow size distribution ranging from 17.17±1.33 to 35.48±0.65 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 Gg:PVA influences the drug entrapment efficiency and release of ranitidine HCl 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 Gg:PVA. The release of ranitidine HCl depends on the extent of cross-linking of the matrix as well as the ratio of Gg:PVA present in the matrix.

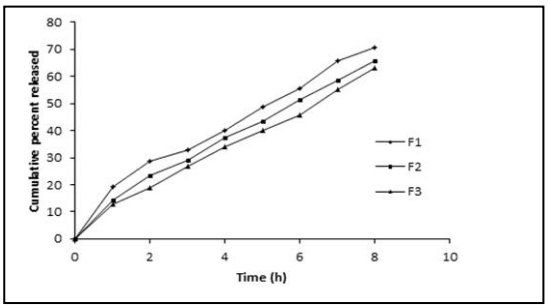

Figure 5: Effect of Gg:PVA ratios on *in-vitro* release profiles of formulation F1, F2 and F3 in pH 1.2 media.

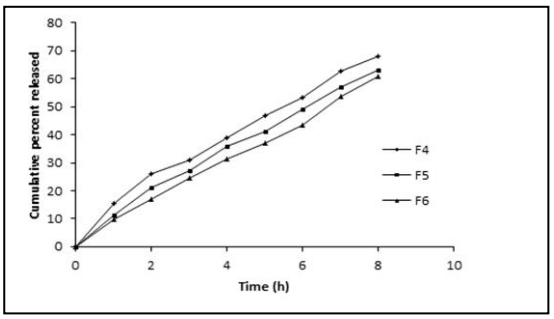

Figure 6: Effect of Gg:PVA ratios on *in-vitro* release profiles of formulation F4, F5 and F6 in pH 1.2 media.

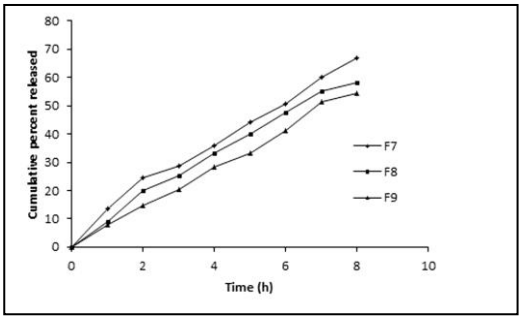

Figure 7: Effect of Gg:PVA ratios on *in-vitro* release profiles of formulation F7, F8 and F9 in pH 1.2 media.

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REFERENCES

1. Ray S, Banerjee S, Maiti S, Laha B, Barik S, Sa B, Bhattacharyya UK. Novel interpenetrating network microspheres of xanthan gum-poly(vinyl alcohol) for the delivery of diclofenac sodium to the intestine-in vitro and in vivo evaluation. Drug Delivery 2010; 17: 508-519.
2. Arya RKK, Singh R, Juyal V. Mucoadhesive microspheres of famotidine: preparation characterization and in vitro evaluation. International Journal of Engineering Science and Technology 2010; 2: 1575-1580.
3. Sanli O, Ay N, Isiklan N. Release characteristics of diclofenac sodium from poly(vinyl alcohol)/sodium alginate and poly(vinyl alcohol)-grafted-poly(acrylamide)/sodium alginate blend beads. Eur J Pharm Biopharm 2007; 65: 204–214.
4. Singh BN, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J Contr Release 2000; 63: 235-259.
5. Yellanki SK, Singh J, Syed JA, Bigala R, Goranti S, Nerella NK. Design and characterization of amoxicillin trihydrate mucoadhesive microspheres for prolonged gastric retention. International Journal of Pharmaceutical Sciences and Drug Research 2010; 2: 112-114.
6. Nasa P, Mahant S, Sharma D. Floating systems: a novel approach towards gastroretentive drug delivery systems. Int J Pharm Pharm Sci 2010; 2: 2-7.
7. Arora S, Ali J, Ahuja A, Khar RK, Baboota S. Floating drug delivery systems: a review. AAPS PharmSciTech 2005; 06: E372-E390.
8. Al-Saidan SM, Krishnaiah YS, Patro SS, Satyanaryana V. In vitro and in vivo evaluation of guar gum matrix tablets for oral controlled release of water-soluble diltiazem hydrochloride. AAPS PharmSciTech 2005; 06: E14-E21.
9. Itokazu, M, Yamemoto K, Yang WY, Aoki T, Kato N, Watanabe K. The sustained release of antibiotics from freeze-dried fibrin-antibiotic compound and efficacies in rat model of osteomyelitis. Infection 1997; 25: 359–363.
10. Kawaguchi H. Functional polymer microspheres. Progress in Polymer Science 2000; 25: 1171–1210.
11. Chandy T, Wilson RF, Rao GH, Das GS. Changes in cisplatin delivery due to surface- coated poly(lactic acid)-poly(epsilon-caprolactone) microspheres. J Biomater Appl 2002; 16: 275–291.
12. Burugapalli K, Bhatia D, Koul V, Choudhary V. Interpenetrating polymer networks based on poly(acrylic acid) and gelatin. I: swelling and thermal behavior. J Appl Polym Sci 2001; 82: 217–227.
13. Rokhade AP, Shelke NB, Patil SA, Aminabhavi TM. Novel interpenetrating polymer network microspheres of chitosan and methylcellulose for controlled release of theophylline. Carbohydr Polymer 2007; 69: 678–687.
14. Banerjee S, Ray S, Maiti S, Sen KK, Bhattacharyya UK, Kaity S, Ghosh A. Interpenetrating polymer network (IPN): a novel biomaterial. International Journal of Applied Pharmaceutics 2010; 2: 28-34.
15. Rokhade AP, Agnihotri SA, Patil SA, Mallikarjuna NN, Kulkarni PV, Aminabhavi TM. Semi-interpenetrating polymer network microspheres of gelatin and sodium carboxymethyl cellulose for controlled release of ketorolac tromethamine. Carbohydr Polymer 2006; 65: 243-252.
16. Kaith BS, Jindal R, Mittal H. Superabsorbent hydrogels from poly(acrylamide-co acrylonitrile) grafted gum ghatti with salt, pH and temperature responsive properties. Der Chemica Sinica 2010; 1: 92-103.
17. Grant SM, Langtry HD, Brogden RN. Ranitidine: an updated review of its pharmacodynamic and pharmacokinetics properties and therapeutic use in peptic ulcer disease and other allied diseases. Drugs 1989; 37: 801–870.
18. Saravanan M, Balaji AB, Kavitha P, Kingsley JD. Controlled delivery of ranitidine in the stomach using magnetic field. West Indian Med J 2009; 58: 87-91.
19. Peppas NA, Wright SL. Drug diffusion and binding in ionizable interpenetrating networks from poly(vinyl alcohol) and poly(acrylic acid). Eur J Pharm Biopharm 1998; 4: 15–29.
20. Kurkuri MD, Aminabhavi TM. Poly(vinyl alcohol) and poly(acrylic acid) sequential interpenetrating network pH sensitive microspheres for the delivery of diclofenac sodium to the intenstine. J Contr Release 2004; 96: 9–20.
21. Hejazi R, Amiji M. Chitosan based gastrointestinal delivery systems. J Contr Release 2003; 89: 151–165.
22. Banerjee S, Chaurasia G, Pal DK, Ghosh AK, Ghosh A, Kaity S. Investigation on crosslinking density for development of novel interpenetrating polymer network (IPN) based formulation. J Sci Ind Res 2010; 69: 777-784.
23. Maiti S, Dey P, Banik A, Sa B, Ray S, Kaity S. Tailoring of locust bean gum and development of hydrogel beads for controlled oral delivery of glipizide. Drug Delivery 2010; 17: 288–300.
24. Roy A, Bajpai J, Bajpai AK. Development of calcium alginate-gelatin based microspheres for controlled release of endosulfan as a model pesticide. Indian J Chem Technol 2009; 16: 388–395.
25. Sambathkumar R, Venkateswaramurthy N, Vijayabaskaran M, Perumal P. Formulation of clarithromycin loaded mucoadhesive microspheres by emulsification internal gelation technique for anti-helicobacter pylori therapy. Int J Pharm Pharm Sci 2011; 3: 173-177.
26. Ritger PL, Peppas NA. A simple equation for description of solute release. II. Fickian and anomalous release from swellable devices. J Contr Release 1987; 5: 37–42.