Carbohydrate Polymers 83 (2011) 1001–1007

Contents lists available at ScienceDirect

Carbohydrate Polymers

journal homepage: www.elsevier.com/locate/carbpol

Interpenetrating polymer network microcapsules of gellan gum and egg albumin entrapped with diltiazem–resin complex for controlled release application

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ARTICLE INFO

Article history:
Received 11 June 2010
Received in revised form 9 September 2010
Accepted 9 September 2010
Available online 17 September 2010

Keywords:
IPN microcapsules
Gellan gum
Egg albumin
Diltiazem HCl
Ion exchange resins
Drug delivery

ABSTRACT

Diltiazem HCl, a water soluble drug was bound to Indion 254®, a cation exchange resin and resulting drug–resin complex was entrapped within interpenetrating polymer network (IPN) microcapsules of gellan gum and egg albumin prepared by ionotropic gelation and covalent crosslinking method. The IPN microcapsules were characterized by SEM, DSC, TGA, XRD and FTIR analyses. The pure drug diltiazem showed rapid and complete dissolution within 60 min, while drug release from drug-resinate was extended for 3 h and that from IPN microcapsules was still slower. The ionically cross-linked microcapsules were capable of releasing drug up to 9 h, and that from dual crosslinked microcapsules was extended up to 15 h. The microcapsules which were prepared with higher concentration of glutaraldehyde released the drug more slowly. The release data were fitted to an empirical equation to determine the transport mechanism.

1. Introduction

The multiple unit controlled drug delivery systems have been found to be superior to single unit systems, as they can be mixed with gastrointestinal (GI) tract fluids and are distributed over a large area (Setty, Sahoo, & Sa, 2005). Recently, the use of natural polymers to prepare multi-unit controlled release dosage forms has been the focus of research (Davis & Huglin, 1990; Desai & Hubbell, 1992; Khare & Peppas, 1993). The natural polymers are preferred because of their non-toxic, low cost, free availability and biodegradability. However, the natural polymers exhibit some limitations, like uncontrolled rate hydration, microbial contamination, and drop in viscosity on storage. These limitations can be reduced following modification by cross-linking, blending, interpenetrating polymer networks (IPN) formation etc. Homopolymers alone cannot meet such divergent demand in terms of both properties and performance. Therefore formation of IPN appears to be a better approach (Lie et al., 2004).

Gellan gum (GG) has been used in ophthalmic drug delivery (Matricardi, Cencetti, Ria, Alhaique, & Coviello, 2009), oral sustained delivery (Agnihotri, Jawalkar, & Aminabhavi, 2006; Kedzierewicz, Lombry, Rios, Hoffman, & Maincentet, 1999; Miyazaki, Aoyama, Kawasaki, Kubo, & Attwoodet, 1999), controlled-release hydrogel with scleroglucan (Coviello, Palleschi, & Grassi, 1998), and floating *in situ* gelling (Rajnikanth, Balasubramaniam, & Mishra, 2007). The egg albumin (ALB) is widely used for various food applications. However, the use of ALB for pharmaceutical applications has received little attention. The ALB, being a protein, contains various functional groups such as $-NH_2$, –COOH, –SH and –OH. Therefore, modifications of these functional groups without altering the structural properties could enable to develop novel hydrogels with improved properties (Rathna, Li, & Gunasekaran, 2004). The IPN beads of ALB with alginate have been reported for controlled release of cefadroxil (Kulkarni, Soppimath, Aminabhavi, & Rudzinski, 2001). However, there is no report on the IPN microcapsules of GG and ALB for controlled drug delivery application. The development of IPN microcapsules of GG and ALB is beneficial because, it contains two cross-linked polymers in a network form to give a three-dimensional network structure, which produces more free volume for the easy entrapment of drugs and improves mechanical strength.

Ion exchange resins are being used as drug carriers for taste masking and controlling release rates (Bhalekar, Avari, & Umalkar, 2007; Sriwongjanya & Bodmeier, 1997; Halder & Sa, 2006a). Drugs can be loaded onto the resins by an exchanging reaction and hence a drug–resin complex (resinate) is formed. Drug is released from the resinates, by exchanging with ions in the GI fluids (Sriwongjanya

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doi:10.1016/j.carbpol.2010.09.017

Table 1
Composition of IPN microcapsules.

Formulation codes	GG (%, w/v)	ALB (%, w/v)	Resinate[a]	Crosslinking agents	
				$CaCl_2$ (%, w/v)	GA[a]
GA1	0.5	1.5	40	5	–
GA2	1.0	1.0	40	5	–
GA3	1.5	0.5	40	5	–
GA4	1.0	1.0	40	10	–
GA5	1.0	1.0	40	15	–
GA6	1.0	1.0	60	15	–
GA7	1.0	1.0	40	5	5
GA8	1.0	1.0	40	5	10
GA9	1.0	1.0	40	5	15

[a] %, w/w of dry polymer.

& Bodmeier, 1998; Gut, Schiek, Haefeli, Walter-Sack, & Burhenne, 2008; Jain, Shah, Rajadhyaksha, Singh, & Amin, 2008).

Diltiazem hydrochloride is widely used in the treatment of angina pectoris and hypertension. It has short half-life (3–4 h) and is administered 3–4 times daily (Shivkumar, Sarsija, & Desai, 2006). The ion-exchange resins can be bound with diltiazem HCl to form reversible complex. The advantages of using diltiazem–resin complex include reducing bitter taste of drug, facilitating development of controlled release dosage form, providing uniform drug absorption, and increasing stability by protecting the drug from hydrolysis. In addition, entrapping the diltiazem–resin complex within IPN matrix can modify the release rate of drug (Junyaprasert & Manwiwattanakul, 2008).

The objective of the present work was therefore to develop and evaluate the IPN microcapsules using GG and ALB by ionotropic gelation and covalent crosslinking method for the controlled release of diltiazem hydrochloride.

2. Experimental

2.1. Materials

Diltiazem hydrochloride and Indion 254® were the generous gift samples from Strides Arco Lab. Ltd. (Bangalore, India) and Ion Exchange India (Pvt.) Ltd. (Mumbai, India). Gellan gum (GG) was purchased from Ozone International, (Mumbai, India). Egg albumin (ALB), glutaraldehyde (GA; 25% (v/v)), calcium chloride, sodium hydroxide, conc. HCl and methanol were purchased from S.D. Fine Chemicals (Mumbai, India). Double distilled water was used throughout the study. All the other chemicals were used without further purification.

2.2. Preparation of diltiazem–resin complex (resinates)

Initially, resins (Indion 254®) were washed with 200 ml of de-ionized water and methanol (2 × 50 ml) to remove impurities. The resins were activated by recycling alternatively thrice with 60 ml of 1 M NaOH and 1 M HCl and washing after each treatment with de-ionized water. The resins in hydrogen/acid form were washed with de-ionized water until the elute was neutral and were then vacuum dried at 50 °C to constant weight. The resinates were prepared by batch process. An accurately weighed amount of diltiazem hydrochloride and resins were taken in 100 ml of distilled water and stirred on a magnetic stirrer until equilibrium was achieved. Time to reach equilibrium was determined by measuring concentration of drug in solution. Resinates obtained were separated by filtration, washed with copious quantity of de-ionized water to remove un-complexed drug. The complexes were dried overnight in a hot air oven at 40 °C and then stored in tightly closed desiccator.

2.3. Preparation of IPN microcapsules

The solution of GG and ALB (total polymer concentration 2% (w/v)) was prepared homogeneously using a magnetic stirrer. An accurately weighed quantity of resinate was added to the above solution and mixed uniformly. Twenty ml of the dispersion was extruded in the form of droplets into aqueous solution of $CaCl_2$ using 25 ml hypodermic syringe through a needle (number 23) under constant stirring. After incubating for additional 15 min in $CaCl_2$ solution, the microcapsules were removed and dried at 40 °C for 10 h.

Further, they were placed in a solution containing different concentrations of glutaraldehyde (GA) and 1N HCl for 30 min at 50 °C. Then the microcapsules were removed and washed with distilled water repeatedly to remove the unreacted GA. The complete removal of the unreacted GA was confirmed by the negative test of the washings with Brady's qualitative reagent (2,4-dinitrophenyl hydrazine). The IPN microcapsules were dried at 40 °C for 10 h and stored in a closed container. The formulation details are given in Table 1.

2.4. Scanning electron microscopic studies (SEM)

The microcapsules were mounted onto stubs using double sided adhesive tape and sputter coated with platinum using a sputter coater (Edward S 150, UK). The coated microcapsules were observed under SEM (JEOL, JSM-6360, Kyoto, Japan) at the required magnification at room temperature. The acceleration voltage used was 10 kV with the secondary electron image as a detector.

2.5. Measurement of microcapsule size

The size of the microcapsules was measured using a digimatic micrometer (MDC-25S Mitutoyo, Tokyo, Japan) having an accuracy of 0.001 mm. The average diameter of the 100 microcapsules per batch was calculated.

2.6. Estimation of drug entrapment efficiency (DEE)

Known amount of microcapsules were incubated in 100 ml USP phosphate buffer of pH 7.4 for complete swelling at 37 °C. Then the microcapsules were crushed in a glass mortar with pestle, the solution was then heated gently for 3 h to extract the drug completely and centrifuged to remove the polymeric debris. The clear supernant solution was analyzed for the drug content using UV–vis spectrophotometer (Model Pharmaspec UV-1700, Shimadzu, Japan) at 236 nm. The drug entrapment efficiency (DEE) was calculated using the following equation:

$$\text{Drug entrapment efficiency} = \frac{\text{experimental drug content}}{\text{theoretical drug content}} \times 100 \quad (1)$$

2.7. Fourier transform infrared spectroscopy (FTIR)

FTIR spectra of the samples were recorded using FTIR spectrophotometer (Nicolet, Model Magna 550, USA). The samples were crushed with potassium bromide to make pellets under hydraulic pressure of 600 kg and scanned between 450 and 4000 cm^{-1}.

2.8. Thermogravimetric analysis (TGA)

TGA was performed on GG, ALB and IPN microcapsules using a microcalorimeter (DuPont-9900, USA) under a dynamic nitrogen atmosphere flowing at a rate of 50 ml/min and at a heating rate of 10 °C/min in the temperature range of 0–600 °C.

2.9. Differential scanning calorimetric analysis (DSC)

The DSC analysis was performed on the diltiazem HCl, drug-free GA6 microcapsules and drug-loaded GA6 microcapsules. The samples were heated from 0 to 300 °C at a heating rate of 10 °C/min under argon atmosphere using a microcalorimeter (DuPont-9900, USA).

2.10. X-ray diffraction studies (XRD)

The XRD study was performed on the diltiazem HCl, drug-free GA6 microcapsules and drug-loaded GA6 microcapsules in order to know the crystallinity of the entrapped drug. The spectra were recorded using a Philips, PW-171, X-ray diffractometer with Cu-NF filtered CuKα radiation. Quartz was used as an internal standard for calibration. The powder X-ray diffractometer was attached to a digital graphical assembly and computer with Cu-NF 25 kV/20 mA tube as a CuKα radiation source in the 2θ range 0–50°.

2.11. Dynamic swelling study

The dynamic swelling behavior of the IPN microcapsules was studied by mass measurement. The microcapsules were incubated with 25 ml phosphate buffer solution pH 7.4 in a Petridish at 37 °C. The microcapsules were taken out at different time intervals using stainless steel grid and blotted carefully without pressing hard to remove the excess surface liquid. The swollen microcapsules were weighed using the electronic microbalance (Model BL-220H, Shimadzu, Japan) having an accuracy of 0.001 mg. The studies were performed in triplicate and average values were taken in data analysis.

2.12. In vitro drug release

In vitro drug release study was carried out in triplicate using a dissolution tester (Electrolab TDT-06P, (USP), Mumbai, India). The dissolution rates were measured at 37.0 ± 0.5 °C and 50 rpm speed. Drug release from the IPN microcapsules was studied in 900 ml acidic medium (pH 1.2) and alkaline medium (pH 7.4 phosphate buffer). At predetermined time intervals, 5 ml aliquots were withdrawn and replaced with the same volume of fresh solution. The samples were passed through a 0.45 μm membrane filter and the amount of drug released was analyzed using UV–vis spectrophotometer at 236 nm following suitable dilutions.

3. Results and discussion

3.1. Preparation of microcapsules

Upon contact with $CaCl_2$, the GG–ALB dispersion forms an ionic cross-linking between two polymer chains of GG and different parts of the same polymer chain entrapping diltiazem:resin complex and un-crosslinked ALB chains. When these ionically cross-linked microcapsules were treated with GA, a bi-functional covalent crosslinking agent, it reacts with both GG and ALB through formation of schiff base (between –CHO groups of GA and $–NH_2$ groups of ALB) and acetal structures (between –CHO groups of GA and –OH groups of GG) to form an IPN matrix (Fig. 1).

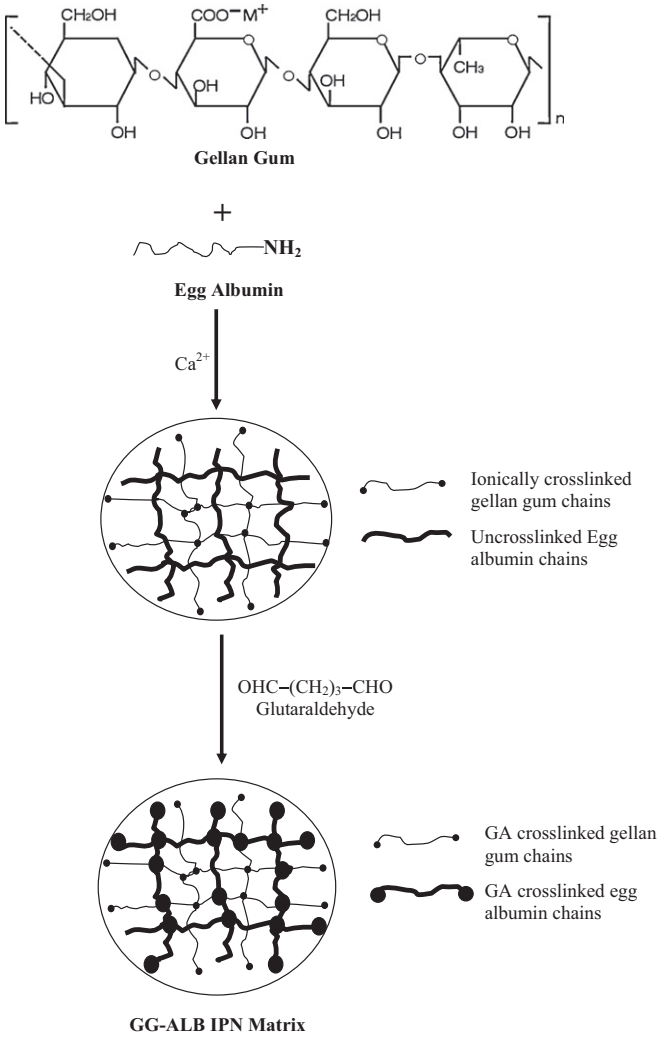

Fig. 1. Schematic representation of GG–ALB IPN matrix.

3.2. Surface morphology and size of the microcapsules

The prepared microcapsules were spherical and surface morphology was found to be rough and dense along with surface foldings as shown in Fig. 2. Size of the microcapsules was in the range of 841–1118 μm (Table 2). It was observed that the size of ionically crosslinked microcapsules (GA2) was decreased after dual crosslinking (GA7), which may be attributed to the rapid shrinking of IPN matrix due to formation of covalent crosslinks between the polymer chains. With an increase in concentration of GA, a decrease in size of the microcapsules was observed. This may be due to the formation of more rigid polymer network at higher crosslink densities. Similar result has been reported earlier at higher crosslink densities (Soppimath, Kulkarni, & Aminabhavi, 2001). Also by increasing the concentration of ALB, an increase in size of the microcapsules was observed, which could be attributed to the formation of bigger droplets due to increase in the viscosity of the solution with increasing concentration of ALB during extruding through a

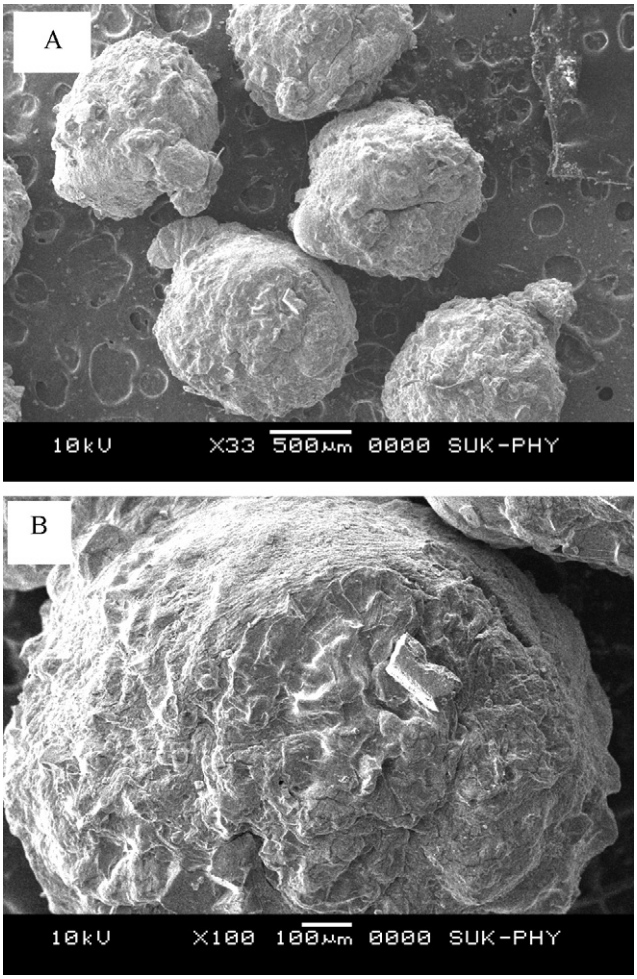

Fig. 2. SEM photographs of group of IPN microcapsules (A) and single microcapsule (B).

needle. On the other hand, as the amount of resinate increases, the size of microcapsules increases because resinate might have occupied the interstitial spaces between polymer segments. This is in agreement with the previously published results (Halder & Sa, 2006b).

3.3. Drug entrapment efficiency

The DEE for the prepared IPN microcapsules was found to be in the range of 68.02–89.06% (Table 2). Keeping all the parameters constant, increase in concentration of $CaCl_2$ decreased the DEE, which may be due to the displacement of bound diltiazem HCl by Ca^{2+} ions, higher the concentration of $CaCl_2$ solution, larger the amount of Ca^{2+} ions diffused inwardly into the resinate loaded microcapsules and consequently the larger the amount of drug displaced from the resinate by Ca^{2+} ions. The free drug diffused out of the microcapsules resulting in decreased DEE. Similar results were observed earlier (Halder, Mukherjee, & Sa, 2005; Halder & Sa, 2005). On the other hand, DEE of the microcapsules prepared by ionic crosslinking was little higher than those prepared by dual crosslinking. In case of dual crosslinked microcapsules, DEE of the microcapsules prepared with lower concentration of GA was lowest as compared to those prepared with higher concentration of GA. At lower concentration of GA, the IPN matrix might be loose and have larger pores due to insufficient crosslinking, which results in higher leakage of drug into crosslinking solution, which may leads to lower DEE. While, at higher concentration of GA, the IPN matrix is stiff and leakage of drug from matrix is low resulting in high DEE. Similar results were also published by other investigators (Rokhade, Shelke, Patil, & Aminabhavi, 2007).

3.4. Fourier transform infrared spectroscopy

The FTIR was used to confirm the crosslinking and IPN structure of matrix. Fig. 3 displays the FTIR spectra of GG (A), ALB (B), placebo IPN microcapsules GA9 (C), diltiazem HCl (D), drug–resin complex (E) and GA6 IPN microcapsules (F). In the case of GG (A), a broad peak at 3425 cm^{-1} is due to the presence of –OH groups glucopyranose ring that are hydrogen bonded. The peaks appearing at 1611 cm^{-1} and 1412 cm^{-1} are due to the presence of carboxylate groups; the peak at 2924 cm^{-1} is attributed to stretching vibrations of $-CH_2$ groups. The peaks appearing at 1157 cm^{-1} and 1030 cm^{-1} are due to ethereal and hydroxylic C–O stretchings. In case of ALB (B), a characteristic peak due to N–H stretching is observed at 3408 cm^{-1}, while N–H bending vibration is indicated by a peak at 1532 cm^{-1}. The aliphatic C–H stretching is observed at 2963 cm^{-1}, while aliphatic C–H bending is observed at 1452 cm^{-1} and 1390 cm^{-1}. The peak appearing at 1648 cm^{-1} indicates amide I band, whereas peaks at 1335 cm^{-1} and 1237 cm^{-1} are due to C–N stretching vibrations. In the case of IPN microcapsules (C), the peaks appeared both in GG and ALB were observed. In addition, a new peak is observed at 1650 cm^{-1} indicating the C=N stretching vibrations of imine groups of Schiff base. This peak is overlapped with that of amide I band of ALB, which is evident from the increased intensity of the peak as compared to ALB spectra. This confirms the crossliking of ALB chains by GA. The peaks appearing at 1163 cm^{-1} and 1044 cm^{-1} are corresponding to acetal groups formed due to the reaction between –OH groups of GG and –CHO groups of GA. During cross-linking, GA reacts with hydroxyl groups of GG and amino groups of ALB in the presence of each other to form interpenetrated network. This confirms the crosslinking and formation of IPN matrix.

The FTIR was also used to know the chemical stability of drug in the IPN matrix. The spectra of diltiazem. HCl (D) showed the characteristic peaks at 3459 cm^1 due to stretching vibration of –NH groups, peak at 2927 cm^{-1} is due to aliphatic –CH stretching vibra-

Table 2
Mean size, DEE, diffusion coefficients (D) and release parameter (n) of IPN microcapsules.

Beads	Mean size (µm) ± S.D.	DEE (%)	D (cm^2/s)	n	r^a
GA1	1118 ± 3.95	68.02 ± 0.052	5.62×10^{-6}	0.45	0.94
GA2	987 ± 3.87	76.12 ± 0.085	5.34×10^{-6}	0.48	0.94
GA3	912 ± 3.69	83.46 ± 0.15	5.07×10^{-6}	0.50	0.95
GA4	883 ± 4.72	86.17 ± 0.45	4.83×10^{-6}	0.51	0.96
GA5	841 ± 4.72	89.06 ± 0.75	4.21×10^{-6}	0.82	0.94
GA6	867 ± 2.15	84.13 ± 0.45	4.33×10^{-6}	0.72	0.94
GA7	962 ± 2.46	82.10 ± 0.08	3.95×10^{-6}	1.01	0.95
GA8	901 ± 1.42	80.87 ± 0.42	3.51×10^{-6}	1.04	0.96
GA9	876 ± 3.89	78.65 ± 0.75	3.13×10^{-6}	0.97	0.98

[a] Correlation coefficient.

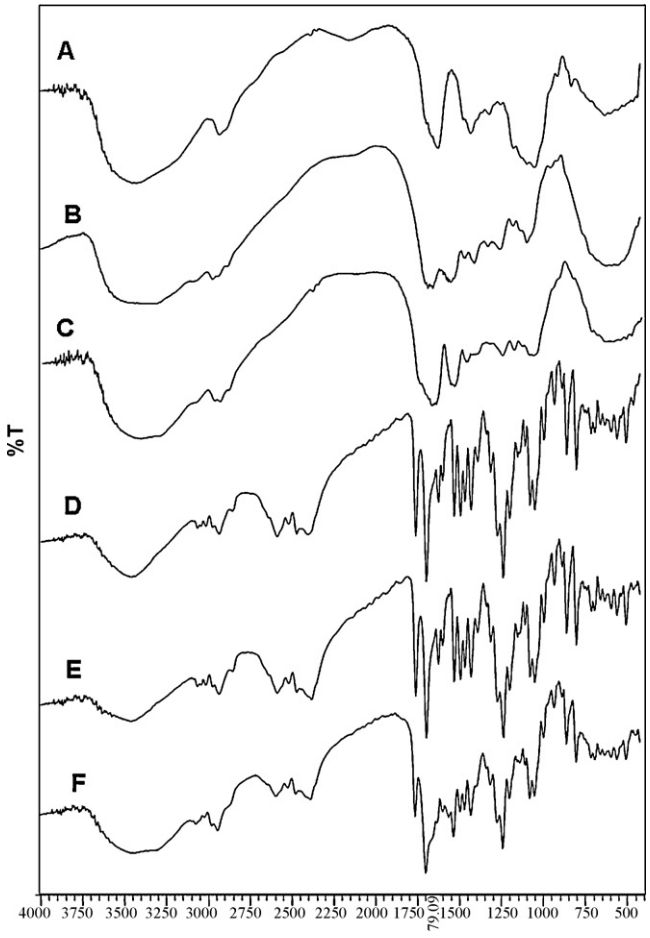

Fig. 3. FTIR spectra of GG (A), ALB (B), GA9 IPN microcapsules (C), diltiazem HCl (D), drug–resin complex (E) and GA6 IPN microcapsules (F).

tions and peaks at 1743 cm^{-1} and 1679 are due to two carbonyl groups present on the diltiazem, the peak at 1217 cm^{-1} is assigned to stretching vibrations of –CN. Whereas in the spectra of resinate (E) and IPN microcapsule GA6 (F), the same characteristics peaks related to diltiazem were noticed with slight variations. This confirms the chemical stability of diltiazem HCl in the IPN matrix.

3.5. Thermogravimetric analysis

Typical thermograms of GG (A), ALB (B) and placebo IPN microcapsules (C) are shown in Fig. 4. The GG starts decomposing after 150 °C and mass loss (12.46%) up to 150 °C may be due to loss of free

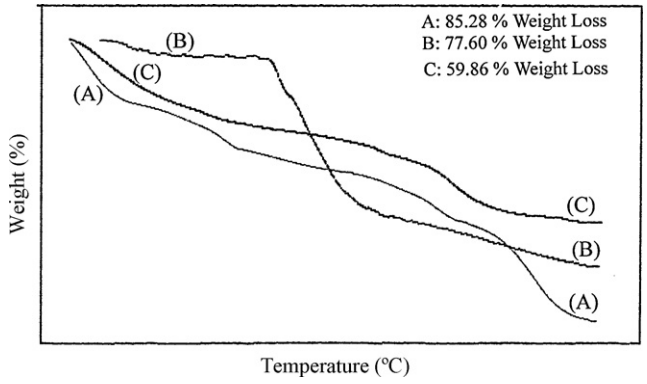

Fig. 4. TGA thermograms of GG (A), ALB (B) and GA9 IPN microcapsules (C).

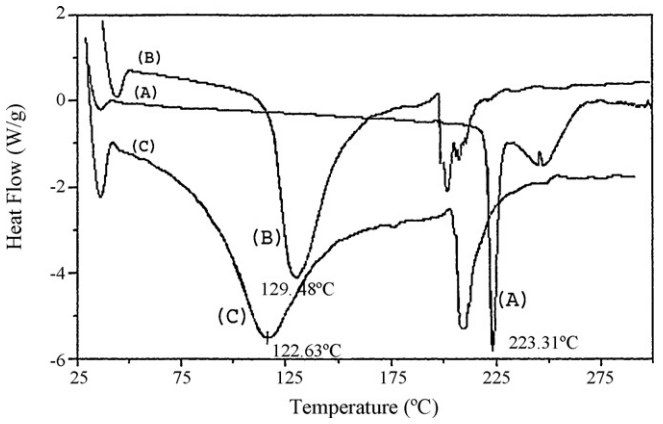

Fig. 5. DSC thermograms of diltiazem HCl (A), drug-free GA6 IPN microcapsules (B) and drug-loaded GA6 IPN microcapsules (C).

and bound water in the polymer. Subsequent mass loss (24.07%) was observed between 150 °C and 260 °C, further a 48.79% of mass loss was observed between 260 °C and 550 °C and reached a value of 85.28% at 600 °C. This may be attributed to the decomposition of polymer. The decomposition of ALB starts after 199 °C and mass loss (6.21%) up to 199 °C is due to the loss of water present in the polymer. A mass loss of 60.14% was observed between 199 °C and 388 °C and reached a value of 77.60% at 600 °C. Whereas, in case of IPN microcapsules, the matrix decomposition started at higher temperature of 255 °C and reached value of 59.86% at 600 °C. The mass loss was found to be constant and percent residual mass of IPN matrix was higher than GG and ALB. Thus, the thermal stability of IPN is greater in comparison with GG and ALB polymers. In case of IPN, since the polymeric chains are more closely tangled together, the thermal stability is higher than those of other polymers. This indicates the formation of IPN including GG and ALB.

3.6. Differential scanning calorimetric analysis

The DSC thermograms for diltiazem HCl (A), drug-free GA6 microcapsules (B) and drug-loaded GA6 microcapsules (C) are presented in Fig. 5. The drug-free IPN microcapsules have shown a sharp endothermic peak at 129 °C, while, drug-loaded IPN microcapsules showed an endothermic peak at 122 °C. This decrease in melting temperature may be due to the formation of loose polymer matrix as a result of creation of extra free space after drug loading. The pure diltiazem HCl has shown a sharp endothermic peak at 223 °C due to melting of the drug, but this peak has not appeared in the drug-loaded microcapsules. This indicates that the drug was uniformly dispersed in an amorphous state in the IPN matrix.

3.7. X-ray diffraction studies

The X-ray diffractograms of diltiazem HCl (A), drug-free GA6 IPN microcapsule (B) and drug loaded GA6 IPN microcapsule (C) are presented in Fig. 6. Diltiazem HCl has shown characteristic intense peaks between the 2θ of 12° and 42° due to its crystalline nature. Whereas in case of both drug-free and drug loaded microcapsules, no intense peaks were observed between the 2θ of 12° and 42°. Also the diffractograms of both drug-free and drug loaded microcapsules are almost identical, indicating the amorphous dispersion of the drug after entrapment into IPN matrix.

3.8. Swelling studies

Fig. 7 depicts the dynamic swelling behavior of IPN microcapsules expressed as w_t/w_0 (where w_0 is the initial weight of the

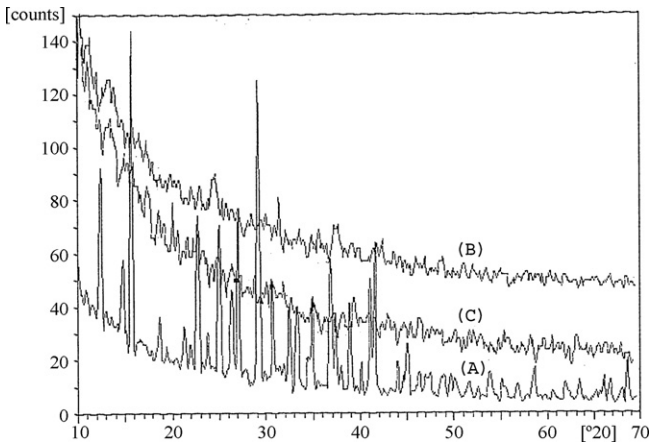

Fig. 6. X-ray diffractograms of diltiazem HCl (A), drug-free GA6 IPN microcapsules (B) and drug-loaded GA6 IPN microcapsules (C).

microcapsules and w_t is the weight of microcapsules at time 't') as a function of time in phosphate buffer pH 7.4. The swelling of microcapsules depends upon the extent of crosslinking. The swelling of IPN microcapsules decreased with an increasing amount of GA which may be due to the formation of stiffer network. At low crosslink density, the polymer network is loose with more hydrodynamic free volume and can absorb more of the solvent resulting in higher swelling. Swelling of the ionically crosslinked beads (GA1–GA6) was greater than the dual crosslinked beads (GA7–GA9).

3.9. In vitro drug release

The drug release was studied in both simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 7.4) and the profiles are depicted in Fig. 8. The results indicate that the pure drug diltiazem HCl showed rapid and complete dissolution within 60 min, whereas drug release from resinate was extended for 3 h and that from IPN microcapsules was still slower. The slow penetration of dissolution fluid into IPN microcapsules together with complex drug release mechanism involving displacement of the drug from the resinate by counter ions present in the dissolution medium and subsequent diffusion of the free drug out of IPN matrix were responsible for extremely slow release of the drug from IPN microcapsules (Halder & Sa, 2005).

The ionically cross-linked microcapsules (GA1–GA6) were capable of releasing drug up to 9 h, while the dual cross-linked microcapsules (GA7–GA9) released the drug up to 15 h depending upon the formulation variables. The ionically crosslinked microcapsules discharged the drug quickly whereas, dual crosslinked microcapsules extended the drug release for longer period. The microcapsules which were prepared with higher concentration of GA released the drug more slowly. This could be due to the fact that at higher crosslinking, free volume of the IPN matrix will decrease, thereby hindering the transport of drug molecules through the matrix. This could also reduce the swelling as well as drug release rate from the matrix. Also increase in initial drug loading increased the drug release (Agnihotri & Aminabhavi, 2005).

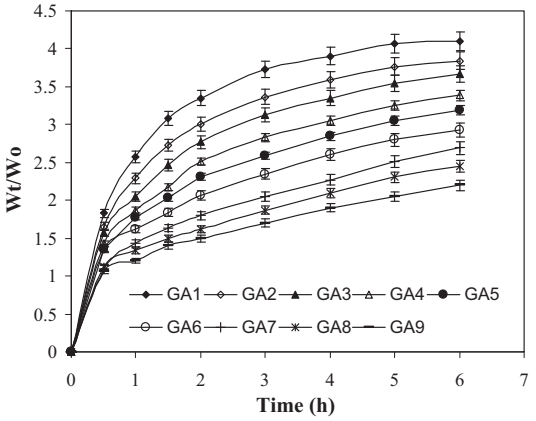

Fig. 7. Swelling behavior of IPN microcapsules.

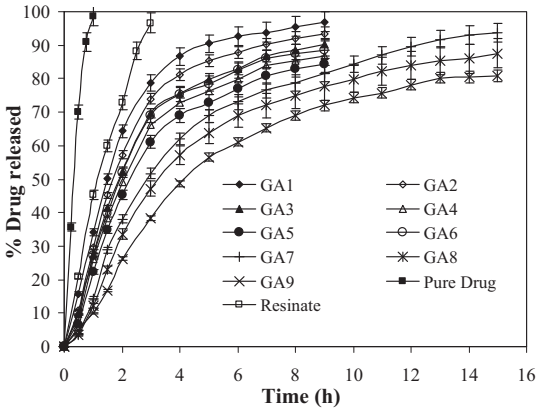

Fig. 8. Diltiazem HCl release profiles through IPN microcapsules.

The diffusion coefficient values, D, for the transport of drug through the IPN microcapsules were calculated using the following relation (Kulkarni, Soppimath, Aminabhavi, Dave, & Mehta, 2000):

$$D = \left(\frac{r\theta}{6M_\infty}\right)^2 \pi \tag{2}$$

where θ is the slope of linear portion of the plot of M_t/M_∞ versus $t^{1/2}$, r is radius of the microcapsules and M_∞ is the total amount of drug loaded. The diffusion coefficients have been estimated based on the Fickian diffusion model and the D values are given in Table 2. These values suggest that the extent of crosslinking showed an effect on the drug release characteristic of IPN microcapsules. The values of D were decreased systematically with increasing amount of crosslinking agent. This may be attributed to the fact that with increasing amount of crosslinking agent, a stiffer IPN matrix is likely to be formed, which would prohibit the transport of drug molecules.

To understand the drug release mechanism in the IPN matrix, release data was fitted to an empirical equation (Ritger & Peppas, 1987):

$$\frac{M_t}{M_\infty} = Kt^n \tag{3}$$

In which M_t is the amount of drug released at time t, and M_∞ is the total amount of drug loaded, n values are the indication of the type of release mechanism. The values of n between 0.45 and 0.85 are an indication of both diffusion controlled and swelling controlled transport mechanism (anomalous/non-Fickian transport); values above 0.85 indicate case II transport (zero order) which relates to polymer relaxation during polymer swelling. The calculated n values along with the correlation coefficients have been shown in Table 2. The values of n depend upon the cross-link density; the n values increase with increase in cross-link density. This may be due to the fact that at higher crosslink density, a stiffer IPN matrix with reduced porosity is likely to be formed, which would restrict the swelling of matrix as well as transport of solutes, as a result the drug release mechanism changes from diffusion controlled release to zero order transport with increased n values (Agnihotri & Aminabhavi, 2005; Toti &

Aminabhavi, 2004; Toti, Soppimath, Mallikarjuna, & Aminabhavi, 2004).

4. Conclusions

IPN microcapsules of GG and ALB were prepared by ionotropic gelation and covalent crosslinking method for the controlled release of diltiazem HCl. The prepared microcapsules were spherical with entrapment efficiency as high as 89% and low burst release rates. The FTIR and TGA analysis confirmed the IPN structure and stability of drug in the IPN matrix. The DSC and XRD studies confirmed the amorphous dispersion of the drug in microcapsules. The swelling of the microcapsules and drug release depends upon the extent of crosslinking. The pure drug diltiazem HCl showed rapid and complete dissolution within 60 min, while drug release from resinate was extended for 3 h and that from IPN microcapsules was still slower. The ionically crosslinked microcapsules discharged the drug quickly whereas, dual crosslinked microcapsules extended the release of drug for longer period. The GG–ALB IPN microcapsules found to be versatile drug carriers as these find wide applications in controlled release of water soluble drugs.

Acknowledgements

Authors are thankful to management of BLDE Association for providing facilities to carryout the research work. We appreciate the help of Mrs. Nutan Agadi of SAIF, Indian Institute of Technology, Mumbai for DSC and TGA analyses.

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