Fibers and Polymers 2011, Vol.12, No.3, 352-358 DOI 10.1007/s12221-011-0352-5

Interpenetrating Polymer Network Matrices of Sodium Alginate and Carrageenan for Controlled Drug Delivery Application

Raghavendra V. Kulkarni*, Vaibhav V. Baraskar, C. Mallikarjun Setty[1], and Biswanath Sa[2]

Department of Pharmaceutics, BLDEA's College of Pharmacy, BLDE University Campus, Bijapur 586 103, Karnataka, India

[1]*Saraswathi College of Pharmaceutical Sciences, Yethbarpally 501504, Moinabad (M), Ranga Reddy (D), India*

[2]*Division of Pharmaceutics, Department of Pharmaceutical Technology, Jadavpur University, Kolkata 700 032, India*

(Received October 8, 2010; Revised December 30, 2010; Accepted January 4, 2011)

Abstract: Interpenetrating polymer network (IPN) matrices of sodium alginate and carrageenan were prepared for controlled release application. The propranolol-resin complex (resinate) loaded matrices were prepared by wet granulation/covalent crosslinking method and subsequently compressed into tablets. The SEM, DSC and XRD studies confirmed the amorphous nature of drug in the IPN matrix and FTIR confirmed the IPN formation and stability of drug within IPN matrix. The pure drug propranolol HCl showed rapid and complete dissolution within 60 min, while drug release from resinate was extended for 2.5 h and that from IPN tablets was still slower and drug release prolonged over 18 h. The crosslinking time of granules affected the release of drug from IPN matrix.

Keywords: IPN matrix, Drug release, Ion exchange resins, Sodium alginate, Carrageenan, Propranolol HCl

Introduction

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 profiles, cost-effectiveness and broad regulatory acceptance [1,2]. Natural polysaccharides are the choice of materials among the hydrophilic polymers used, because they are nontoxic and biodegradable [3]. However, the natural polysaccharides exhibit some limitations, like uncontrolled rate of hydration, microbial contamination and drop in viscosity on storage. These limitations can be reduced following modification by cross-linking, blending etc. Therefore formation of interpenetrating polymer networks (IPN) appears to be a better approach [4].

IPN is a blend of two polymers in a network form, at least one of which is synthesized and/or crosslinked in the immediate presence of the other [5,6]. To date many natural and synthetic polymers have been extensively used for preparing IPNs [7]. Some of the applications of IPNs include artificial implants, dialysis membranes and drug delivery systems [8]. The IPNs used as controlled release systems are capable of delivering drugs at constant rate over an extended period of time. IPN has more complicated network structures and possesses improved mechanical properties; in such systems, the extent of crosslinking can be monitored to control the drug release [9,10].

Sodium alginate (SA) is a natural polysaccharide composed of 1,4-linked-β-D-mannuronic acid and α-L-guluronic acid residues. It is extensively used as a gelling agent in food industry and has a unique property of gel-formation in the presence of multivalent cations in aqueous media. The gelation and crosslinking of alginate is achieved by the exchange of sodium ions with multivalent cations or it can also be crosslinked covalently using glutaraldehyde [9]. Such a crosslinked aginate is useful in controlled release of bioactive molecules [11-13].

Carrageenans (CG) are hydrophilic, high molecular weight [14], anionic linear heteropolysaccharides extracted from marine algae *Rhodophyceae*. These are sulfate esters of galactose and 3,6-anhydrogalactose copolymers, linked by alternating α-1,3 and β-1,4 glycosidic linkages [15]. Carrageenans have been successfully applied to different purposes in controlled release technology [16-18].

Ion exchange resins are being used as drug carriers for taste masking and controlling release rates [19,20]. These resins are cross-linked water-insoluble polymers carrying ionizable functional groups on their structure. Drug is released from the resinates, by exchanging with ions in the stomach fluids and followed by drug diffusion. Mohamadnia *et al.*, have reported the IPN beads of CG and SA for controlled release of betamethasone acetate [21]. Sriwongjanya and Bodmeier have studied the effect of ion exchange resins on propranolol HCl release from hydroxypropylmethylcellulose matrix tablets [22]. However, there are no reports on the controlled release of propranolol HCl through ion exchange resin based compressed IPN matrix tablets of SA and CG.

Hence, objective of the present study was to develop ion exchange resin based compressed IPN matrix tablets of SA and CG for controlled release of a water soluble drug, propranolol HCl. The prepared IPN tablets were characterized by Fourier transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC), X-ray diffraction (X-RD) studies and scanning electron microscopy (SEM).

*Corresponding author: pharma_75raghu@yahoo.com

Experimental

Materials

Propranolol HCl and Indion 254® were the generous gift samples from Cipla Pvt. Ltd. (Mumbai, India) and Ion Exchange India (Pvt) Ltd. (Mumbai, India). Carrageenan (CG) was purchased from Hi-Media laboratories (Mumbai, India). Sodium alginate (SA), glutaraldehyde (GA; 25 % v/v), lactose, magnesium stearate, and starch were purchased from S.D. fine Chemicals (Mumbai, India). Double distilled water was used throughout the study. All other chemicals were used without further purification.

Preparation of Drug-Resin Complex (Resinate)

The resinates were prepared by batch process. Accurately weighed amounts of propranolol HCl and ion-exchange resin (Indion 254®) were taken in 100 m*l* 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 de-ionized water to remove un-complexed drug. The complexes were dried overnight in hot air oven at 40 °C and then stored in tightly closed desiccator [23].

Preparation of IPN Granules and Compression

Different formulations were prepared by wet granulation method. Required quantities of propranolol HCl, resinate, SA and CG were mixed thoroughly and a sufficient volume of granulating agent (starch paste 5 % w/v) was added slowly. After enough cohesiveness was obtained, the mass was sieved through 22/44 mesh. The granules were dried at 40 °C for 12 h and thereafter kept in a desiccator for 12 h at room temperature. Once dry, the granules retained on 44 mesh were mixed with 10 % of fines (granules that passed through 44 mesh). Further, the prepared granules were crosslinked by placing them in a solution containing glutaraldehyde (GA) and 1N HCl for 5, 10, 20, and 30 min at 50 °C. Many studies have been reported in the literature to evaluate the safety of glutaraldehyde and it has been proven that it is non-carcinogenic and safe [24,25]. Then the granules 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 granules were dried at 40 °C for 10 h and compressed into tablets using a rotary tablet compression machine (Karnavati Minipress I, Ahmedabad, India). The total weight of tablets was 500 mg and each tablet contains resinate equivalent to 40 or 60 mg propranolol HCl and other pharmaceutical ingredients as listed in Table 1. Further, prepared tablets were evaluated for weight variation, hardness test and friability test.

Drug Content Uniformity

Ten tablets were randomly selected and incubated in 100 m*l* USP phosphate buffer of pH 7.4 for complete swelling at 37 °C. Then the tablets 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-visible spectrophotometer (Model Pharmaspec UV-1700, Shimadzu, Japan) at 290 nm.

Scanning Electron Microscopic Studies

The samples propranolol HCl, resinate and fractured F1 tablets were mounted onto stubs using double sided adhesive tape and sputter coated with platinum using a sputter coater (Edward S 150, UK). The coated samples 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.

Fourier Transform Infrared Spectroscopy

The samples were crushed with KBr to make pellets under hydraulic pressure of 600 kg, and then the FTIR spectra were recorded between 400 and 4000 cm^{-1}.

Differential Scanning Calorimetric Analysis

The samples propranolol HCl, drug free F5 tablets and drug loaded F5 tablets were heated from 0-300 °C at a

Table 1. Composition of SA-CG IPN matrix tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Propranolol. HCl	40	-	-	-	-	-	-	-	-
Resinate*	-	187	187	187	187	187	187	187	234
Sodium alginate	120	180	160	140	120	120	120	120	120
Carrageenan	120	60	80	100	120	120	120	120	120
Lactose	215	68	68	68	68	68	68	68	21
Talc	3	3	3	3	3	3	3	3	3
Mg. Stearate	2	2	2	2	2	2	2	2	2
Glutaraldehyde**	5	5	5	5	5	10	20	30	30

*Resinate equivalent to 40 mg or 60 mg of Propranolol HCl and **crosslinking time (min).

heating rate of 10 °C/min under argon atmosphere using a microcalorimeter (DuPont-9900, USA) and then thermograms were obtained.

X-Ray Diffraction Studies

The spectra of the samples propranolol HCl, drug free F5 tablets and drug loaded F5 tablets 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 °.

Equilibrium Swelling Study

The equilibrium swelling of the IPN tablets was studied by mass measurement. Accurately weighed tablets were incubated with 100 m*l* phosphate buffer solution pH 7.4 at 37 °C. The tablets were taken out after 12 h and blotted carefully without pressing hard to remove the excess surface liquid. The swollen tablets were weighed using the electronic microbalance. The percent water uptake (Q) after 12 h was calculated using the following equation

$$Q = \frac{W_2 - W_1}{W_1} \times 100 \quad (1)$$

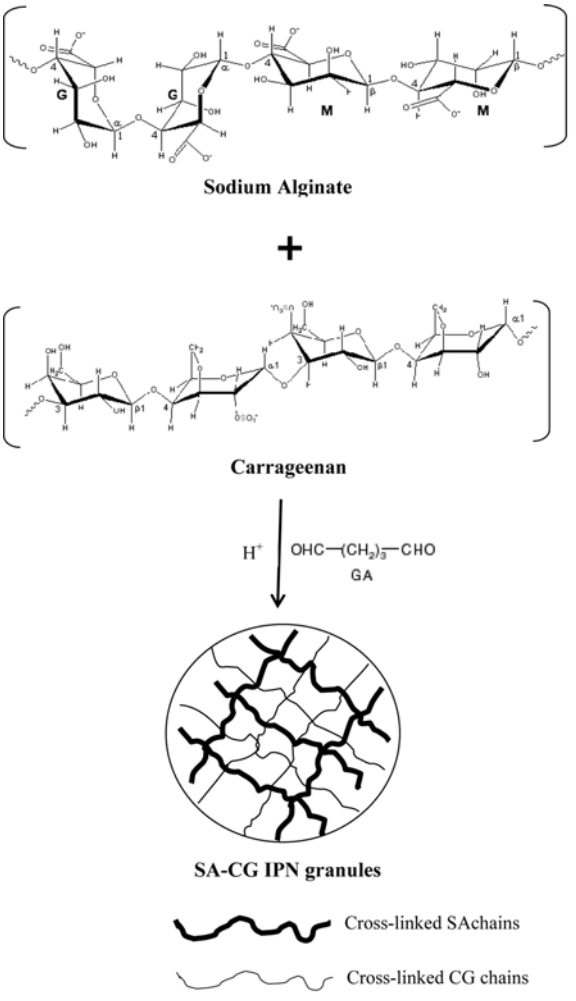
Where W_1 is mass of the dry tablet and W_2 is the mass of swollen tablet.

In Vitro Drug Release Study

In vitro drug release study was carried out using a USP-23 rotating dissolution tester. The dissolution was measured at 37.0±0.5 °C and 50 rpm speed. Drug release from the IPN tablets was studied in 900 m*l* acidic medium (pH 1.2) for 2 h and in alkaline medium (pH 7.4 phosphate buffer) till end of the study. At predetermined time intervals, 5 m*l* aliquots were withdrawn and replaced with the same volume of fresh solution. The amount of drug released was analyzed using UV-visible spectrophotometer at 290 nm.

Results and Discussion

A water soluble antihypertensive drug, Propranolol HCl was bound to Indion 254®, a cation exchange resin and the resulting drug-resin complex (resinate) was loaded within



Scheme 1. Schematic representation of the prepared IPN granules.

Table 2. Data obtained from evaluation of SA-CG IPN matrix tablets

Formulation codes	Weight (mg)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)	Swelling ratio	Release mechanism (n)
F1	510	5.2	0.42	98.2	5.451	0.59
F2	511	5.5	0.24	97.6	4.912	0.68
F3	506	5.6	0.25	99.1	4.763	0.63
F4	503	5.8	0.23	97.4	4.592	0.62
F5	500	5	0.31	98.4	4.300	0.59
F6	498	5.6	0.18	99.5	3.454	0.71
F7	496	5.3	0.14	98.7	2.883	0.74
F8	511	5.5	0.18	98.3	2.231	0.75
F9	495	5.7	0.19	98.56	2.364	0.74

the granules of SA and CG prepared by wet granulation method. Further, on treating the granules with GA, a bi-functional covalent crosslinking agent, an acetal structure has been formed between the -CHO groups of GA and -OH groups of SA and CG strands to form an IPN including SA and CG (Scheme 1). The hardness, friability and drug contents of all the IPN tablets were found to be uniform and results are given in Table 2.

Scanning Electronic Microscopy

The surface characteristics of propranolol HCl (A), resinate (B) and fractured F5 tablets (C) were studied by SEM analysis (Figure 1). The propranolol HCl shows drug crystals, while resinate shows smaller crystals as compared to propranolol HCl, indicating the reduced crystallinity of drug after complexation with resin. Whereas fractured surface of tablets shows no crystals, indicating the amorphization of drug after entrapping into granules and subsequent compression to tablet.

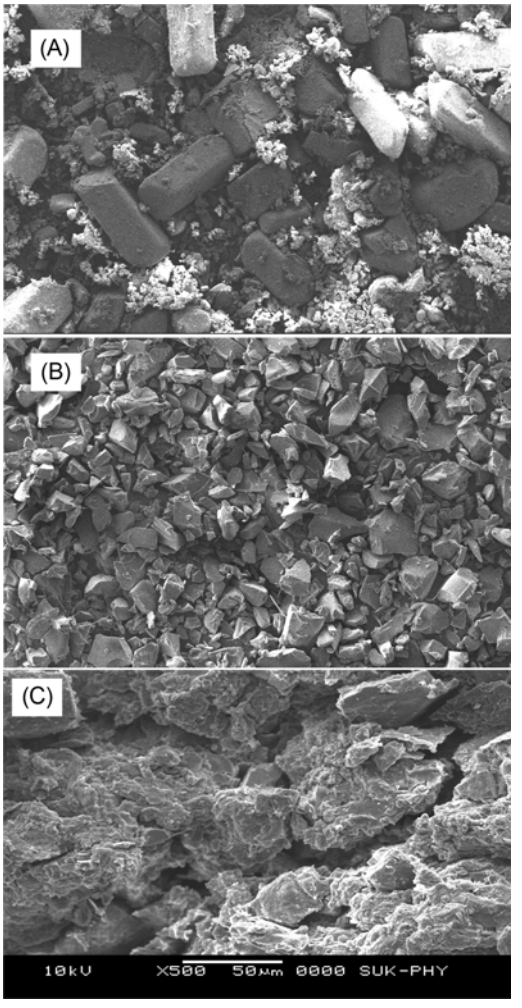


Figure 1. SEM photographs of propranolol HCl (A), resinate (B) and fractured surface of F5 tablets (C).

FTIR Analysis

The FTIR was used to confirm the crosslinking and IPN structure of the matrix. Figure 2 displays the FTIR spectra of SA (A), CG (B), and placebo IPN tablets F8 (C). In case of SA, the broad peak appearing at 3477 cm^{-1} corresponds to the associated -OH groups stretching vibrations of hydroxyl groups; the peak appearing at 1610 cm^{-1} corresponds to the deformation of carbonyl group of SA; the peak appearing at 2927 cm^{-1} is due to the C-H stretching of cyclic aldehyde and the peaks appeared at 1030 and 1096 cm^{-1} are due to the C-O stretching of alcoholic groups. In case of CG, the peak observed at 3400 cm^{-1} is due to stretching of -OH groups; peak at 2933 cm^{-1} corresponds to C-H stretching. The peaks at 851, 945, 1066, 1239, and 1646 cm^{-1} are due to *d*-galactose-4-sulfate, 3,6-anhydro-*d*-galactose, glycosidic linkage, ester sulfate stretchings and carbonyl functional groups respectively. While in the spectra of IPN matrix, the peak at 3400 cm^{-1} is due to the -OH group stretching vibrations of -OH groups of the polysaccharides; a sharp peak appearing at 1655 cm^{-1} corresponds to the carbonyl functional groups of polysaccharides. The peak at 1458 cm^{-1} is due to symmetric stretching of the carboxylate groups, whereas the peak appearing at 1022 cm^{-1} represents the C-O-C stretching vibrations. The peak appearing at 1285 cm^{-1} is corresponding to the formation of acetal structures due to the reaction between OH groups of SA-CG and -CHO groups of GA. During cross-linking, GA reacts with the -OH groups of SA and CG in the presence of each other to form interpenetrated network through the formation of acetal structures. This could be further supported by the presence of sharp high intensity peak at 2925 cm^{-1} due to $-CH_2$ groups of the alkyl chain formed by cross-linking [26]. This confirms the crosslinking and formation of IPN matrix.

FTIR was also used to determine the stability of drug within the IPN matrices (Figure 3). It was observed that the

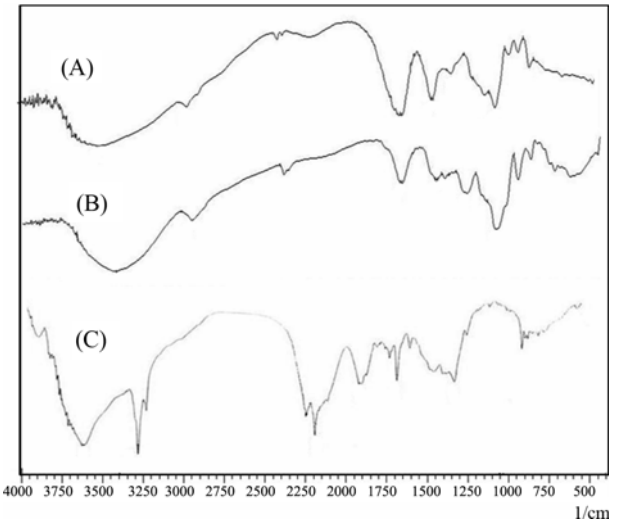


Figure 2. FTIR spectra of sodium alginate (A), carrageenan (B) and IPN tablet F8 (C).

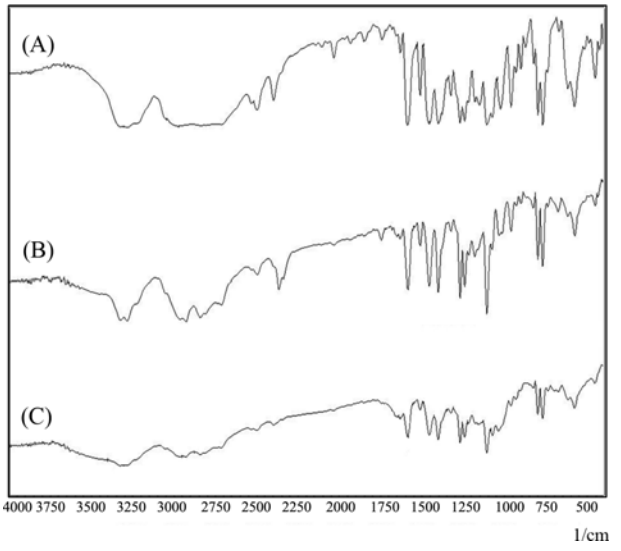


Figure 3. FTIR spectra of propranolol HCl (A), resinate (B) and drug loaded F5 tablet (C).

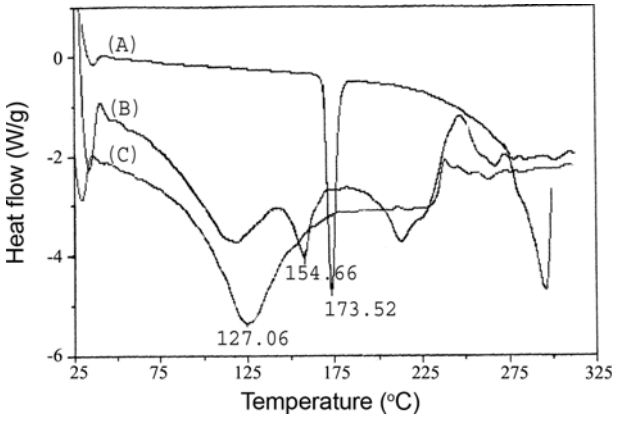


Figure 4. DSC thermograms of propranolol HCl (A), drug free F5 tablets (B) and drug loaded F5 tablets (C).

propranolol HCl shown characteristic peaks at 3282 cm^{-1} due to -NH stretching, 2974 cm^{-1} due to aliphatic -CH stretching, 1587 cm^{-1} due to ketone, 1242 and 1268 cm^{-1} due to amine functional groups, 1107 cm^{-1} due to -OH groups, 770 and 791 cm^{-1} are due to aromatic functional groups. The similar peaks were also observed in the spectra of resinate and IPN tablets with slight modifications. Hence, it shows that the drug is stable in the IPN matrix.

DSC Analysis

The DSC analysis of plain propranolol HCl (A), drug-free F5 tablets (B) and drug-loaded F5 tablets (C) was carried out and the results are shown in Figure 4. The drug-free tablet has shown an endothermic peak at 154 °C indicating the melting temperature of polymer; the peak at about 115 °C may be due to associated bound and unbound water in the matrix and the remaining peaks at about 215 & 240 °C can be assigned for the thermal decomposition of the matrices. While drug-loaded tablets showed an endothermic peak at 127 °C. The plain propranolol HCl has shown a sharp endothermic peak at 173 °C due to melting of the drug, but this peak is not seen in the drug-loaded tablets. This indicates that the drug was uniformly dispersed in an amorphous state in the IPN matrix.

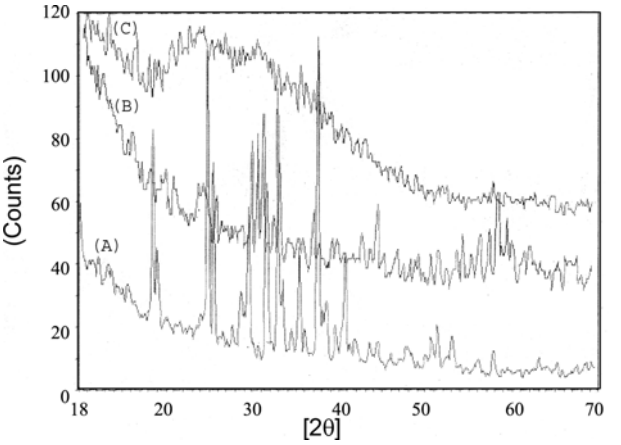


Figure 5. X-ray diffractograms of propranolol HCl (A), drug free F5 tablets (B) and drug loaded F5 tablets (C).

X-ray Diffraction Studies

The X-ray diffractograms of propranolol HCl (A), drug free F5 tablets (B) and drug-loaded F5 tablets (C) are presented in Figure 5. Propranolol HCl has shown characteristic intense peaks between the 2θ of 18 ° and 42 ° due to its crystalline nature. Whereas, in case of drug free and drug loaded tablets, no intense peaks related to drug were noticed between the 2θ of 18 ° and 42 °. This indicates the amorphous dispersion of the drug after entrapment into IPN tablets.

Equilibrium Swelling

The release of entrapped drug from IPN matrix depends on the swelling behavior, as the polymer matrix swells, pores of network open and release of the entrapped solute occurs [27]. Therefore the equilibrium swelling study of the prepared IPN tablets was carried out in phosphate buffer pH 7.4 and the results are shown in Table 2. The swelling of IPN tablets depends upon the extent of crosslinking. The swelling decreased with increasing crosslinking density which may be due to the formation of stiffer IPN matrix. At low crosslinking density, the network is loose with a greater hydrodynamic free volume and can absorb more of the solvent resulting in higher swelling, while at higher crosslinking; the network is rigid with least hydrodynamic free volume leading to decreased swelling. Similar results were reported earlier [28].

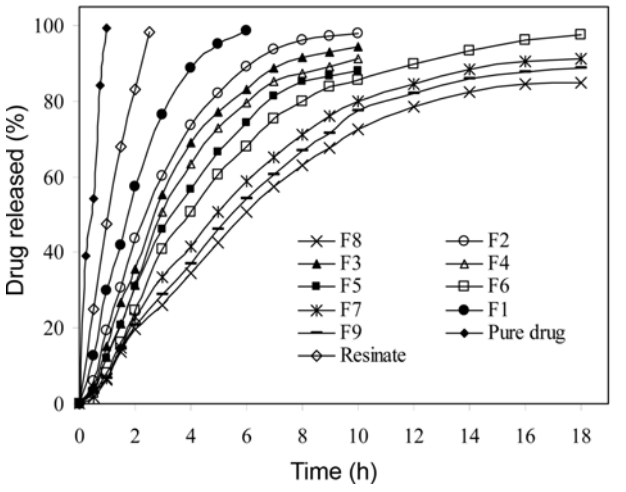


Figure 6. Drug release profiles of SA-CG IPN matrix tablets.

In Vitro Drug Release

The drug release profiles as shown in Figure 6 indicate that the pure drug propranolol HCl showed rapid and complete dissolution within 60 min, whereas resinate extended the drug release for 2.5 h. and that from IPN tablets was still slower. The slow penetration of dissolution fluid into IPN matrix together with complex drug release mechanism involving displacement of the drug from the resinate by the counter ions present in the dissolution medium and subsequent diffusion of the free drug out of IPN matrix were responsible for the slow release of the drug from IPN tablets [29]. The F1 tablets containing pure propranolol HCl have shown drug release for 6 h, while the resinate loaded tablets (F2 to F9) were capable of releasing drug up to 18 h depending upon the formulation variables. The time of exposure of granules to GA solution affected the release rate of drug. The formulations which were exposed to GA solution for 30 min released the drug more slowly than those exposed 5 min. This could be due to the fact that more exposure of formulations to GA solution increases the crosslinking density and at higher crosslinking, the free volume of the polymer matrix decreases, thereby hindering the transport of drug molecules through the matrix. This could also reduce the swelling as well as drug release from the matrix. On the other hand, an increase in initial drug loading increased the release rate of drug from IPN matrix. Similar results were also reported earlier [30].

To understand the drug release mechanism in the IPN matrix, release data was fitted to an empirical equation [31]:

$$\frac{M_t}{M_\infty} = Kt^n \quad (2)$$

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 calculated n values have been shown in Table 2. The values of n depend upon the crosslinking time; the n values increase with increase in crosslinking time and calculated n values suggested that the mechanism of drug release followed non-Fickian transport.

Conclusion

Propranolol HCl, a water soluble drug was bound to Indion 254®, a cation exchange resin and the resulting drug-resin complex was successfully loaded within novel IPN granules of SA and CG prepared by wet granulation method, further they were compressed into matrix tablets. The SEM, DSC and XRD studies confirmed the amorphous nature of the drug in the IPN matrix. The FTIR confirmed the IPN formation and stability of drug within IPN matrix. The pure drug propranolol HCl showed rapid and complete dissolution within 60 min, while drug release from resinate was extended for 2.5 h and that from IPN tablets was still slower. The F1 tablets loaded with pure propranolol HCl have shown drug release for 6 h, while the resinate loaded tablets were capable of releasing drug up to 18 h depending upon the formulation variables. This study demonstrated that the drug release rate could be controlled by ion exchange resins and extent of crosslinking, which is important for application of the prepared IPN matrices for controlled drug delivery 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 analysis.

References

1. L. Maggi, R. Bruni, and U. Conte, *Int. J. Pharm.,* **195**, 229 (2000).
2. U. Conte and L. Maggi, *Biomaterials*, **17**, 889 (1996).
3. M. C. Bonferoni, S. Rossi, M. Tamayo, J. L. Pedraz, G. A. Dominguez, and C. Caramella, *J. Control. Release*, **26**, 119 (1993).
4. M. Changez, K. Burugapalli, V. Koul, and V. Chowdary, *Biomaterials,* **24**, 527 (2003).
5. T. T. Hsieh, K. H. Hsieh, G. P. Simon, and C. Tiu, *Polymer*, **40**, 3153 (1999).
6. J. D. Kosmala, D. B. Henthorn, and L. B. Peppas, *Biomaterials,* **21**, 2019 (2000).
7. R.V. Kulkarni and B. Sa, *Drug Dev. Ind. Pharm.,* **34**, 1406 (2008).
8. R.V. Kulkarni and B. Sa, *Cur. Drug Del.,* **5**, 256 (2008).
9. A. R. Kulkarni, K. S. Soppimath, T. M. Aminabhavi, and W. E. Rudzinski, *Eur. J. Pharm. Biopharm*., **51**, 127 (2001).

10. A. P. Rokhade, S. A. Agnihotri, S. A. Patil, N. N. Mallikarjun, P. V. Kulkarni, and T. M. Aminabhavi, *Carbohydrate Polym*., **65**, 243 (2006).
11. A. Blandino, M. Macias, and D. Cantero, *Enz. Microb. Techn.,* **27**, 319 (2000).
12. C. Bregni, J. Degrossi, R. Garcia, M. C. Lamas, R. Firenstein, and D. D'Aquino, *Ars Pharmaceutica*, **41**, 245 (2000).
13. N. Isiklan, *J. Appl. Polym. Sci.,* **99**, 1310 (2006).
14. M. Mitsuiki, Y. Yamamoto, A. Mizuno, and M. Motoki, *J. Agric. Food Chem.,* **46**, 3528 (1998).
15. S. Naim, B. Samuel, B. Chauhan, and A. Paradkar, *AAPS Pharm. Sci. Tech*., **5**, 25 (2004).
16. M. Hariharan, T. A. Wheatley, and J. C. Price, *Pharm. Dev. Technol.,* **2**, 383 (1997).
17. O. Sipahigil and B. Dortune, *Int. J. Pharm.,* **228**, 119 (2001).
18. V. K. Gupta, M. Hariharan, T. A. Wheately, and J. C. Price, *Eur. J. Pharm. Biopharm.,* **51**, 241 (2001).
19. S. Borodkin and D. P. Sundberg, *J. Pharm. Sci*., **60**, 1523 (1971).
20. M. Sriwongjanya and R. Bodmeier, *Int. J. Pharm.,* **158**, 29 (1997).
21. Z. Mohamadnia, M. J. Zohuriaan-Mehr, K. Kabiri, A. Jamshidi, and H. Mobedi, *J. Bioact. Compat. Polym.,* **22**, 342 (2007).
22. M. Sriwongjanya and R. Bodmeier, *Eur. J. Pharm. Biopharm.,* **46**, 321 (1998).
23. A. Halder and B. Sa, *J. Microencapsu.,* **23**, 899 (2006).
24. NTP, *Natl. Toxicol. Program Tech. Rep. Ser.,* **490**, 1 (1999).
25. J. Garcia-Sellers, A. Pascual, E. Funes, J. A. Pagan, J. D. Lopex, J. M. Negra, and J. Hernandez, *Allergol. Immunopathol.*, **31**, 63 (2003).
26. K. S. Soppimath, A. R. Kulkarni, and T. M. Aminabhavi, *J. Biomater. Sci. Polym. Ed*., **11**, 27 (2000).
27. S. M. More, R. V. Kulkarni, B. Sa, and N. V. Kalyane, *J. Appl. Polym. Sci.,* **116**, 1732 (2010).
28. K. S. Soppimath, A. R. Kulkarni, and T. M. Aminabhavi, *J. Control. Rel.,* **75**, 331 (2001).
29. A. Halder and B. Sa, *Int. J. Pharm.,* **290**, 45 (2005).
30. S. A. Agnihotri and T. M. Aminabhavi, *Drug Dev. Ind. Pharm*., **31**, 491 (2005).
31. P. L. Ritger and N. A. Peppas, *J. Control. Release.,* **5**, 37 (1987).