Polym. Bull. (2012) 68:1905–1919
DOI 10.1007/s00289-011-0675-9

ORIGINAL PAPER

Preparation and characterization of pH sensitive poly(vinyl alcohol)/sodium carboxymethyl cellulose IPN microspheres for in vitro release studies of an anti-cancer drug

K. Madhusudana Rao · B. Mallikarjuna · K. S. V. Krishna Rao · M. N. Prabhakar · K. Chowdoji Rao · M. C. S. Subha

Received: 18 July 2011 / Revised: 21 September 2011 / Accepted: 27 November 2011 /
Published online: 6 December 2011

Abstract Interpenetrating polymeric network microspheres (IPNMs) consisting of poly(vinyl alcohol) and sodium carboxymethylcellulose were prepared by water-in-oil emulsion method and were cross-linked with glutaraldehyde. 5-Fluorouracil (5-FU), an anti-cancer drug, was loaded into IPNMs via in situ method. These IPNMs have been characterized by Fourier transform infrared spectroscopy, which confirms the cross-linking of IPNMs through glutaraldehyde. Differential scanning calorimetry and X-ray diffraction analysis of the drug-loaded IPNMs have confirmed uniform molecular dispersion of 5-FU in the IPNMs. Particle size measured using optical microscopy gave an average size of 80–250 μm. Scanning electron microscopy also confirmed the formation of microspheres with smooth surface and spherical shape. Encapsulation efficiency of 5-FU in these IPNMs was achieved up to 62%. Drug release profiles of the IPNMs at different pH conditions (pH 1.2 and 7.4) confirmed that microspheres formed are pH sensitive, resulting controlled release of drug during in vitro dissolution experiments. It has been analyzed with an empirical equation to understand the diffusion nature of drug through the IPNMs. Both encapsulation efficiency and release patterns are found to depend on the nature of the cross-linking agent as well as amount of drug loading. In vitro release studies indicated the release of 5-FU for more than 10 h.

Keywords Sodium carboxymethylcellulose (NaCMC) · Poly(vinyl alcohol) (PVA) · Microspheres · pH sensitive · Drug delivery

K. Madhusudana Rao · B. Mallikarjuna · M. C. S. Subha (✉)
Department of Chemistry, Sri Krishnadevaraya University, Anantapur, India
e-mail: mcssubha3@gmail.com

K. S. V. Krishna Rao
Department of Chemistry, Yogi Vemana University, Kadapa, India

M. N. Prabhakar · K. Chowdoji Rao
Department of Polymer Science and Technology, Sri Krishnadevaraya University, Anantapur, India

Introduction

Interpenetrating polymeric networks (IPNs) have potential applications in the drug delivery and biomedical field. IPN has lead to the development of bioengineering tissues, such as bone substitutes, tissue, and cartilage scaffolds [1, 2]. Autologous tissue engineering provides an alternative for allogenic tissue transplantation. The study of IPN for drug delivery systems and tissue engineering may lead to a better understanding of critical diseases. The concepts of high swelling capacity, specificity, and sensitivity play a crucial role in targeting delivery of drugs. By understanding the nature of drug delivery systems and their durability in the body, which can interact with the systems, can be identified. IPN has various advantages as a biomaterial and is widely used as carrier systems for delivery of the short biological half-life drugs. There has been a spiky growth in the speed of discovery and development of IPN over the past few years. Current research supports the theory that IPN can provide the resources to deliver drugs at a prolonged controlled release to specific targets. Once optimized, these targeted systems will provide the better treatment options. So, it can be inferred that IPN-based biomaterials for tissue engineering and drug delivery system are expected to become a useful matrix substance for various therapeutic applications in the future. The chemical and physical combination methods and properties of multipolymers have been of great practical and academic interest for controlled release of drugs because they provide a convenient route for the modification of properties to meet specific needs. Among these methods, considerable interest has been given to the development of IPN's based on drug delivery systems [3–5]. IPNs have been recognized as popular responsive polymers having enhanced physical properties, easy fabrication of devices, manipulation of device properties, etc., as compared with conventional blends of their components. This would open up avenues to use IPN's in designing the novel controlled release systems. A combination of judicially selected natural and synthetic polymers based IPN's has been found to be useful in enhancing the release of short half-lived drugs under physiological conditions. In order to achieve this, the properties of natural and synthetic polymers have been modified by grafting, blending and other means [6]. Blending of synthetic polymers into cellulose and modified celluloses are widely accepted [7, 8].

It is well known that sodium carboxymethyl cellulose (NaCMC) is carboxymethyl ether of cellulose; non-toxic, biocompatible, biodegradable, and abundant [9–12]. Poly(vinyl alcohol) (PVA) has been used in a wide variety of fields since its discovery in 1924 [13] because of its desirable properties such as non-toxicity and non-carcinogenicity. It finds extensive applications as biomaterials [14, 15] such as contact lenses, artificial blood vessels, artificial intestines [13], and artificial kidneys [15]. Studies have been carried out for the drug release with PVA hydrogels, which are biocompatible, chemically stable, and desirable for both bioseparations and cell encapsulations [14–17]. However, PVA is a highly hydrophilic polymer and has poor stability in water; thus, its solubility must be prevented for use in aqueous systems. To overcome this problem, PVA should be insolubilized by blending [18], copolymerization [19], grafting [20, 21], and cross-linking [22, 23]. Recently our laboratory developed modified IPN-based carbohydrate polymers for CR systems of

various types of drugs [24–26]. Aminabhavi and coworkers [27] have developed semi Interpenetrating network microspheres (IPNMs) of gelatin and NaCMC for controlled release studies of ketorolac tromethamine. Sequential IPNMs of PVA and poly acrylic acid were prepared for controlled release studies of diclofenac sodium [28]. A microspherical formulation of PVA and guar gum hydrogel microspheres for the controlled delivery of nifedine by emulsion cross-linking method was developed for treatment in severe hypertension [29]. IPN-based microspherical formulation was also used for the prolong delivery of anti-cancer drug such as capecitabine by formation of chitosan-poly(ethylene oxide-*g*-acrylamide) inter molecular rigid network [30] and 5-fluorouracil (5-FU) hydrogel microspheres of chitosan and pluronic F-127 for controlled release of drugs [31]. Novel pH sensitive microgels based on chitosan, acrylamide-grafted PVA, and hydrolyzed acrylamide-grafted-PVA used in the controlled release of an antibiotic drug cefadroxil [8].

All compositions of blends of NaCMC and PVA are miscible [32]. NaCMC is an ionic polyelectrolyte that contains carboxyl groups and is pH sensitive. From the literature [33, 34], it is understood that the swelling property of physically cross-linked PVA gels is very poor when compared to the dry state and does not respond to the environmental changes. Responsive microspheres can be prepared by mixing with functional components like carboxy methyl cellulose. As the CMC contains many carboxylate groups that exhibit pH sensitivity can be mixed with PVA and used for drug release studies. PVA is virtually a linear polymer with small hydrate groups. So we introduced NaCMC to PVA cross-linked with GA to get both physical and chemical cross-linking. This is advantage for controlled release applications to increase the bioavailability of short half-lived drugs compared to other reported papers [29–31]. Hence, in the present work the authors have developed PVA/NaCMC blend microspheres for controlled drug release application by water-in-oil (W/O) emulsion method and loaded with 5-FU as a model drug. Controlled release capability and reducing toxicity of polymeric carriers are important for drug delivery applications. 5-FU is an antimetabolic drug, used extensively in cancer chemotherapy [35–40] and is an antimetabolite, which is used to prevent the subsequent scarring following trabeculectomy and to improve the prognosis for long-term retinal reattachment. 5-FU is an acidic, water soluble [41], hydrophilic drug, and is an antineoplastic agent of extensive use in clinical chemotherapy for the treatment of solid tumors. It has been widely used in drug administration due to its large number of secondary effects that accompany its conventional administration. So, we introduced 5-FU into PVA–NaCMC IPNMs. The resulting microspheres are capable of being pH responsive character.

Experimental

Materials

PVA having mol wt 125,000, NaCMC with high viscosity grade (500–800 cPs), analytical reagent grade of glutaraldehyde solution 25% (v/v), *n*-hexane, and light liquid paraffin were all purchased from S.D. fine chemicals, Mumbai, India.

Span-80 was purchased from Loba Chemicals, Mumbai, India. Petroleum ether, b.p. 60–80 °C, was received from Ranbaxy Fine Chemicals Ltd., New Delhi, India. 5-FU was purchased from Himedia chemicals, India. All chemicals were used without further purification.

Preparation of IPNMs

IPNMs of PVA and NaCMC were prepared by emulsion cross-linking method [42]. In brief, PVA was dissolved in distilled water by continuously stirring at 80 °C until a homogeneous solution was obtained. After cooling to ambient temperature, NaCMC was added in the above PVA solution and stirred overnight to obtain a clear solution. Then, drug was dissolved in the above polymer solution. This solution was added slowly to a mixture of petroleum ether and light liquid paraffin (40:60, w/w) containing 1% (w/w) Span-80 under constant stirring at 300 rpm speed for 10 min. To this emulsion, 1 mL of 0.1 M hydrochloric acid and GA was added slowly and further stirred for 30 min. The hardened microspheres were separated by filtration, washed with *n*-hexane and water to remove the oil and excess amount of unreacted GA. Microspheres thus formed dried under vacuum at 40° for 24 h and stored in desiccator for further analysis and characterization. Totally, eight formulations were prepared by varying the drug concentration, cross-linker (GA) and % of NaCMC. The representation of IPN is as shown in Scheme 1.

Estimation of drug loading and encapsulation efficiency

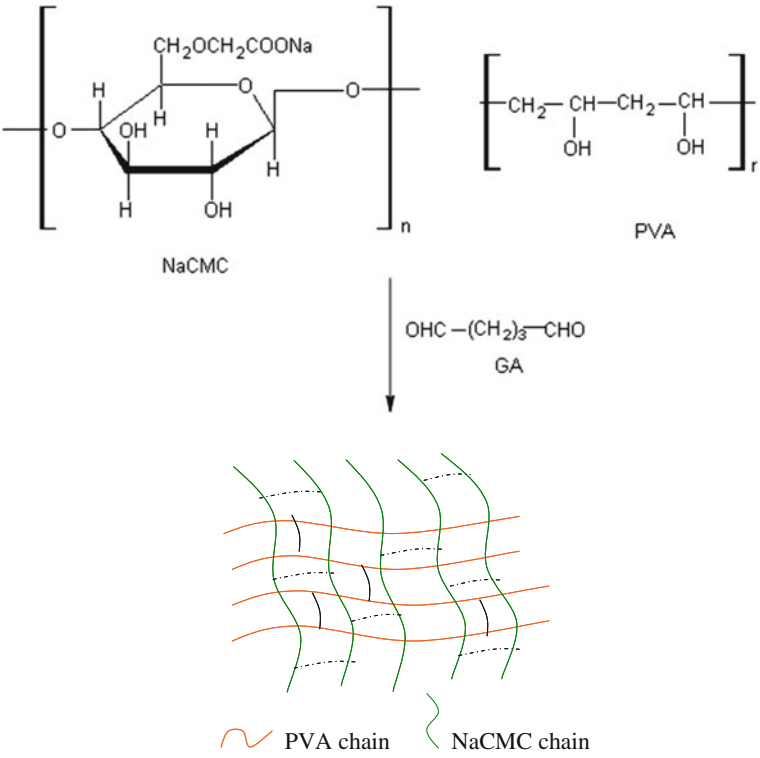
The drug-loaded microspheres (10 mg) were pulverized and incubated in 10 mL of 0.02 M phosphate buffer (pH 7.4) at room temperature for 24 h. The suspension was agitated with agate mortar and filtered through filter paper. The drug solution was assayed spectrophotometrically for 5-FU content at the wavelength of 270 nm. The results of % drug loading and encapsulation efficiency were calculated using following equations.

$$\%\ \text{Drug loading} = \left(\frac{\text{Amount of drug in microspheres}}{\text{Amount of microspheres}}\right) \times 100$$

$$\%\ \text{Encapsulation efficiency} = \left(\frac{\text{Actual loading}}{\text{Theoretical loading}}\right) \times 100$$

In vitro release study

Dissolution was carried out using Tablet dissolution tester (Lab India, Mumbai, India) equipped with eight baskets. Dissolution rates were measured at 37 ± 0.5 °C at constant speed of 100 rpm. Drug release from the microspheres was studied in 0.1 M HCl and in 7.4 pH phosphate buffer solutions. At regular intervals of time, sample aliquots were withdrawn and analyzed using UV spectrophotometer (Lab India, Mumbai, India) at the fixed λ_{max} value of 270 nm. After each sample



Scheme 1 Cross-linking reaction between PVA and NaCMC

collection, the same amount of fresh medium at the same temperature was added to the release medium to maintain the sink condition. All measurements were carried out in triplicate, and values were plotted with standard deviation errors.

Fourier transform infrared (FTIR) spectroscopy

FTIR spectral measurements performed with Nicolet, Model Impact 410 (USA) instrument to confirm the cross-linking reaction between PVA and NaCMC microspheres. Polymeric microspheres finely ground with KBr to prepare pellets under a hydraulic pressure of 600 kg/cm^2 and spectra scanned between 4,000 and 500 cm^{-1} for plain PVA, plain NaCMC and cross-linked microspheres.

DSC analysis

Differential scanning calorimetric (DSC) curves were recorded on a TA instruments (Model: STA, Q_{600} USA). The sample was weighed between 10 and 12 mg. The samples were heated from 50 to 400 °C at a heating rate of 10 °C/min in nitrogen atmosphere (flow rate of 100 mL/min).

X-ray diffraction (X-RD) studies

X-RD measurement of plain drug, drug-loaded microspheres, and plain microspheres were recorded using a Rigaku Geiger flex Diffractometry (Tokyo, Japan) equipped with Ni-filtered Cu Kα radiation ($\lambda = 1.548$ Å). The dried microspheres of uniform thickness were mounted on sample holder, and the patterns were recorded in the range 0°–50° at the speed of 50/min.

Particle size and scanning electron microscopy

To determine the particle size and size distribution, ~100–200 microspheres were taken on a glace slide and their sizes were measured using an optical microscope under regular polarized light. Scanning electron microscope (SEM) micrographs of microspheres were obtained under high resolution (Mag 300× 5kv) Using JOEL MODEL JSM 840A, SEM, equipped with phoenix energy dispersive analysis of X-ray (EDAX).

Results and discussions

FTIR spectroscopy

Figure 1 shows the FTIR spectra of (a) plain NaCMC, (b) plain PVA, and (c) plain IPNMs. FTIR spectral data were used to confirm the cross-linking IPNM chains by GA. FTIR spectra of plain PVA show a band at 3,453 cm^{-1} due to the –O–H stretching vibration. The peak at 2,927 cm^{-1} was due to the –C–H stretching vibration and the peak at 1,065 cm^{-1} was due to the –C–O stretching vibration. The FTIR spectra of plain NaCMC shows a band at 3,460 cm^{-1} due to –O–H stretching vibration, The band at 2,928 cm^{-1} shows the aliphatic stretching vibration. The peaks at 1,632 and 1,478 cm^{-1} were due to asymmetric and stretching vibrations of –COO group. The band at 1,080 cm^{-1} represents the –C–O–C– stretching [43]. In case of plain IPNMs, the –OH stretching frequency 3,423 cm^{-1} shifted toward lower side indicates the development of hydrogen bonding between NaCMC with PVA and the intense peak at 1,080 cm^{-1} indicating the formation of acetal between NaCMC, PVA by GA [44]. All these changes show a strong evidence of the intermolecular interactions, cross-linking, and good molecular compatibility between NaCMC and PVA.

Differential scanning calorimetry (DSC)

DSC curves for plain PVA–NaCMC microspheres (a), 5-FU loaded microspheres (b), and pure 5-FU drug (c) are shown in Fig. 2. The drug, 5-FU, exhibit sharp peak at 287 °C due to polymorphism and melting. However, this peak is not appeared in the curve of 5-FU loaded microspheres, suggesting that most of the drug was uniformly dispersed in polymer matrices at molecular level.

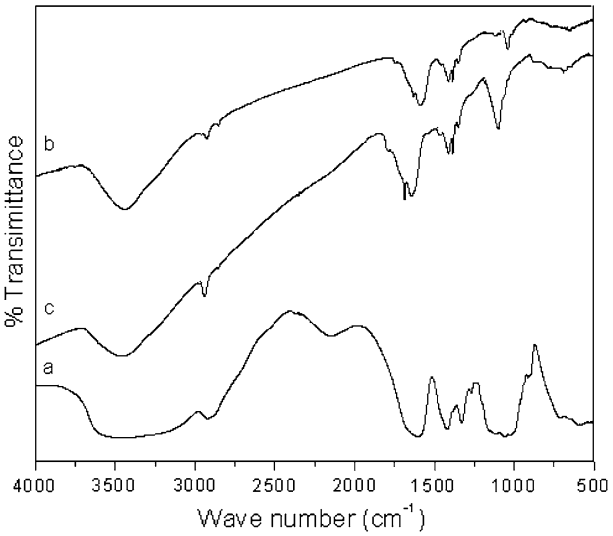


Fig. 1 FTIR spectra of (*a*) plain NaCMC, (*b*) plain PVA, and (*c*) plain IPNMs

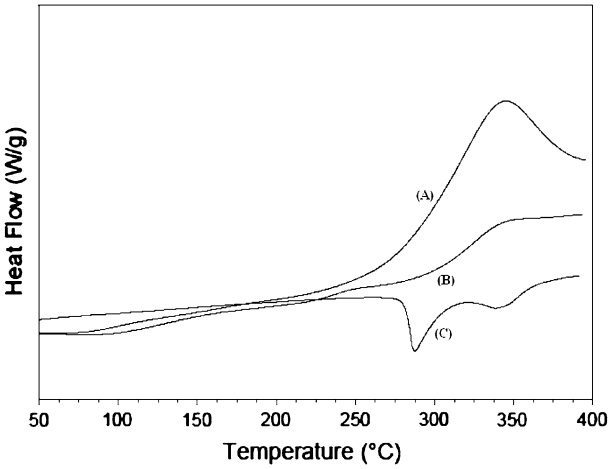


Fig. 2 DSC curves of (*a*) plain PVA–NaCMC IPNMs, (*b*) 5-FU loaded IPNMs, and (*c*) pure 5-FU

X-RD studies

X-RD study helps to find the crystallinity of drug in the IPNMs. X-RD analysis of (a) pure 5-FU, (b) Plain PVA–NaCMC IPNMs, and (c) 5-FU loaded IPNMs are shown in Fig. 3. X-RD of plain IPNMs (b) semi crystalline peak was obtained at 19.5° due to hydrogen bonds between carboxyl groups of NaCMC and hydroxyl groups of PVA. The most intensive peaks of 5-FU are observed at 2θ of 17°, 29°, and 32° suggesting its crystalline nature. But, these peaks are not found in

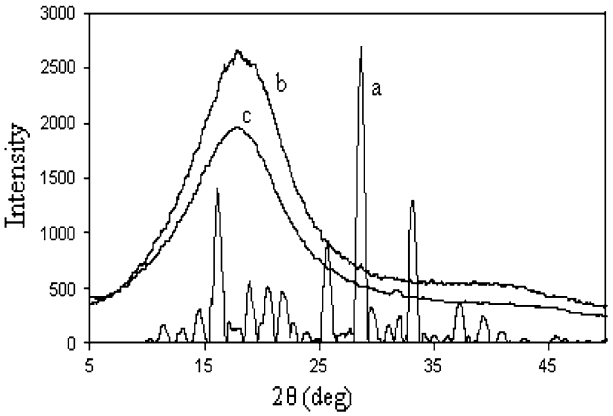


Fig. 3 X-RD peaks for (*a*) pure 5-FU, (*b*) plain PVA–NaCMC IPNMs, and (*c*) 5-FU loaded IPNMs

drug-loaded IPNMs, indicating that the drug is dispersed at molecular level in the polymer matrix. But compared to plain IPNMs, the drug-loaded IPNMs showed a decrease in intensity at 19.5° due to interaction between drug and polymer chains.

Particle size and scanning electron microscopy

The results of particle size of microspheres were in the range 80–250 μm. The variations of particle size with GA content and polymer composition are shown in Fig. 4a, b. As GA content increases the average size of microspheres decreases. This was due to the increased resistance to the water diffusing out from the microspheres during the microsphere formation. A similar observation was reported by Kulkarni et al. [45] from their drug delivery studies. The % of polymer composition also affected the size of microspheres. As % of NaCMC increases the average size of microspheres increased. This may be due to higher viscosity of the internal phase, which might have rendered higher resistance to the shearing of emulsion, thereby increasing the microspheres size. Figure 5a, b shows the scanning electron micrograph of the 5-FU loaded PVA/NaCMC microspheres and found that they are in the size range of around 200 μm and surface of the particles are smooth. This also confirms the size of the microspheres.

Encapsulation efficiency

Encapsulation efficiency of drug-loaded microspheres depends on drug content, cross-linking, and polymer composition [46]. Effects of GA and NaCMC content on encapsulation efficiency of drug-loaded microspheres are given in Table 1. The encapsulation efficiency of 5-FU increases with increasing amount of NaCMC. This can be attributed to the fact that at higher concentrations, NaCMC viscosities leading to a less diffuse matrix structure that hinder drug escape from the microspheres during the microsphere formation. This can also explains on the basis of PVA content in the blend composition. The decreasing content of PVA in the

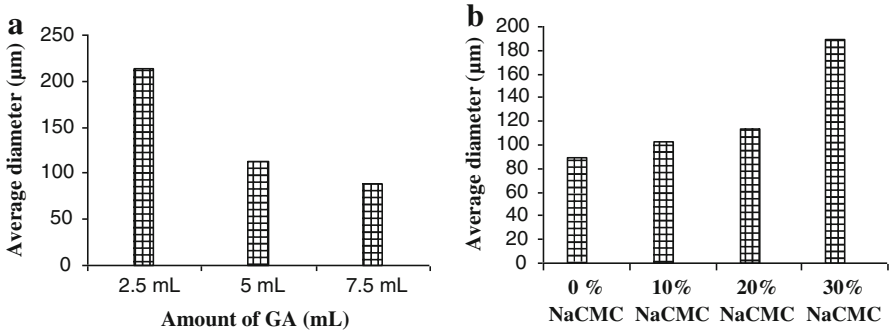


Fig. 4 Size and size distribution of IPNMs **a** effect of GA content and **b** effect of NaCMC

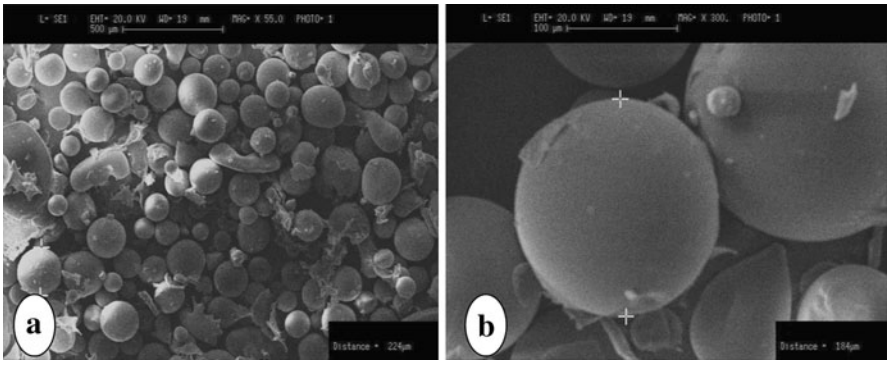


Fig. 5 SEM micrographs of IPNMs: **a** group of microspheres at low magnification and **b** single microsphere at high magnification

blend composition increases trend in encapsulation efficiency was observed. This is due to PVA produced a compact network of macromolecular chains during the microspheres formation. GA also effects the encapsulation efficiency of 5-FU. The increasing content of GA for the formation of microspheres decreases trend in encapsulation efficiency was observed. This is due to increase in cross-linking density the microspheres will become more rigid thereby reducing the free volume spaces within the polymer matrix.

Drug release kinetics

Drug release kinetics was analyzed by plotting cumulative release data versus time and fitting these data to the exponential equation of the type.

$$\frac{M_t}{M_\alpha} = kt^n$$

Here, M_t/M_α represents the fractional drug release at time t, k is a constant characteristic of the drug–polymer system, and n is an exponent parameter

Table 1 Results of % of encapsulation efficiency and release kinetics parameters of different formulations

Formulation codes	% of PVA	% of NaCMC	% of Drug	GA (mL)	% of EE ± SD	*k*	*n*	Correlation coefficient *r*
P1	90	10	7.5	5	54.9 ± 1.6	0.02131	0.57	0.9322
P2	90	10	10	5	56.4 ± 1.4	0.02965	0.54	0.9822
P3	90	10	15	5	58.1 ± 2.6	0.04213	0.50	0.9732
P4	90	10	10	7.5	55.8 ± 1.6	0.01368	0.67	0.9731
P5	90	10	10	2.5	62.3 ± 1.8	0.01217	0.65	0.9688
P6	80	20	10	5	56.5 ± 1.4	0.01652	0.68	0.9485
P7	70	30	10	5	58.9 ± 1.9	0.01509	0.72	0.9509
P8	100	–	10	5	49.6 ± 1.5	0.00913	0.73	0.9465

EE encapsulation efficiency, *SD* standard deviation

characterizing the release mechanism. Using the least squares procedure, we have estimated the values of n and k for all the eight formulations, and these values are given in Table 1. The log value of percent drug dissolved is plotted against log time for each formulation according to Eq. 1. If $n = 0.5$, drug diffuses and releases out of the polymer matrix following the Fickian diffusion. For $n > 0.5$, anomalous or non-Fickian type drug diffusion occurs. If $n = 1$, a completely non-Fickian or case II release kinetics is operative. The intermediary values ranging between 0.5 and 1.0 are attributed to the anomalous type of diffusive transport [48, 49].

In this study, the values of k and n have shown a dependence on the extent of cross-linking, % drug loading, and NaCMC content of the matrix. Values of n for microspheres prepared by varying the amount of NaCMC in the microspheres of 10, 20, and 30% by keeping 5-FU (10%) and GA (5 mL) constant, ranged from 0.5 to 0.73 (see Table 1) leading to the drug diffuses and erosion controlled release from the polymer matrix following a non-Fickian type diffusion. This could be possibly due to a reduction in the regions of low microviscosity and closure of microcavities in the swollen state. Similar findings have been observed elsewhere [50].

In vitro release study

Effect of drug concentration

Figure 6 shows the release profiles of 5-FU loaded PVA/NaCMC IPNMs at different amount of drug loadings. Release data showed that P3 formulation containing the highest amounts of drug (15%) displayed fast and higher release rates than P1 formulation containing a small amount of drug (7.5%). A prolonged release is observed for the formulation containing lower amount of 5-FU. In other words, with a decreasing amount of drug in the matrix, it is noticed that the release rate becomes quite slower due to the availability of more free void spaces through which a lesser number of drug molecules could transport.

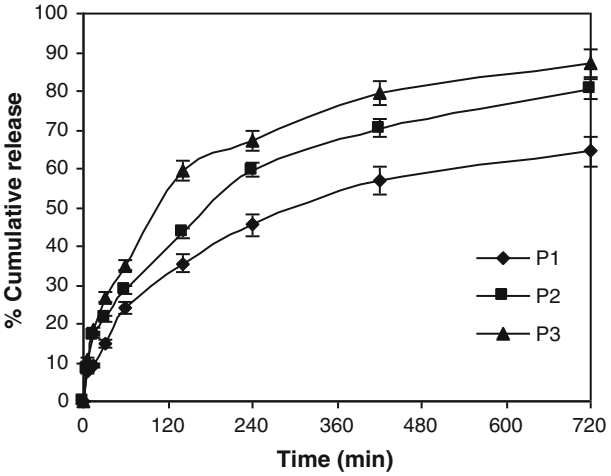


Fig. 6 % cumulative release of 5-FU through microspheres containing 90:10 ratio of PVA/NaCMC with different amount of 5-FU (*P1*) 7.5%, (*P2*) 10%, and (*P3*) 15%

Effect of cross-linking agent

The % cumulative release data versus time plots for varying amounts of GA, i.e., 2.5, 5.0, and 7.5 mL at the fixed amount of the drug (10%) are displayed in Fig. 7 and it is observed that the % cumulative release is quite faster and larger at the lower amount of GA (i.e., 2.5 mL), whereas the release is quite slower at higher amount of GA (i.e., 7.5 mL). probably because at higher concentration of GA, polymeric chains become rigid due to the contraction of microvoids, thus decreasing %

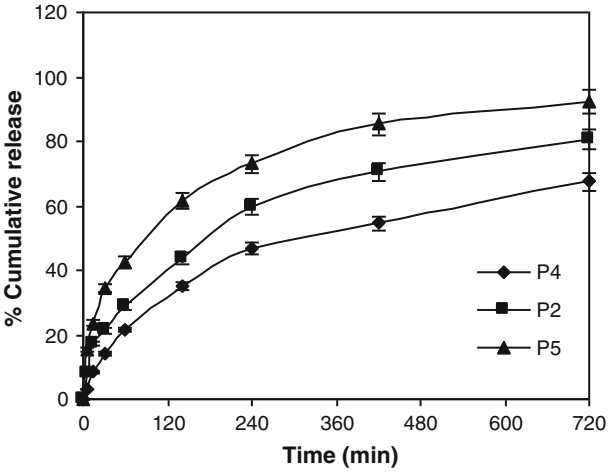


Fig. 7 % cumulative release of 5-FU through microspheres containing 90:10 ratio of PVA/NaCMC with 10% of drug with different amount of GA (*P5*) 2.5 mL, (*P2*) 5 mL, and (*P4*) 7.5 mL

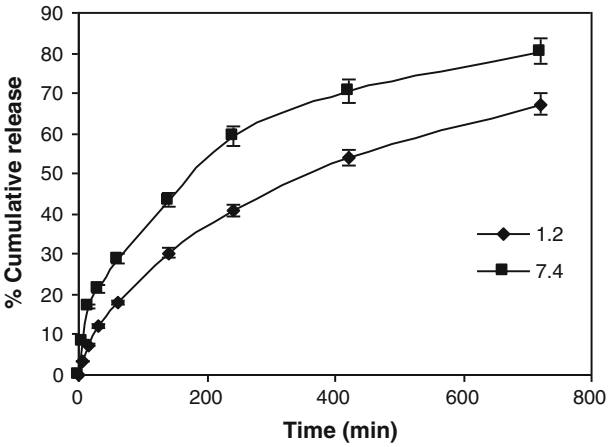


Fig. 8 % cumulative release of P2 formulation at pHs 1.2 and 7.4

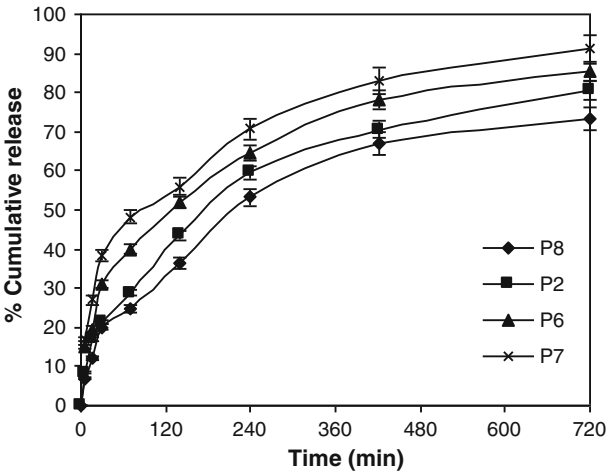


Fig. 9 % cumulative release of 5-FU through microspheres containing 15% of drug and 5 mL of GA with variation of NaCMC (*P2*) 10%, (*P6*) 20%, (*P7*) 30%, and (*P8*) pure PVA

cumulative release of 5-FU through the IPNMs. As expected, the release becomes slower at higher amount of GA, but becomes faster at lower amount of GA.

Effect of pH and NaCMC

As there are many carboxylic groups on NaCMC chains, it can be expected that the complex will behave in a pH sensitive fashion. Figure 8 shows the % of cumulative release rates at pHs 1.2 and 7.4. For the pH 1.2, the cumulative release was very low. This is due to hydrogen bonds formed and the attraction between the PVA and NaCMC chains. In phosphate buffer saline (pH 7.4), the cumulative release is high,

this is due to some of carboxylic groups become ionic, and repelling effect increases. So, the % of cumulative release is higher in higher amount of NaCMC present in the matrix. The effect of NaCMC content in formulations P2, P6, P7, and P8 on release rates are also presented in Fig. 9. In formulation P7, the % of cumulative release is more than P6 and P2 due to more number of carboxyl groups present in the P7 formulation, so repelling effect also increases between carboxyl ions. This can also be attributed by the fact that as the NaCMC content in the polymer matrix increases, swelling of the matrix also increases due to the extremely hydrophilic nature of NaCMC. This can be further substantiated that P8 formulation shows the least % of cumulative release as it contains 0% of NaCMC.

Conclusions

pH sensitive 5-FU loaded PVA/NaCMC IPNMs microspheres were prepared by W/O emulsion method using span-80 as the surfactant. DSC analysis of the drug-loaded microspheres confirmed the molecular level dispersion of drug in the microspheres. Particle size measured using optical microscopy gave an average size 80–250 μm. SEM pictures have shown the formation of spherical microspheres with smooth surface. The encapsulation efficiency was found to vary between 49 and 62% depending upon the blend composition, cross-linking and the amount of drug loading. Drug release studies indicated controlled release of 5-FU for more than 10 h from IPNMs microspheres.

Acknowledgment We thank University Grants Commission, New Delhi, for providing financial support to one of the authors (Mr. K. Madhusudana Rao) under UGC-RFSMS (File No. F 4-1/2006 (BSR)/11-23/2008 (BSR) dt: January 2011.

References

1. Clarke KM, Lantz GC, Salisbury SK, Badylak SF, Hiles MC, Voytik SL (1996) Intestine submucosa and polypropylene mesh for abdominal wall repair in dogs. J Surg Res 60:107–114
2. Desgrandchamps F (2000) Biomaterials in functional reconstruction. Curr Opin Urol 10(3):201–206
3. Kulakarni AR, Soppimath KS, Aminabhavi TM, Rudzinski WE (2000) In-vitro release of cefradroxil-loaded sodium alginate interpenetrating network beads. Eur J Pharm Biopharm 51:127–133
4. Mundargi RC, Sangamesh AP, Aminabhavi TM (2006) Evaluation of acrylamide-grafted-xanthan gum copolymer matrix tablets for oral controlled delivery of antihypertensive drugs. Carbohydr Polym 69:130–141
5. Krishna Rao KSV, Kiran Kumar ABV, Madhusudana Rao K, Subha MCS, Lee Y III (2008) Semi-IPN hydrogels based on poly(vinyl alcohol) for controlled release studies of chemotherapeutic agent and their swelling characteristics. Polym Bull 61:81–90
6. Krishna Rao KSV, Madhusudana Rao K, Nagendra Kumar PV, Chung II-D (2010) Novel chitosan-based pH sensitive micro-networks for the controlled release of 5-fluorouracil. Iran Polym J 19:265–276
7. Krishna Rao KSV, Subha MCS, Vijaya Kumar Naidu B, Sairam M, Mallikarjuna NN, Aminabhavi TM (2006) Controlled release of diclofenac sodium and ibuprofen through beads of sodium alginate and hydroxy ethyl cellulose blends. J Appl Polym Sci 102:5708–5718
8. Krisha Rao KSV, Nadiu BVK, Subha MCS, Sairam M, Aminabhavi TM (2006) Novel chitosan-based pH-sensitive interpenetrating network microgels for the controlled release of cefadroxil. Carbohydr Polym 66:333–344

9. Charpentier D, Mocanu G, Carpov A, Chapelle S, Merle L, Muller G (1997) New hydrophobically modified carboxymethylcellulose derivatives. Carbohydr Polym 33:177–186
10. Ito H, Shibata T, Miyamoto T (1986) Formation of polyelectrolyte complexes between cellulose derivatives and their blood compatibility. J Appl Polym Sci 31:2491–2500
11. Wach RA, Mitomo H, Yoshii F, Kume T (2001) Hydrogel of biodegradable cellulose derivatives. II. Effect of some factors on radiation-induced crosslinking of CMC. J Appl Polym Sci 81:3030–3037
12. Kim J, Yun S, Ounaies Z (2006) Discovery of cellulose as a smart material. Macromolecules 39:4202–4206
13. Horiike S, Matsuzawa S, Yamaura K (2002) Preparation of chemically crosslinked gels with maleate-denatured poly (vinyl alcohol) and its application to drug release. J Appl Polym Sci 84:1178–1184
14. Sreenivasan K (1997) On the restriction of the release of water-soluble component from polyvinyl alcohol film by blending β-cyclodextrin. J Appl Polym Sci 65:1829–1832
15. Orienti I, Trere R, Luppi B, Bigucci F, Cerchiara T, Zuccari G, Zecchi V (2002) Hydrogels formed by crosslinked poly (vinyl alcohol) as sustained drug delivery systems. Arch Pharm 335:89
16. Kim SY, Lee YM (1999) Drug release behavior of electrical responsive poly(vinyl alcohol)/poly(acrylic acid) IPN hydrogels under an electric stimulus. J Appl Polym Sci 74:1752–1761
17. Kweon DK, Kang DW (1999) Drug-release behavior of chitosan-g-poly (vinyl alcohol) copolymer matrix. J Appl Polym Sci 74:458–464
18. Feng X, Huang RYM (1996) Preparation and performance of asymmetric polyetherimide membranes for isopropanol dehydration by pervaporation. J Membr Sci 109:165–172
19. Lee KH, Kim HK, Rhim JW (1995) Pervaporation separation of binary organic-aqueous liquid mixtures using crosslinked PVA membranes III. Ethanol–water mixtures. J Appl Polym Sci 58:1707–1712
20. Huang RYM, Yeom CK (1991) Development of cross-linked poly(vinyl alcohol) (type II) and permeation of acetic acid–water mixtures. J Membr Sci 62:59–73
21. Isiklan N, Sanli O (2004) Permeation and separation characteristics of acetic acid/water mixtures through poly (vinyl alcohol-g-itaconic acid) membranes by pervaporation, evapomeation and temperature-difference evapomeation. J Appl Polym Sci 93:2322–2333
22. Isiklan N, Sanli O (2005) Separation characteristics of acetic acid-water mixtures by pervaporation using poly (vinyl alcohol) membranes modified with malic acid. Chem Eng Process 44:1019–1027
23. Sanli O, Asman G (2004) Release of diclofenac through glutaraldehyde crosslinked poly(vinyl alcohol)/poly(acrylic acid). J Appl Polym Sci 91:72–77
24. Prasad CV, Madhu Sudhan Rao K, Mallikarjuna B, Subha MCS, Chowdoji Rao K (2010) Synthesis and characterization of SA-g-MAA co-polymer: effect of grafting and process variables on controlled release of an anti-bacterial drug.Adv Mater Res 123:387–390
25. Lakshmi Narayana Reddy C, Yerriswami B, Venkata Prasad C, Subha MCS, Chowdoji Rao K (2010) Controlled release chlorphenaramine maleate through IPN beads of sodium alginate-g-methylmethacrylate. J Appl Polym Sci 118:2342–2349
26. Yerri swamy B, Venkata Prasad C, Reddy CLN, Chowdoji Rao K, Subha MCS (2011) Interpenetrating polymer network microspheres of hydroxy propyl methyl cellulose/poly (vinyl alcohol) for control release of ciprofloxacin hydrochloride. Cellulose 18:349–357
27. Rokhade AP, Agnihotri SA, Patil SA, Mallikarjuna NN, Kulkarni PV, Aminabhavi TM (2006) Semi-interpenetrating polymer network microspheres of gelatin and sodium carboxymethyl cellulose for controlled release of ketorolac tromethamine. Carbohydr Polym 65:243–252
28. Kurkuri MD, Aminabhavi TM (2004) Poly(vinyl alcohol) and poly(acrylic acid) sequential interpenetrating network pH-sensitive microspheres for the delivery of diclofenac sodium to the intestine. J Control Release 96:9–20
29. Soppimath KS, Kulkarni AR, Aminabhavi TM (2000) Controlled release of antihypertensive drug from the interpenetrating network poly (vinyl alcohol) guar gum hydrogel microspheres. J Biomater Sci Polym 11:27–43
30. Agnihotri SA, Aminabhavi TM (2006) Novel interpenetrating network chitosan poly(ethylene oxide-g-acrylamide) hydrogel microspheres for the controlled release of capecitabine. Int J Pharm 324:103–115
31. Rokhade AP, Shelke NB, Patil SA, Aminabhavi TM (2007) Novel hydrogel microspheres of chitosan and pluronic F-127 for controlled release of 5-fluorouracil. J Microencapsul 24(3):274–288
32. Shehap AM (2008) Thermal and spectroscopic studies of polyvinyl alcohol/sodium carboxy methyl cellulose blends. Egypt J Solids 31:75–91

33. Hassan CM, Peppas NA (2000) Cellular PVA hydrogels produced by freeze/thawing. J Appl Polym Sci 76:2075–2079
34. Mitsumita T, Suemitsu Y, Fujji K, Fujji T, Taniguchi T, Koyama K (2003) pH-response of chitosan, κ-carrageenan, carboxymethyl cellulose sodium salt complex hydrogels. Polymer 44:7103–7111
35. Matsuyama H, Teramoto M, Urano H (1997) Analysis of solute diffusion in poly (vinyl alcohol) hydrogel membrane. J Membr Sci 126:151–160
36. Heidelberger C (1982) Cancer medicine, 2nd edn. Lea and Febiger, Philadelphia, pp 801–824
37. Waxman S, Scanlon KJ, Greenspan EM (1982) Clinical interpretation and practice in chemotherapy. Raven Press, New York, pp 39–52
38. Sommadossi JP, Gewirtz DA, Diasio RB, Aubert C, Cano JP, Goldman ID (1982) Rapid catabolism of 5-fluorouracil in freshly isolated rathepatocytes as analyzed by high performance liquid chromatography. J Biol Chem 257:8171–8176
39. Einmahl S, Zignani M, Varesio E, Heller J, Veuthey JL, Tabatabay C, Gurny R (1999) Concomitant and controlled release of dexamethasone and 5-fluorouracil from poly (ortho ester). Int J Pharm 185:189–198
40. Fournier E, Passirani C, Colin N, Bretona P, Sagodiraa S, Benoitb JP (2004) Development of novel 5-FU-loaded poly (methylidene malonate 2.1.2)-based microspheres for the treatment of brain cancers. Eur J Pharm Biopharm 57:189–197
41. Ermis D, Yuksel A (1999) Preparation of spray-dried microspheres of indomethacin and examination of the effects of coating on dissolution rates. J Microencapsul 16:315–324
42. Tabata Y, Ikada Y (1989) Synthesis of gelatin microspheres containing interferon. Pharm Res 6:422–427
43. Williams DH, Fleming I (1980) Spectroscopic methods in organic chemistry, 3rd edn. Mc Graw Hill Book Company, London, ch 3, p 75
44. Xiao C, Lu Y, Zang C (2001) Preparation and characterization of konjac glucomannan and sodium carboxymethylcellulose blend films. J Appl Polym Sci 80:26–31
45. Kulkarni PV, Keshavayya J, Kulkarni VH (2007) Effect of method of preparation and variables on controlled release of insoluble drug form chitosan microspheres. Polym Adv Technol 18:814–821
46. Anita GS, Manjeshwar LS, Aminabhavi TM (2010) Controlled release of theophylline from interpenetrating blend microspheres of poly(vinyl alcohol) and methyl cellulose. J Appl Polym Sci 116:1226–1235
47. Ritger PL, Peppas NA (1987) A simple equation for description of solute release II. Fickian and Anomolous release from swellable devices. J Control Release 5:37–42
48. Siepmann J, Peppas NA (2001) Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Adv Drug Deliv Rev 48:139–157
49. Aminabhavi TM, Naik HG (1998) Chemical compatibility study of geomembrane-sorption/desorption, diffusion and swelling phenomena. J Hazard Mater 60:175–203
50. Lyu SP, Sparer R, Hobot C, Dang K (2005) Adjusting drug diffusivity using miscible polymer blends. J Control Release 102:679–687