Interpenetrating polymeric network hydrogels for potential gastrointestinal drug release

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Abstract: New interpenetrating polymeric network (IPN) hydrogels based on chitosan (C), poly(*N*-vinyl pyrrolidone) (PVP) and poly(acrylic acid) (PAAc), crosslinked with glutaraldehyde (G) and *N*,*N*′-methylenebisacrylamide (MBA), were prepared and investigated for potential gastrointestinal drug delivery vehicles utilizing a model drug, amoxicillin. IPN hydrogels were synthesized by simultaneous polymerization/crosslinking of acrylic acid monomer in the presence of another polymer (C) and crosslinker (G, MBA). Three different concentrations of glutaraldehyde were used (0.5, 1.0 and 2.0 w/w) to control the overall porosity of the hydrogels, named C-P-AAc/0.5, C-P-AAc/1.0 and C-P-AAc/2.0, respectively. Spectroscopic and thermal analyses such as Fourier transform infrared spectroscopy, thermogravimetric analysis and thermomechanical analysis were performed for IPN characterization. Equilibrium swelling studies were conducted for pH and temperature response behavior. Swelling studies were also carried out in simulated gastric fluid of pH = 1.1 and simulated intestinal fluid of pH = 7.4 to investigate possible site-specific drug delivery. It was found that the release behavior of the drug from these IPN hydrogels was dependent on the pH of the medium and the proportion of crosslinker in the IPN. It was observed that amoxicillin release at pH = 7.4 was higher than at pH = 1.1. The analysis of the drug release showed that amoxicillin was released from these hydrogels through a non-Fickian diffusion mechanism.

Keywords: IPN hydrogels; drug release; pH-sensitive release; amoxicillin; poly(acrylic acid)

INTRODUCTION

Interpenetrating polymeric networks (IPNs) comprise two or more independent polymer networks that are formed in the presence of one another. Chitosan, chitin and gelatin are among the most widely used natural polymers while polyacrylamide, poly(acrylic acid) (PAAc), poly(*N*-isopropyl acrylamide) and poly(*N*-vinyl pyrrolidone) (PVP) are examples of the most commonly used synthetic ones to prepare IPNs. IPN properties such as porosity, elasticity, degree of swelling and responsive behavior to a stimulus can be tuned by the appropriate choice of the network-forming polymers and suitable crosslinking agent and its proportion.[1–4] IPN hydrogels are very promising and versatile materials for biomedical applications. For example, they can be used in controlled release systems that are capable of delivering drugs at a constant rate over an extended period of time, and in tissue engineering as scaffolds that can match the extracellular matrix properties. Nevertheless, homopolymeric and copolymeric structures alone cannot meet such divergent demands in terms of both properties and performance. Therefore, a composite or an IPN of two or three different polymers would be a better approach.[3,5]

Stimuli-sensitive hydrogels are environmentally sensitive materials that response to changes in their environment by changing their physical and chemical characteristics such as swelling, shrinking, degrading, bending or curling. These stimuli can be pH, temperature, ionic strength or even solute metabolites. IPN hydrogels emerge as useful materials for certain applications such as localized antibiotic delivery in the acidic environment of gastric fluid. One of the most important advantages of these hydrogels is their formulation that remains almost the same, and their extended residence time at the target sites in comparison with conventional hydrogels.[2,6]

Chitosan, PVP and PAAc have been much investigated in stimuli-sensitive drug release studies.[2,3] Although chitosan is a biocompatible and naturally occurring polymer, the chemistry associated with it is somehow cumbersome, and it has poor mechanical properties, i.e. chitosan beads and films are very brittle.[4,7,8] These undesirable properties of a polymer can limit its bio-applications. PVP is a synthetic polymer, and is commonly used in the textiles and cosmetics industries as well as in pharmaceuticals and medical applications.[5,9] PAAc-based hydrogels are also extensively investigated for bioadhesive

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release devices.[3] For that reason, in the present work, we investigate the suitability of a system that utilizes these three polymers, chitosan (C), PVP and PAAc, to synthesize an IPN system that can be used for gastrointestinal drug delivery devices. Cylindrical shaped IPN hydrogels were prepared for oral administration and characterized. Two different crosslinkers (glutaraldehyde (G) and *N*,*N*′-methylenebisacrylamide (MBA)) were used to control the network properties. These IPNs were named as C-P-AAc. IPNs loaded with a model drug, amoxicillin (used in the treatment of diseases caused by *Helicobacter pylori*), were used for drug release studies. Mechanical properties and pore size of the polymeric materials were investigated in order to optimize the IPN carrier for possible oral administration.

EXPERIMENTAL

Chemicals

Chitosan ($M_w \sim 600\,000\,g\,mol^{-1}$) was purchased from Fluka (Steinheim, Switzerland) and PVP (M_w 40 000 g mol^{-1}) was obtained from Calbiochem (Darmstadt, Germany). Acrylic acid (AAc), hydrochloric acid, potassium chloride, disodium hydrogen phosphate and potassium dihydrogen phosphate were purchased from Merck (Darmstadt, Germany). MBA and glutaraldehyde (25% w/w) used as crosslinkers and ammonium persulfate as redox initiator were obtained from Merck (Schuchardt, Germany). The model drug, amoxicillin trihydrate, was also a product of Fluka (Steinheim, Switzerland). All chemicals were of analytical grade and were used as received. Double-distilled water was used for all the experiments.

Preparation of IPNs

PVP, crosslinkers and AAc solution were added to a solution of chitosan (10 mL, 1 wt% in 0.8 wt% acetic acid) under continuous mixing. Chitosan, PVP and AAc were used in 4.0:4.0:90 weight ratio. The ratios (w/w) between glutaraldehyde and chitosan in the IPNs were 0.5, 1 and 2. The weight ratio of MBA to AAc was 2:100. Ammonium persulfate solution (25 μL, 5 wt%) was added to this mixture. The mixture was placed in PVC straws of 3 mm diameter. A gel formed after 5 h of reaction time at ambient temperature. After 24 h, the IPNs were obtained in long cylindrical shapes, and were cut into pieces of 4–5 mm in length and washed with distilled water. They were then dried in air and vacuum, and stored for further use.

Fourier transform infrared (FTIR) analysis

FTIR spectra of C, C-P and C-P-AAc IPNs were recorded using a Mattson FTIR spectrophotometer to determine their structure and intermolecular interactions. Thoroughly ground IPN samples were mixed with dried KBr, and discs were prepared by compression under vacuum. Spectra were recorded with a resolution of 1 cm^{-1}.

Thermogravimetric analysis (TGA)

Thermal stability investigations were conducted with a Shimadzu 50 thermogravimetric analyzer. TGA was performed on *ca* 10 mg samples under nitrogen atmosphere with a nominal gas flow rate of 25 mL min^{-1} and a heating rate of 10 °C min^{-1} up to 600 °C.

Thermomechanical analysis (TMA)

The thermomechanical properties of the IPNs were investigated utilizing a Shimadzu 501 thermomechanical analyzer. To determine the maximum penetration, TMA of the IPNs was performed in the temperature range 20–120 °C under 1 g cm^{-2} load.

Swelling studies

Swelling studies of IPNs were done as dynamic and cycled equilibrium swellings. In dynamic swelling experiments, C-P-AAc IPNs were placed in solution at pH 1.1 (KCl–HCl) and pH 7.4 (Na_2HPO_4–KH_2PO_4) at 37 °C. During swelling, gels were removed from the water bath at regular time intervals and after drying superficially with filter paper, and weighing, they were returned into the same swelling bath. The increase in radii of the cylindrical swollen gels was measured with a micrometer, and the swelling parameters and diffusion types were determined.

The effects of temperature and pH on the swelling behavior of the IPNs were investigated by cycled equilibrium swelling, in which the gels were alternately swelled to their equilibrium swelling values for 24 h at 20 °C, and at 37 °C at each pH value (1.1 and 7.4) for 30 days.

Release studies

Drug loading was carried out by adding 50 mg amoxicillin per gram of precursor IPN before polymerization/crosslinking reactions. After polymerization, the hydrogels were optically transparent indicating complete solubility of the drug (amoxicillin) in the polymer matrix. The *in vitro* release studies of the entrapped drug were carried out by placing the drug-loaded IPN samples into 10 mL KCl–HCl solution with pH 1.1 at 37 °C in a shaker. After 0.5 h, 3 mL of the drug-containing solution were taken out and the concentration was measured at $\lambda_{max} = 271$ nm using a Shimadzu 160A UV-visible spectrophotometer (and a previously constructed calibration curve). The release media were replenished periodically with fresh KCl–HCl solutions (10 mL). The dilution effects were taken into account for calculations of the released drug. The release studies were continued until no more change was observed in the absorbance value of the medium. The same release experiments were also carried out for a Na_2HPO_4–KH_2PO_4 solution at pH 7.4 and 37 °C. The amount of released amoxicillin

Polym Int **56**:1371–1377 (2007)
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was quantified and its corresponding release graph constructed.

RESULTS AND DISCUSSION

FTIR analysis

Figure 1 depicts schematically the IPN synthesis. After the synthesis, and cleaning procedure, FTIR spectra of the dried hydrogels were obtained, and are shown in Fig. 2. In the figure, the corresponding spectra of chitosan crosslinked with gluraraldehyde, C-P and C-P-AAc/2 samples were used to evaluate the structural changes. The chitosan spectrum exhibits bands at 1676 cm^{-1} (amide I) and 1574 cm^{-1} ($-NH_2$ bending). The absorption bands at 1165 cm^{-1} (antisymmetric stretching of the C–O–C bridge), 1089 and 1038 cm^{-1} (skeletal vibrations involving the C–O stretching) arise from chitosan and are characteristic of saccharide structures.[10] The band at 1651 cm^{-1} in the chitosan spectrum was attributed to the formation of C=N, due to the imine reaction between amino groups of chitosan and aldehyde groups in glutaraldehyde. It is observed that there is a change in the intensity of the absorption band in the range 2800–3500 cm^{-1}, corresponding to –OH groups of chitosan in the C-P spectrum. This change can be attributed to hydrogen bonding between C=O groups of PVP and –OH groups of chitosan. The absorption bands at 1421, 1446 and 1472 cm^{-1} were assigned to the characteristic vibrations of the pyrrolidone ring[11] and the absorption band at 1668 cm^{-1} corresponds to amide I.[12]

The bands in the range 3000–3600 cm^{-1} and at 1715 cm^{-1} indicate –OH and C=O groups of carboxyl moieties, respectively, in the spectrum of C-P-AAc/2 IPN. When the acrylic acid is polymerized in the presence of chitosan, inter- and intramolecular linkages are formed between carboxyl groups from PAAc and positively charged amino groups of chitosan.[13] The bands at 2930 and 2850 cm^{-1} can be attributed to the presence of $-NH_3^+$ in C-P-AAc IPNs. From this spectral analysis, it can be concluded that a polymeric network is formed, due to crosslinks of chitosan with glutaraldehyde and PAAc with MBA, and also between chitosan molecules.

TGA

Figure 3(a) shows thermograms of dried samples of chitosan, C-P and C-P-AAc/0.5 obtained under

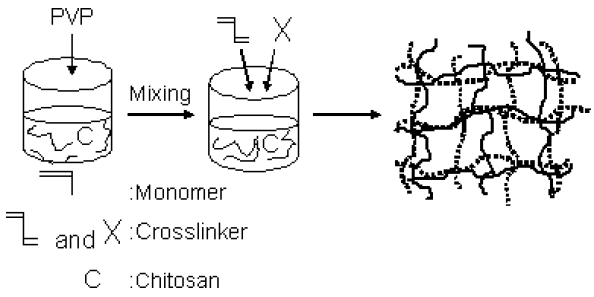

Figure 1. Schematic of C-P-AAc IPN synthesis.

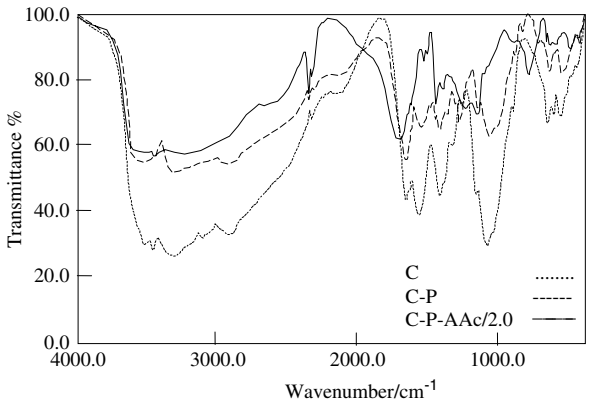

Figure 2. FTIR spectra of C, C-P and C-P-AAc/2.0 IPN.

nitrogen atmosphere at a heating rate of 10 °C min^{-1} from 0 to 600 °C. The thermogravimetric curve of chitosan in Fig. 3(a) shows three degradation steps, which is consistent with the results of Khalid *et al*. for chitosan films.[7] The first step up to 157 °C can be attributed to the loss of bound water; the second step ranging from 218 to 300 °C corresponds to chitosan partial degradation; the third step ranging from 300 to 600 °C represents the total degradation of chitosan. Thermal stability of C-P-AAc/0.5 IPN to 410 °C increases in comparison with chitosan and C-P polymers (Fig. 3(a)). In the case of IPN, since the polymer chains are more closely entangled together, the thermal stability of the IPN is higher than that of the other polymers. This can be evidence of the formation of an IPN including chitosan, PVP and PAAc polymers.

Figure 3(b) shows the effect of the crosslinker concentration on the thermal stability of IPNs. As can be seen, the thermal stability of IPNs has increased dramatically with the increase in the glutaraldehyde concentration. When glutaraldehyde concentration increased twofold (from 0.5 to 1), the weight loss decreased drastically from *ca* 5 to 40% at around 500 °C. A further increase in the amount of glutaraldehyde did cause some significant decrease in the amount of weight loss. Hence, C-P-AAc/1.0 can be considered as a threshold towards more thermally stable interpenetrating structures.

TMA

TMA thermograms of C-P-AAc IPNs obtained under 1 g cm^{-2} load are shown in Fig. 4. The values of maximum penetration of C-P-AAc/0.5, C-P-AAc/1.0 and C-P-AAc/2.0 IPNs were found as 8.0, 5.4 and 3.2 μm, respectively, up to about 50 °C. The measurements performed over 50 °C show higher penetration depths as shown in Fig. 4. It is clear that the decrease in the values of maximum penetration is due to the increased thermal stability and the mechanical strength with the increased amount of crosslinker (glutaraldehyde) in the IPN network structure.

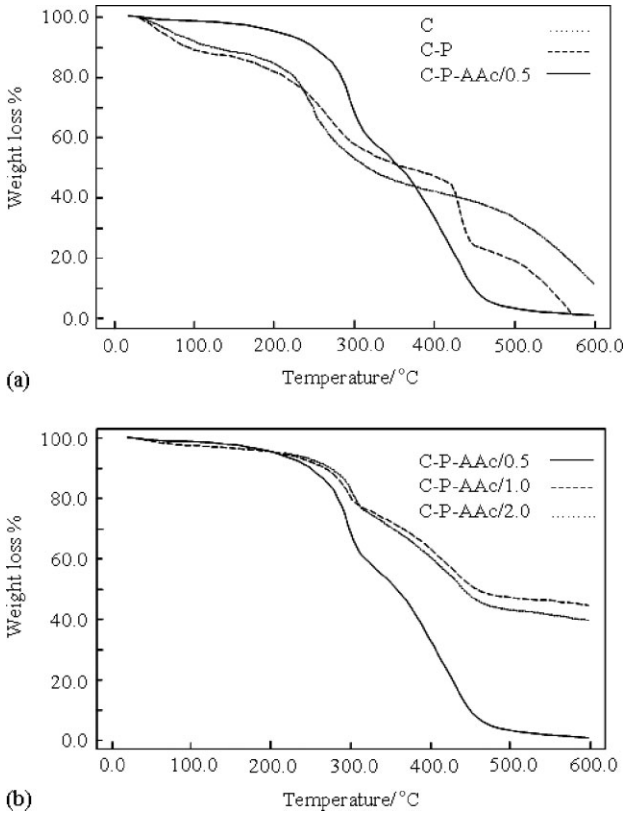

Figure 3. (a) Thermograms of C, C-P and C-P-AAc/2.0 IPN. (b) Effect of crosslinking density on C-P-AAc IPNs.

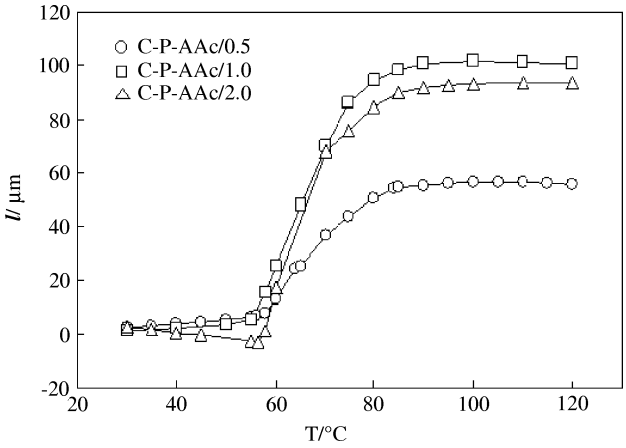

Figure 4. Penetration–temperature curves for various IPNs.

Swelling studies

To investigate the time-dependent swelling behavior of the IPNs in buffer solutions with different pH values, dynamic swelling studies were performed.

The percentage swelling S is calculated from the following relationship:

$$S = \frac{M_t - M_0}{M_0} \times 100\% \qquad (1)$$

where M_0 is the weight of dry gel at time 0 and M_t is the weight of swollen gel at time t.

Swelling curves of IPNs with different amounts of crosslinkers at pH 1.1 and pH 7.4 at 37 °C are shown in Fig. 5: it can be seen that swelling increased with time

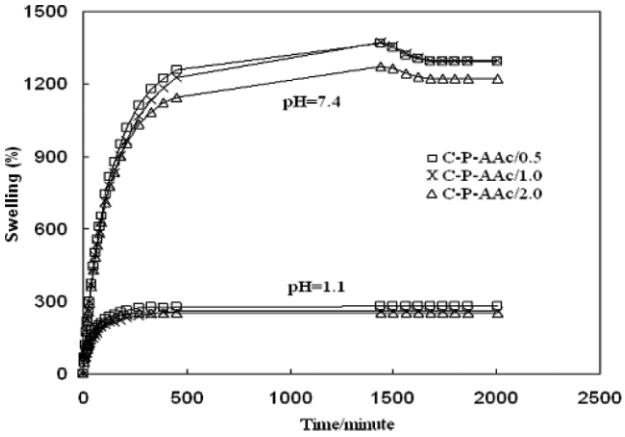

Figure 5. Dynamic swelling curve of C-P-AAc IPNs with different crosslinker proportions and different buffer solutions.

and leveled off around 250 min at pH = 1.1, and after 500 min at pH = 7.4. The maximum value of swelling, named equilibrium swelling (S_{eq}), is given Table 1 for different IPNs. Figure 5 and Table 1 show that the values of equilibrium swelling of IPNs decreased with increasing glutaraldehyde concentrations in the IPNs. The degree of swelling of a hydrogel depends on its network structure, which is controlled by the concentration of the crosslinker. An increase in the amount of crosslinking agent leads to a denser network of the IPN.

The following equation is used to determine the nature of diffusion of buffer solutions into IPNs:

$$F = kt^n \qquad (2)$$

where F is the fractional uptake at time t, k is a constant incorporating the characteristics of the macromolecular network and the penetrant and n is the diffusional exponent that indicates the transport mechanism. Equation (2) is valid for the first 60% of the fractional uptake. Fickian diffusion and Case II transport are defined by n values which correspond to 0.5 and 1, respectively. Anomalous transport behavior (non-Fickian diffusion) is intermediate between Fickian and Case II. That is reflected by n which is between 0.5 and 1.[3] For IPN hydrogels, the number determining the type of diffusion (n) was found over 0.50 at both pH values. Hence the diffusion of solutions into the hydrogels is generally non-Fickian in character. When the diffusion exhibits an anomalous behavior, the relaxation and diffusion times are of the same order of magnitude. As the solvent diffuses into

Table 1. Equilibrium swelling parameter of IPNs for different pH values

	S_{eq} (%)	
IPN	pH 1.1	pH 7.4
C-P-AAc/0.5	280	1300
C-P-AAc/1.0	260	1295
C-P-AAc/2.0	250	1220

Polym Int **56**:1371–1377 (2007)
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the hydrogel, rearrangement of the chains does not occur immediately.

Our results indicated that IPNs exhibited greater swelling at pH 7.4 when compared with that at pH 1.1. This can be explained by ionic interactions of the carboxyl groups of PAAc in intestinal pH conditions. Macromolecular chains in the IPN network swell extensively due to ionization of PAAc at pH 7.4 or higher values. The developed (ionized carboxylic acid groups) charges on the network lead to electrostatic repulsion among the charged $-COO^-$ groups, resulting in extensive swelling of the IPN.[13] Otherwise, the values of swelling of IPNs at pH 1.1 may be explained in terms of ionic interactions of the amino group of chitosan in stomach pH conditions. This protonation of the $-NH_2$ group in chitosan ensures chain relaxation, leading to faster hydrogen bond dissociation and efficient solvent diffusion. Also, digital camera images of IPNs relative to dry and swelled cases were obtained and are shown in Fig. 6.

To obtain basic information on the temperature-sensitive swelling behavior of the IPNs, alternating swelling experiments between 20 and 37 °C were also carried out at two different pH values (pH = 1.1 and 7.4). The change of degree of swelling of C-P-AAc/0.5 IPNs as an example is plotted in Fig 7. The swelling degree of C-P-AAc/0.5 IPNs increases with increasing temperature. PAAc hydrogels show a typical positive swelling change with temperature indicating the occurrence of upper critical solution temperature (UCST) behavior.[14]

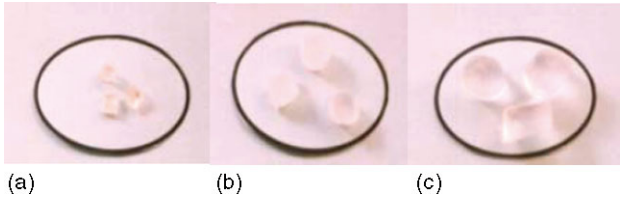

Figure 6. Digital camera images of C-P-AAc IPNs in different conditions: (a) dry; (b) swelled at pH 1.1; (c) swelled at pH 7.4 and 37 °C.

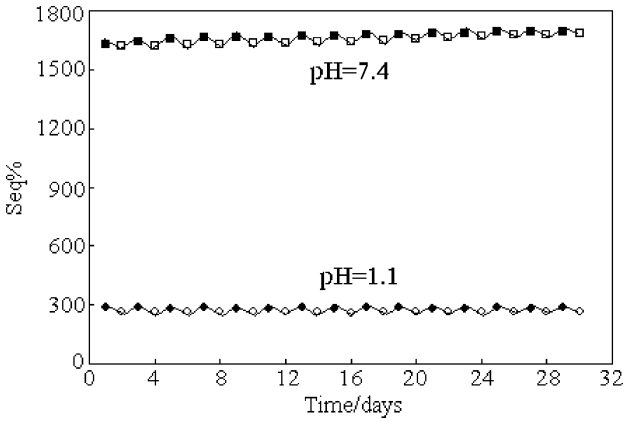

Figure 7. Temperature-sensitive swelling behavior of C-P-AAc/0.5 IPNs: ◇, 20 °C; ◆, 37 °C; □, 20 °C; ■, 37 °C.

The IPNs synthesized in this work contain PAAc. To investigate the pH-responsive behavior of IPNs, certain amounts of C-P-AAc/0.5 IPNs were placed in universal buffer solutions with pH values varying from 2.5 to 10 at physiological temperature (37 °C) in a water bath at constant temperature. The equilibrium swelling value *versus* pH graph is shown in Fig. 8. The change in S_{eq}% value between pH 4 and 7 is typical for PAAc hydrogels. The pK_a value for PAAc is 4.75;[13] above this value dissociation of the acid groups takes place in the structure, resulting in the expansion of the IPN network. This behavior can be exploited in swelling controlled releasing systems since C-P-AAc IPNs are polyelectrolytes capable of swelling at the pH of intestines.[7,8]

In order to determine the most appropriate IPN for possible drug delivery application, alternating swelling experiments between two extreme pH values (1.1 and 7.4) with different amounts of crosslinker-containing C-P-AAc hydrogels were also performed. Each IPN was placed in a buffered solution of corresponding pH for 24 h and its swelling equilibrium values were determined. Figure 9 shows the plot obtained from

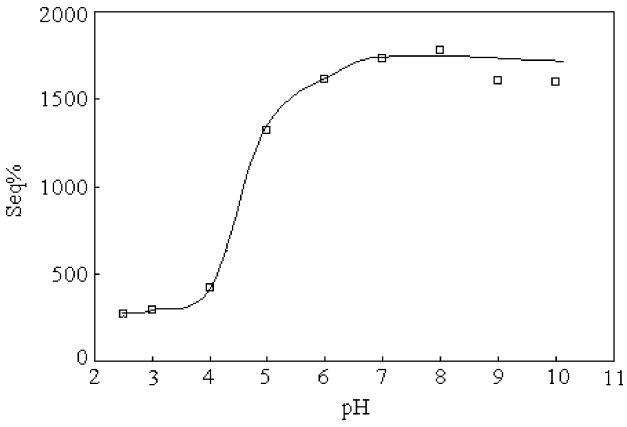

Figure 8. pH-sensitive swelling behavior of C-P-AAc/0.5 IPNs (37 °C).

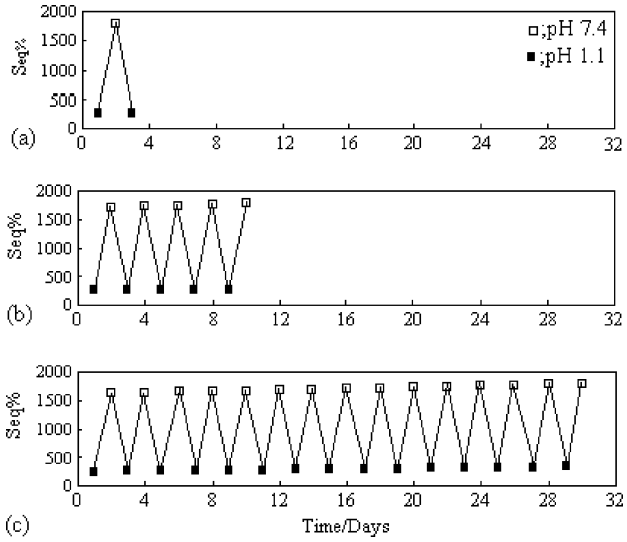

Figure 9. Alternating pH-sensitive swelling behavior of IPNs (37 °C): (a) C-P-AAc/0.5; (b) C-P-AAc/1.0; (c) C-P-AAc/2.0.

such swelling experiments. At the end of the third day the C-P-AAc/0.5 IPN was disintegrated, while the C-P-AAc/1.0 IPN lasted 10 days. On the other hand, the C-P-AAc/2.0 IPN retained its shape and integrity during the whole period of the experiments (30 days). From this result it can be presumed that the C-P-AAc/2.0 IPN structure is mechanically the strongest and can be used as the most suitable network structure for long-term delivery devices.

Drug release

Amoxicillin was selected as a model drug. Its chemical structure is shown Fig. 10(a). HCl–KCl (pH = 1.1) and Na_2HPO_4–KH_2PO_4 (pH = 7.4) solutions were used as releasing media. The percentage cumulative release (R) of amoxicillin from the IPNs was calculated using

$$R = \frac{M_t}{M_0} \times 100\% \quad (3)$$

where M_t is the amount of drug released at time t and M_0 is the initial loaded drug amount. Figure 10(b) depicts the percentage cumulative release (R) of amoxicillin from the IPNs at pH = 1.1 and 7.4, at 37 °C. The values of R are presented in Table 2. Figure 10(b) shows that drug release is pH dependent. The percentage cumulative release of amoxicillin from the IPNs was higher in the basic medium than in the acidic medium. The diffusion of the drug molecules out of the IPNs containing PAAc was enhanced because of swelling at higher pH. The extent of release increases as the hydrogel swelling increases due to the increase in pH, which leads to ionization of the carboxyl groups. It was observed that release results are very similar to swelling results. This parallel behavior is plausible since drug release from IPNs into solutions is *swelling-controlled*. From Fig. 10 it can also be said that the amount of drug released is not affected as significantly as at high pH (7.4) than low pH (1.1) with the increase in the amount of crosslinker. The percentage cumulative release of drug was 100% for C-P-AAc/0.5, 98% for C-P-AAc/1.0 and 96% for C-P-AAc/2.0 at pH 7.4.

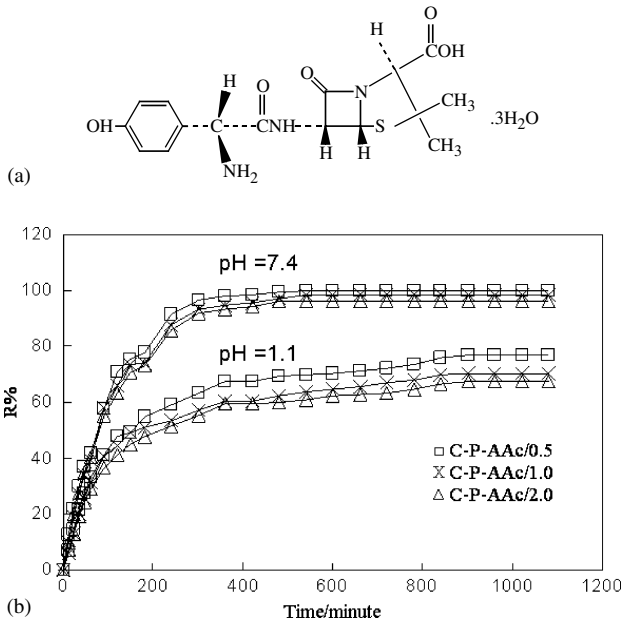

Figure 10. (a) Chemical structure of amoxicillin. (b) *In vitro* amoxicillin release profiles from IPNs at 37 °C.

Table 2. Release parameter of IPNs for different pH values

	R (%)	
IPN	pH 1.1	pH 7.4
C-P-AAc/0.5	77	100
C-P-AAc/1.0	70	98
C-P-AAc/2.0	67	96

The relative importance of macromolecular relaxation on the mechanism of drug release can be easily assessed by fitting experimental release data to the following equation and determining the exponent, n_{rel}:

$$C = \frac{C_t}{C_{eq}} = kt^{n_{rel}} \quad (4)$$

It is of paramount importance that Eqn (4) be applied only to the first 60% of the total amount of drug released. Here, C_t and C_{eq} are the amounts of drug released at time t and at equilibrium, respectively, k is a constant, and n_{rel} is the diffusional exponent.[15,16] From the plot of ln C *versus* ln t, the drug diffusion parameter, n_{rel}, was calculated. The exponent n_{rel} is an important indicator of the mechanism of transport and, in general, has a value between 0.5 and 1.0. When $n_{rel} = 0.5$, the release is Fickian. When $n_{rel} = 1.0$, the release is zero order; that is, the release is constant with time. In between these values, $0.5 < n_{rel} < 1.0$, the release is described as anomalous. The closer n_{rel} is to 1, the closer the release pattern is to a steady-state release.[17] The values of n_{rel} calculated in this work are in the range 0.7–1.0 at both pH values. It it possible that the release of amoxicillin could occur through a swelling-controlled mechanism.

CONCLUSIONS

A new pH-sensitive drug delivery system based on chitosan, PVP and PAAc is proposed. IPN hydrogels of C-P-AAc crosslinked with MBA and glutaraldehyde obtained in cylindrical shapes were evaluated for their mechanical and thermal behavior. TGA and TMA results suggested that the thermal stability and thermomechanical properties of IPNs were improved with an increase in amount of crosslinker (glutaraldehyde) in the IPNs structure.

The swelling kinetics of IPNs investigated at pH = 1.1 and 7.4 at 37 °C, together with amoxicillin release studies performed under the same conditions suggested that the swelling and release experiments follow second-order kinetics. The released amount of drug from the IPNs was higher at pH 7.4 than at 1.1. This phenomenon was explained on the basis of higher

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degree of swelling due to de-protonation of carboxylic groups in the network at pH = 7.4. Furthermore, the release time of amoxicillin from C-P-AAc IPNs to the simulated fluids (simulated gastric fluid SGF and simulated intestinal fluid) with different pH values was found to be in the range 7–10 h which is consistent with gastrointestinal transit time of oral dosage forms in the human body. Consequently, IPN hydrogels developed in this study may serve as a potential device for the delivery of drugs in which the primary target is the stomach or the upper small intestine.

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