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Vitamin B12 diffusion and binding in crosslinked poly(acrylic acid)s and poly(acrylic acid-co-*N*-vinyl pyrrolidinone)s

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ABSTRACT

The diffusion mechanism of vitamin B12 in two types of crosslinked hydrogels, poly(acrylic acid) (cPAA) and copolymers of acrylic acid and *N*-vinyl pyrrolidinone (cP(AA-NVP)) was studied. The PAA and P(AA-NVP) synthesized by three different degrees of crosslinking have limited water absorption capabilities ranging from 3% to 18%. In the copolymers permeability of B12 is controlled by both intramolecular and intermolecular hydrogen-bonding between the pyrrolidinone and carboxylic acid side chains. The diffusion kinetic data in two types of polymers were best described by Peppas models instead of Higuchi models. Permeation from both crosslinked PAA and P(AA-co-NVP) copolymers followed a Super Case II transport mechanism, most likely driven by macromolecular chain relaxation and swelling of hydrophilic polymers. A special FTIR spectroscopic method for drug binding study, FTIR difference spectroscopy, is used to probe the strong interactions between vitamin B12 and the side chains of the hydrogels. The FTIR differential spectra of B12 in PAA hydrogels revealed dramatic changes of the spectral marker bands of B12 after binding in the crosslinked gels, indicating significant interactions occurring in the amide and phosphate moieties of B12. Such interactions retard the diffusion of vitamin B12.

1. Introduction

Hydrogels are polymeric networks that are formed by chemical or physical crosslinking of individual polymer chains, but absorb large quantities of water in aqueous solutions. The strong hydrophilic nature of hydrogels may present many unique physicochemical properties that make them advantageous for biomedical applications including drug delivery (Tanaka et al., 1980; Lin and Metters, 2006). Limited water-absorption capabilities (ca. 5–10 wt%) of certain polymeric networks, for example, poly(lactic acid) (PLA) or poly(lactide-co-glycolide) (PLGA), exhibit the ability to retain the drugs for longer periods (O'Hagan et al., 1994; Rafati et al., 1997).

In practice, the networks can be formed by various methods: γ-irradiation (^{60}Co) (Minkova et al., 1989; Lambov et al., 1997a,b; Rosiak and Ulansky, 1999a; Rosiak and Yoshii, 1999b) or UV irradiation (Tsvetanov et al., 1998; Doytcheva et al., 2001) on different biomaterials. Chemically crosslinked hydrogels were developed in the past as carriers for drugs (Vervoort et al., 1998; Qiu and Park, 2001). The controlled drug delivery devices can assure a sustained release and targeted effect (Griffith, 2000). The great advantage of the drug-controlled release from the hydrogels is a possibility for improvement of patient compliance (Park, 1993; Peppas and Brazel, 1994). In recent years, polyacrylic acid (PAA) and its copolymers have often been used as carriers in drug-release systems, because of their multifunctional nature, unique properties and good biocompatibility (Dittgen et al., 1997; Barbu et al., 2005; Devine et al., 2006). Barbu et al. (2005) have studied vinylpyrrolidone-co-(meth)acrylic acid inserts for ocular drug delivery. Copolymeric hydrogels constituting of vinylpyrrolidone and acrylic or methacrylic acid repeat units have been prepared and investigated for their ability to act as controlled release vehicles in ophthalmic drug delivery. In vitro release experiments showed that some of these materials could be useful vehicles for the delivery of drugs such as pilocarpine or chloramphenicol, while in vivo studies, using the rabbit model, confirmed their high potential for the controlled ocular delivery of pilocarpine hydrochloride.

Inter-polymer complexes between poly(vinyl pyrrolidinone) (PVP) and poly(acrylic acid) have been investigated in order to develop new mucoadhesive drug carriers by taking the advantages of hydrogen-bonding between the carboxyl groups of PAA and the carbonyl groups of PVP. The adhesive forces of the PVP/PAA inter-polymer complexes could be higher than that of commercial Carbopol 971. Moreover, the adhesive force and the drug-release rate can be controlled by changing the mole ratios of PVP and PAA as

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well as the pH values. The complex appears to be an adequate carrier for the mucoadhesive drug delivery system (Chun et al., 2002).

A controlled release of vitamin B12 can increase its blood serum levels and liver concentrations in human for prevention or treatment of cobalt deficiency. Sustained levels of B12 can be maintained in the patient's system to alleviate the symptoms of allergic rhinitis (hay fever), allergic asthma, pernicious anemia (Armstrong et al., 2001), and ease pain associated with a generalized or focal peripheral neuropathic condition, such as carpal tunnel syndrome (Stuart, 2007). In this study, we investigate the PAA-based hydrogels chemically crosslinked for retarded release of vitamin B12. Crosslinked copolymers of acrylic acid (AA) with *N*-vinyl pyrrolidinone (NVP) were synthesized and their interactions with B12 during diffusion were compared with crosslinked homopolymers of acrylic acid. The copolymer can form both intra- and inter-polymer complexes between the PVP and PAA components, and its vitamin B12 release kinetics is compared with that of PAA. Strong specific interactions between B12 and the crosslinked polymer gels are found to be significantly present in such systems by using FTIR difference spectroscopy.

2. Materials and method

2.1. Materials and instrumentation

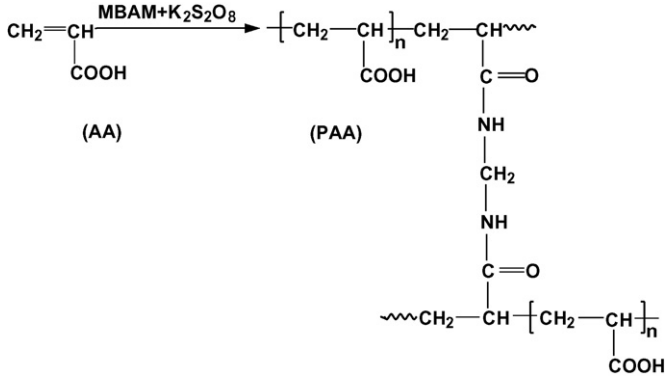
Acrylic acid, potassium persulfate, vitamin B12 (α-(5,6-dimethylbenzimidazolyl)cobamidcyanide), N,N′-methylenebis(acrylamide) (MBAM), and poly(*N*-vinyl pyrrolidinone) available from Sinopharm were used as received. *N*-vinyl pyrrolidinone (NVP) monomer was obtained from Hangzhou Nanhang Co.

Infrared spectra (IR) were collected on Thermo Nicolet Nexus 310 Fourier transform (FT) infrared spectrometer. UV–visible absorption spectra were recorded on HP8453 spectrophotometer.

2.2. Preparation of crosslinked PAA and PAA-PVP copolymer hydrogels

0.600 g of AA were diluted by 10 mL of distilled water, and mixed thoroughly with the initiator potassium persulfate (by 1 wt% of AA) and the crosslinker MBAM at an AA/MBAM weight ratio of 8%, 12%, and 16%, and heated for 1 h at 70 °C to form PAA gels (see the reaction in Scheme 1). The nominal crosslinking ratio, XR, was defined as the ratio of moles of crosslinker MBAM per mole of total polymer repeating unit, in percentage. After cooling, the gels were soaked in distilled water for 4–5 h to remove unreacted AA, and dried in vacuum at 80 °C for 5 h to form crosslinked PAA membranes with constant weights.

0.500 g of AA, 0.100 g of NVP (molar ratio = 7.7:1.0), and MBAM with a weight percentage of 8%, 12% and 16%, respectively, were diluted with 10 mL of distilled water, and mixed thoroughly with potassium persulfate at 1 wt%. The mixtures were heated at 70 °C for 1 h to form hydrogels. After cooling the gels were soaked in distilled water for 3–5 h, and vacuum dried at 80 °C for at least 5 h to form uniform crosslinked copolymer membranes with constant weights.



Scheme 1. Crosslinking of Acrylic Acid by MBAM.

2.3. Characterization

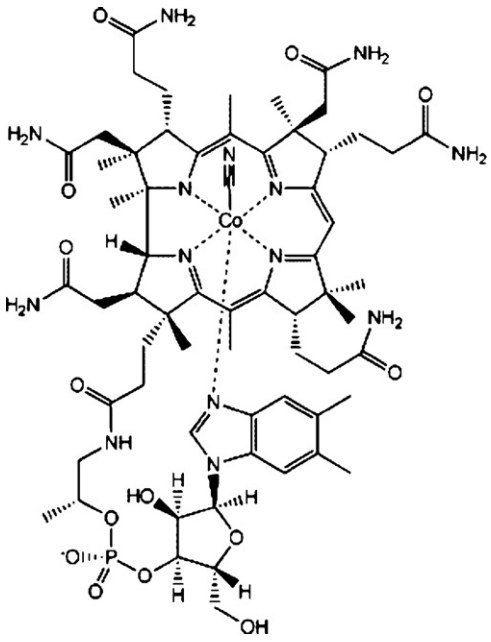
The equilibrium swelling ratios ESR% were calculated after the dried gels were swollen completely with water and their weights (m_e) were measured to calculate the absorbed water weight by subtracting the dried gel weight (m_d):

$$\text{ESR } (\%) = \frac{m_e - m_d}{m_d} \times 100\%$$

Permeation test was performed by using a horizontal Valia-Chien cell assembly held on a magnetic stirrer. A hydrogel film was sandwiched between two circular windows, each on a half-cell positioned side-by-side. 200 mL of phosphate buffer (50 mM, pH 7.0) water were added to fill the receptor half-cell. The donor half-cell was filled with 200 mL of a vitamin B12 solution (0.005 g/mL, in 50 mM phosphate buffer, pH 7.0). 20 mL of the permeated solution were withdrawn from the receptor cell at a time interval of every 1 h and 20 mL of distilled water was added immediately to compensate the receptor solution.

In order to determine the concentration of vitamin B12 (see chemical structure in Scheme 2), 10 mL of B12 solutions were prepared in phosphate buffer (50 mM, pH 7.0) distilled water at different concentrations (x, in 10^{-2} g/mL), and the absorbance values (y) at 362 nm were measured to obtain a standard calibration line $y = 18074x + 0.0281$ with a linear regression coefficient of $R^2 = 0.9998$.

In the binding study, FTIR spectra were obtained from the vacuum dried hydrogel membranes before and after vitamin B12 had diffused in the above permeation tests. The FTIR spectrum of the B12-free membrane was subtracted from that of the permeated membrane in order to cancel out the spectroscopic signals of the membrane material. The resulting difference spectrum shows the spectral features that were attributed to those of vitamin B12 in the membrane, as well as the features that were ascribed to the



Scheme 2. Structure of vitamin B12.

Table 1
Equilibrium swelling ratio (ESR%), permeability coefficient (P), and release exponent (n) of PAA and P(AA-co-NVP) hydrogels with different nominal crosslinking ratios (XR, in percentage).

Hydrogel sample	cPAA 8%	cPAA 12%	cPAA 16%	cP(AA-NVP) 8%	cP(AA-NVP) 12%	cP(AA-NVP) 16%
XR (%)	3.7	5.6	7.5	4.0	6.0	7.9
ESR (%)	9.25	5.68	3.68	18.5	8.3	4.48
P (cm/h)	0.0397	0.0277	0.0128	0.0367	0.0365	0.0301
n	1.735	2.135	2.222	1.414	1.650	1.128

side chain groups of the polymers tightly bound to B12, therefore giving the perturbed spectral bands of the polymers that cannot be subtracted out.

3. Results and discussion

3.1. Diffusion of vitamin B12 in crosslinked PAA and P(AA-co-NVP) hydrogels

The first type of PAA hydrogels was synthesized by polymerization of acrylic acid with three different weight percentages (8%, 12% and 16%) of crosslinker N,N′-methylenebis(acrylamide). In comparison, the second type of hydrogels was synthesized by copolymerization of acrylic acid and *N*-vinyl pyrrolidinone in a fixed molar ratio = 7.7:1.0, with three different weight percentages (8%, 12% and 16%) of crosslinker N,N′-methylenebis(acrylamide) used. The hydrogels thus prepared, cPAA and cP(AA-co-NVP), are flexible membranes with a limited water absorption capability. The nominal crosslinking ratio, XR, defined as the ratio of molar amount of crosslinker MBAM to that of polymer repeating unit, in percentage, varies only from 3.7% to 7.9% for the cPAA and cP(AA-co-NVP) membranes. As shown in Table 1, with increasing amount of the crosslinker used in the preparation, the equilibrium swelling ratio (ESR) of the hydrogels decreases. Table 1 also indicates that the copolymer bearing a large pyrrolidinone ring swelled more than the homopolymer PAA. As the amount of crosslinking agent was increased, the space used as the diffusional space between the crosslinks became smaller.

In vitro release profiles of vitamin B12 in cPAA and cP(AA-co-NVP) are shown in Figs. 1 and 2, respectively. They represent the early release kinetics of the B12 solute. Linear regression of

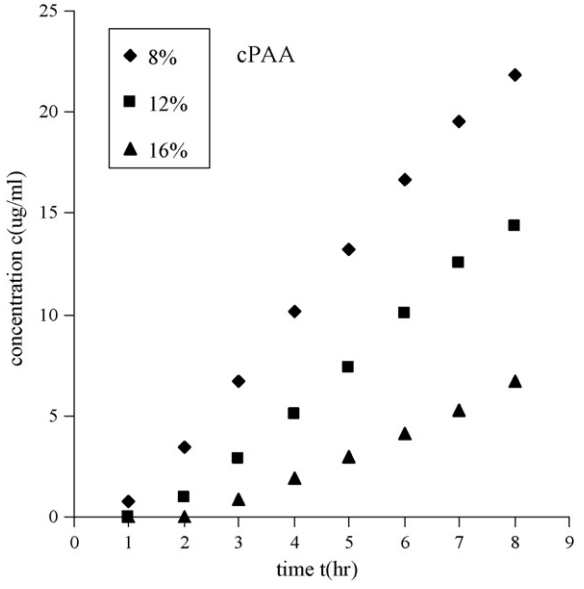


Fig. 1. In vitro release profiles of vitamin B12 in cPAA with (♦) 8 wt%; (■) 12 wt%; (▲) 16 wt% of crosslinker MBAM.

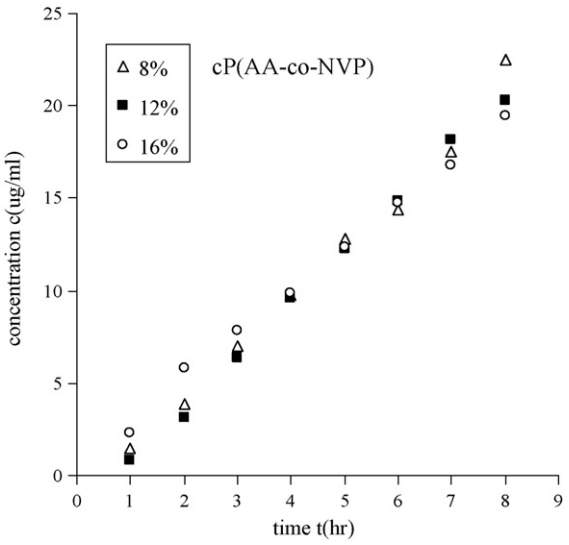


Fig. 2. In vitro release profiles of vitamin B12 in cP(AA-co-NVP) with (△) 8 wt%; (■) 12 wt%; (○) 16 wt% of crosslinker MBAM.

B12 concentration (c, in μg/mL) in the acceptor half-cell *versus* time (t, in h) gives the relationships for release in all cPAA and cP(AA-co-NVP) prepared, listed in Table 2. Apparently, permeation of B12 through the hydrogel membranes was almost linear. In cPAA, the higher the nominal crosslinking ratio, the slower vitamin B12 is permeated. However, in the copolymers cP(AA-co-NVP), the amount of B12 permeated becomes quite insensitive to the amount of the crosslinker used, in contrast to the behavior of cPAA. In these copolymers, the molar percentage of the NVP repeating unit is about 11% in the macromolecular network, much higher than the nominal crosslinking ratio introduced by the MBAM used. The pyrrolidinone side chains can form both intramolecular and intermolecular hydrogen-bonding with the carboxylate side chains, resulting in higher "crosslinks" in this type of copolymer gels. Thus the B12 release kinetics in the copolymers is controlled by both the chemical crosslinker introduced and the new hydrogen-bonding between the side chains.

Permeability coefficients (P) were calculated by using the following equation (Peppas and Wright, 1996, 1998):

$$-\ln\left(1-\frac{2C_t}{C_o}\right)=\frac{2A}{V}Pt \quad (1)$$

Table 2
Apparent correlation between the vitamin B12 concentration c in the acceptor half-cell and time t during the in vitro diffusion of B12 in PAA and P(AA-Co-NVP) hydrogels with different degrees of crosslinking. R^2: correlation coefficient.

Hydrogel sample	Correlation
cPAA 8%	$c = 3.1040t - 2.4415$, $R^2 = 0.9982$
cPAA 12%	$c = 2.1678t - 3.1022$, $R^2 = 0.9908$
cPAA 16%	$c = 1.0043t - 1.7762$, $R^2 = 0.9724$
cP(AA-NVP) 8%	$c = 2.8694t - 1.7291$, $R^2 = 0.9897$
cP(AA-NVP) 12%	$c = 2.8519t - 2.1485$, $R^2 = 0.9982$
cP(AA-NVP) 16%	$c = 2.3524t + 0.5695$, $R^2 = 0.9966$

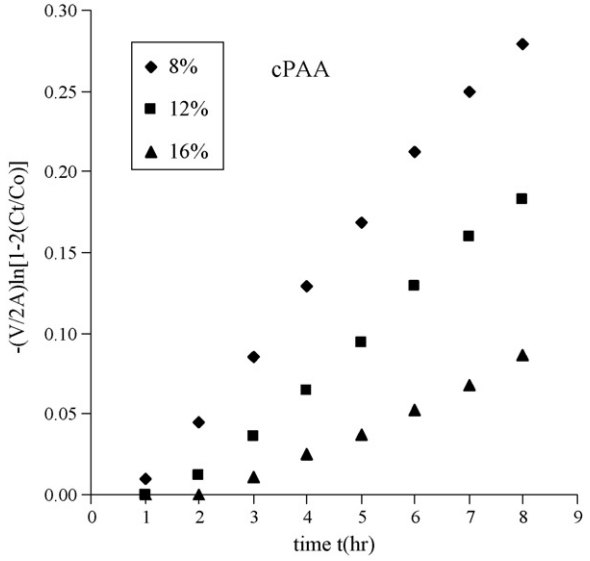


Fig. 3. Determination of the permeability coefficient for vitamin B12 through cPAA hydrogels crosslinked by 8 wt% (♦), 12 wt% (■) and 16 wt% (▲) of MBAM.

where C_t is the concentration of vitamin B12 in the receptor half-cell at time t, C_0 is the initial concentration of B12 in the donor half-cell (0.005 g/mL), V is the volume of the each half-cell (200 mL), A is the effective area of the permeation window (1 cm^2), and P is the permeability coefficient of the membrane. A plot of $-(V/2A)\ln[1-2(C_t/C_0)]$ *versus* t gave the slope P. The calculated permeability coefficients P are shown in Figs. 3 and 4 for two types of polymers, respectively. Table 1 also summarizes the permeability coefficients for the two types of polymer hydrogel samples. For cPAA hydrogels, the permeability coefficients P are reduced dramatically when the nominal crosslinking ratio XR is increased. The P value is reduced by more than 68% when the nominal crosslinking ratio is doubled from 3.7% to 7.5%. However, for cP(AA-co-NVP) copolymer, the permeability coefficients P are reduced marginally when the nominal crosslinking ratio XR is increased; the value of the copolymer is reduced by less than 20% when the nominal crosslinking ratio is almost doubled from 3.7% to 7.4%, and the values are actually higher than those of the corresponding cPAA hydrogels at the same nominal crosslinking ratios. The presence of the large pyrrolidinone ring brings about more open pores for B12 diffusion even though the copolymers have more crosslinking sites introduced by hydrogen-bonding.

3.2. Cumulative release analyzed by different kinetic models

Peppas et al. used a simple empirical equation to describe the general solute release behavior from controlled release polymer matrices (Korsmeyer et al., 1983):

$$\ln M_t = n \ln t + C \tag{2}$$

where M_t is the cumulative fraction of drug released, C is the kinetic constant, t is release time and n is the diffusional exponent for drug release. The above equation could adequately describe the release of solutes from slabs, spheres, cylinders and discs, regardless of the release mechanism (Ritger and Peppas, 1987). The log value of cumulative amount ($\ln M_t$) of B12 released at time t is plotted against $\ln t$. In general, if the diffusional exponent $n < 0.45$, the diffusion is Fickian; when $0.45 < n < 0.89$, the drug diffusion follows non-Fickian transport mechanism, corresponding to coupled effect of diffusion and polymer relaxation/erosion; $n > 0.89$, the diffusion is mainly aided by polymer erosion. $n = 1$ indicates zero-order release mechanism (Case II transport mechanism). Values of $n > 1$ indicate Super Case II transport mechanism, implying swelling and relaxation of hydrophilic polymer chains help to transport.

The following equation is used to estimate the cumulative amount of vitamin B12 released

$$M_t = \frac{V\rho_n + \sum_{i-1}^{n-1} \rho_i V_i}{A} \tag{3}$$

where M_t is cumulative release amount (in grams), A is the effective permeation area (1 cm^2), V is the receptor half-cell volume (200 mL), ρ_n and ρ_i are the receptor half-cell's concentration at the nth sampling and at the ith sampling, respectively, V_i is the sampling volume (20 mL). We find that the cumulative release of B12 can be fitted by the above Peppas Eq. (2) very well for both cPAA and cP(AA-co-NVP) (see Figs. 5 and 6). The fitting results are listed in Table 3. It is of note that the linear regression coefficients R^2 are in the range from 0.9871 to 0.9935. The release exponent values (n) of all the hydrogels are found to be larger than 1, indicating a swelling- and relaxation-assisted Super Case II transport mechanism. Furthermore, the release exponents from the copolymer hydrogels are lower than those from the cPAA hydrogels.

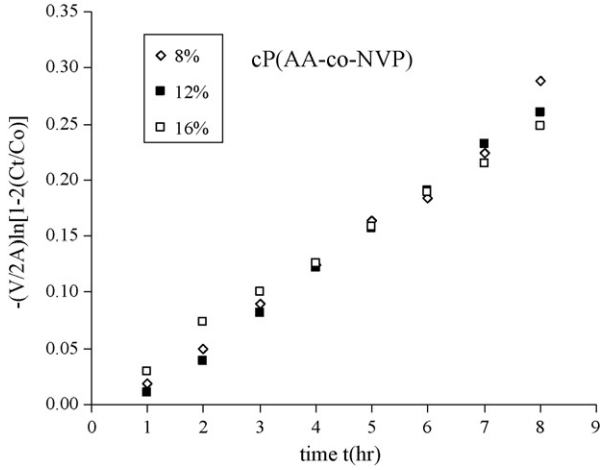


Fig. 4. Determination of the permeability coefficient for vitamin B12 through cP(AA-co-NVP) hydrogels crosslinked by 8 wt% (◊), 12 wt% (■) and 16 wt% (□) of MBAM.

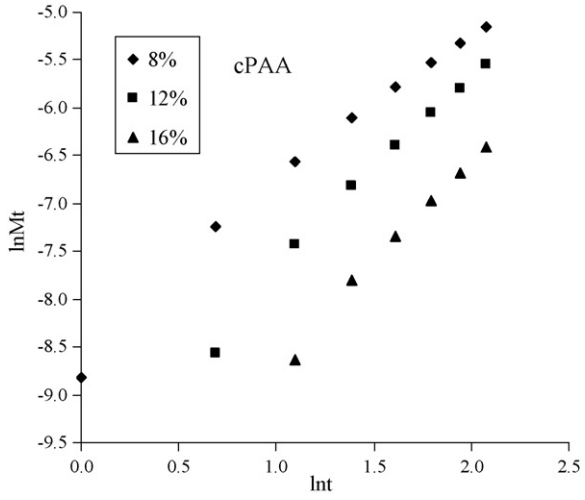


Fig. 5. Diffusion of B12 through cPAA analyzed by Peppas equation. (♦) 8 wt%; (■) 12 wt%; (▲) 16 wt% of MBAM.

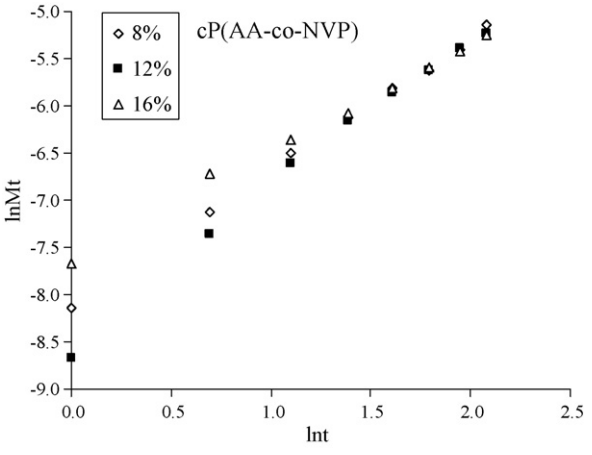


Fig. 6. Diffusion of B12 through cP(AA-co-NVP) analyzed by Peppas equation. (◇) 8 wt%; (■) 12 wt%; (△) 16 wt% of MBAM.

The diffusion of vitamin B12 was also examined by using Higuchi model,

$$M_t = kt^{1/2} + b. \quad (4)$$

In every case, the fitting results using Higuchi model are found to be worse than those obtained by using the Peppas Eq. (2). As shown in Table 3, the linear regression coefficients R^2 from the Higuchi model are only 0.9590, 0.9080, and 0.885, respectively, for cPAA. Similar correlation coefficients worse than those from the Peppas Eq. (2) were obtained for cP(AA-co-NVP) hydrogels.

3.3. FTIR study of binding of vitamin B12 in PAA and P(AA-co-NVP) hydrogels

In order to understand vitamin B12 transport mechanism, Fourier transform infrared spectroscopy was used to probe interactions between B12 and polymer matrix. In the past, the technique is usually employed by recording the raw data of FTIR spectra of the polymer membranes and the membranes with drugs loaded. The spectra are often dominated by the intense bands of the polymer matrix, and even broad intense water bands, with a few minor bands showing the identity of the drug inside. The spectroscopic features of the drug solutes are more often buried under the broad polymer bands. In this study, a special FTIR spectroscopy technique, FTIR difference spectroscopy, is employed to probe direct measurements of changes in the B12's corrin ring resulting from B12/macromolecule interactions and surrounding groups of B12 from the side chains of the polymers. In this method, the FTIR spectra were obtained from the vacuum dried hydrogel membranes before and after vitamin B12 had diffused in the above permeation tests. The FTIR spectrum of the B12-free membrane could be subtracted out from that of the permeated membrane, and the intense spectroscopic signals of the hydrogel material unperturbed during drug solute binding were cancelled out. The resulting difference spectrum shows the spectral features that are attributed to those of vitamin B12 in the hydrogel, as well as the features that were

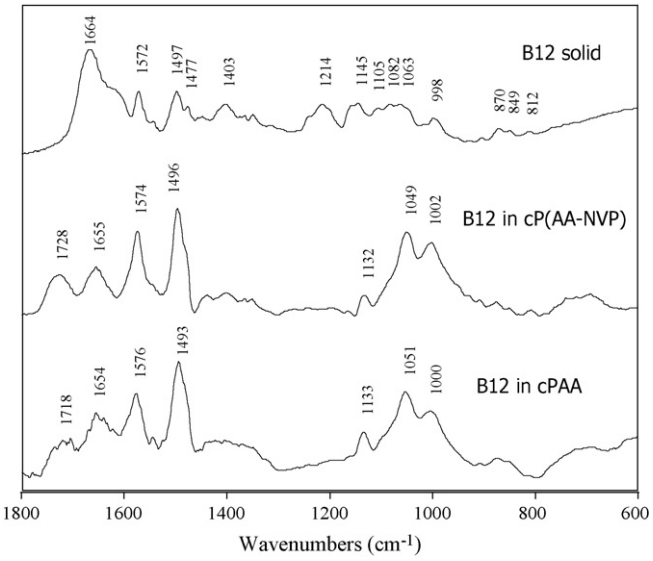


Fig. 7. FTIR spectra of B12 in the range 1800–600 cm^{-1}: (a) free B12 in solid state; (b) bound to cP(AA-co-NVP); (c) bound to cPAA.

ascribed to the side chain groups of the polymers tightly bound to B12, giving the perturbed spectral bands of the polymers that cannot be subtracted out.

Structural markers have been identified for corrinoids moiety of B12 in the physiological state. The major band (denoted as Band B), which occurs at ca. 1664 cm^{-1} in the solid powder state (Fig. 7), is due to the amide I C=O stretching mode of the propionamide side chains of the corrin ring (Taraszka et al., 1991) (see Scheme 2 for B12 structure). Upon binding in the hydrogels of PAA with nominal crosslinking ratio XR = 3.7% and of P(AA-co-NVP) with nominal crosslinking ratio XR = 4.0%, the frequency of Band B is downward shifted to about 1655 cm^{-1} in Fig. 7 due to the greater hydrogen-bonding properties of surrounding functional groups that stabilize the charged amide resonance form. Since Band B monitors the interaction of the propionamides in B12 with the polymer matrix, the spectral changes indicate that these groups are important in B12 binding. A medium intensity band at 1572 cm^{-1} (denoted as Band C) is attributed to a breathing mode of the corrin ring of B12 on the basis of the band's solvent independence and its sensitivity to changes in axial ligation (Taraszka et al., 1991). As the σ-donating strength of the axial ligands coordinated to the cobalt metal is weakened, the frequency of Band C increases by a few wavenumbers in the hydrogels, possibly indicating a shortening of the corrin conjugated system. Band A, the known cyanide stretching frequency at 2135 cm^{-1} (see Fig. 8), probes the cobalt-carbon distance in cyanocorrinoids of B12. As the frequency of Band A increases to 2140 cm^{-1} upon binding in the hydrogels, the cobalt–cyanide bond strength decreases (Fig. 8).

New bands near 1728 or 1718 cm^{-1} have appeared in the spectra of B12 bound in the hydrogels (Fig. 7). These bands are due to the carboxylic acid groups surrounding the B12 that have changed their interactions after binding of B12. Previous FTIR study indicated

Table 3
Mathematic modeling and drug-release kinetics of B12 from different hydrogels (R^2: correlation coefficient).

Hydrogel sample	Peppas equation	Higuchi equation
cPAA (8%)	$\ln M_t = 1.7348 \ln t - 8.6134$, $R^2 = 0.9871$	$M_t = 0.00314t^{1/2} - 0.0036$, $R^2 = 0.9590$
cPAA (12%)	$\ln M_t = 2.1353 \ln t - 9.8948$, $R^2 = 0.9905$	$M_t = 0.00213t^{1/2} - 0.0027$, $R^2 = 0.9080$
cPAA (16%)	$\ln M_t = 2.2223 \ln t - 10.977$, $R^2 = 0.9925$	$M_t = 0.00091t^{1/2} - 0.0012$, $R^2 = 0.885$
cP(AA-co-NVP) (8%)	$\ln M_t = 1.4142 \ln t - 8.1073$, $R^2 = 0.9982$	$M_t = 0.00292t^{1/2} - 0.0032$, $R^2 = 0.9402$
cP(AA-co-NVP) (12%)	$\ln M_t = 1.6498 \ln t - 8.5488$, $R^2 = 0.9933$	$M_t = 0.0029t^{1/2} - 0.0033$, $R^2 = 0.9576$
cP(AA-co-NVP) (16%)	$\ln M_t = 1.1284 \ln t - 7.6067$, $R^2 = 0.996$	$M_t = 0.00257t^{1/2} - 0.0025$, $R^2 = 0.9645$

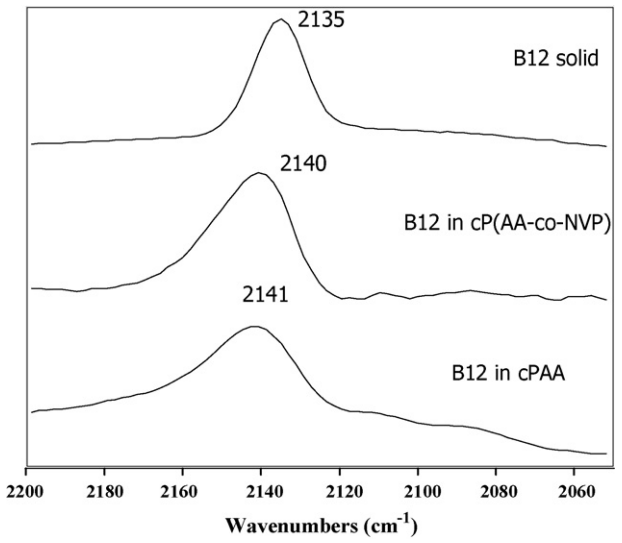


Fig. 8. FTIR spectra of B12 in the range 2200–2050 cm^{-1}: (a) free B12 in solid state; (b) bound to cP(AA-co-NVP); (c) bound to cPAA.

that the carboxylic acid side chains in PAA have a band at this region (Dong et al., 1997), which is a good indicator of the hydrogen-bonding forms of the carboxylic acid group. The 1060 cm^{-1} band in B12 before binding (Fig. 7) is assigned to the PO_3^- degenerate stretching of the phosphate moiety in B12; the 998 cm^{-1} band is assigned to PO_3^- symmetric stretching (Tsuboi, 1974). The two absorption bands at 1060 and 998 cm^{-1} are sensitive to direct metal–phosphate coordination. The FTIR spectra of the structurally known nucleotides with metals, containing direct metal–phosphate bonding, showed shifting and splitting of these two bands, whereas the infrared spectra of the complexes containing an indirect metal–phosphate interaction, through coordinated water molecules exhibited no considerable changes in these vibrational frequencies (Tajmir-Riari and Theophanides, 1985). The infrared spectra in Fig. 7 showed that the bands due to the phosphate groups in B12 near 1060 and 998 cm^{-1} have not only moved slightly to 1050 and 1000 cm^{-1}, but increased their intensities significantly in the cPAA and copolymers, indicating direct interactions between the phosphate groups in B12 and metal ions.

It's interesting to compare the present results with those similar hydrogels reported in the literature. The cPAA and cP(AA-co-NVP) hydrogels bear some resemblance to the commercial carbomers or crosslinked Povidone in terms of chemical compositions. Llabot et al. (2004) have studied the drug release from carbomer/carbomer sodium salt matrices as mucoadhesive drug delivery model. In vitro mucoadhesion water absorption and drug release of nystatin from matrices of commercial carbomer (C) and lyophilized carbomer sodium salt (CNaL) mixtures were evaluated. Matrices in which carbomer was replaced by lyophilized carbomer showed an increase of both water uptake and release rates. Moreover, the release of nystatin from matrices CL/CNaL exhibited kinetics with Super Case II ($n > 1$) mechanism. However, for C/CNaL matrices, drug release was slower and exhibited a complex biphasic profile with a first stage characterized by either an anomalous ($n < 1$, for C > 50%) or a Case II ($n \sim 1.0$, C < 50%) mechanisms. After that period, the mechanism changed to Super Case II transport ($n > 1$).

Dengre et al. (2000) have studied release of vitamin B12 from hydrogels composed of poly(*N*-vinyl-2-pyrrolidone) and crosslinked polyacrylamide as a function of the degree of crosslinking and pH of the external swelling media. The three drug-loaded hydrogel samples synthesized with different crosslinking ratios of 0.3, 0.7, and 1.2 (in mol%) follow different drug-release mechanisms, that is, chain relaxation with zero-order, non-Fickian and Fickian, or diffusion-controlled mechanisms. This seems to be rather more complicated than what we find here.

Yaung and Kwei (1998) have studied swelling and controlled release of pH-sensitive hydrogels based on poly(vinylpyrrolidone)–poly(acrylic acid) (PVP–PAA) semi-interpenetrating networks (semi-IPN). The photopolymerized complexes of poly(vinylpyrrolidone)–poly(acrylic acid) prepared from a mixture of PVP and acrylic acid showed that caffeine release rate from the semi-IPN film followed Fick's law. The rate of release was higher in dissolution media having pH above a critical value of about 3.8. Control of caffeine release from the semi-IPN film was realized by changing cyclically the pH of dissolution medium between 0.1N HCl solution and pH 6.0 phosphate buffer.

4. Conclusions

The vitamin B12 release kinetics in the copolymers cP(AA-co-NVP) is controlled by both the new hydrogen-bonding between the pyrrolidinone and carboxylic side chains, as well as the chemical crosslinker introduced, unlike the homopolymer cPAA. The permeability coefficient of the hydrogels decreases with the increasing degree of crosslinking and decreasing swelling ratio. At the same degree of crosslinking for cPAA and cP(AA-co-NVP), the copolymers have larger swelling ratios and permeability coefficients than the cPAA. This can be caused by the pyrrolidinone ring larger than the carboxylic acid side group, therefore creating larger free spaces.

The diffusion of B12 can be described by the Peppas equation. The diffusion mechanism of B12 is a Super Case II transport with the diffusion exponent $n > 1$. Similar mechanism was found in certain types of commercial carboxylmethyl cellulose, carbomers, and alginate gels in neutral pH (Llabot et al., 2004; Tanwar et al., 2007; Sriamornsak and Sungthongjeen, 2007). FTIR difference spectroscopy reveals that strong specific interactions have perturbed the propionamides, cobalt–cyanide bond, and the phosphate groups in B12, leading to the retarded diffusion of B12 through the hydrogels.

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