Synthesis and Properties of Hydrogels of Poly(Acrylic-Co-Acroloyl β-Cyclodextrin)

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ABSTRACT: Novel acrylic monomers (β-CD-A and β-CD-6-EA) containing β-cyclodextrin (β-CD) with different extent of substitution were prepared by using dicyclohexylcarbodiimide (DCC) as a condensation agent at room temperature. Two kinds of functional hydrogels were also synthesized by copolymerization of β-CD-A and β-CD-6-EA with acrylic acid (AAc) using a redox initiator system in aqueous solution. The nuclear magnetic resonance (^{1}H NMR), infrared spectroscopy (IR), thermogravimetric analysis (TGA) were employed to character the molecular structures of β-CD modified monomers and their copolymers. The swelling experiments indicate that the hydrogels with different equilibrium swelling ratio (ESR) possess obvious pH-sensitivity and distinct dynamic swelling behavior. Using an anti-cancer drug, chlorambucil (CHL), able to form complexes with β-CD in water, as a model compound, the controlled drug release behaviors of these hydrogels were investigated. The release behavior of CHL from two kinds of hydrogels synthesized reveals that the release rate of CHL can be effectively controlled by pH values, cross-linking density, and β-CD content. In addition, it is found that the β-CD with the proper frame and concentration can increase release efficiency of CHL from the hydrogels. © 2009 Wiley Periodicals, Inc. J Appl Polym Sci 113: 3068–3077, 2009

Key words: β-cyclodextrin; hydrogel; pH-sensitivity; controlled drug release

INTRODUCTION

The functional polymers used as controlled drug release carriers were extensively studied. The researches were mainly focused on the syntheses and preparations of various systems, such as injectable microparticles based on poly(ethylene glycol) and ploy(propylene fumarate) biodegradable polymers,[1,2] the nanospheres based on poly(ethylene glycol)/poly-(D,L-Lactide)amphiphilic diblock copolymers,[3] membrane-encased polymer millirods based on poly(D,L-Lactide-co-glycolide)[4], chitosan-alginate sponges,[5] and so on. In these studies, various small molecular drugs including anticancer drugs and antibacterial drugs were also encapsulated into the polymer matrixes to obtain a sustained controlled release. Although many novel polymers with various functional architectures for applications of drug release carriers have been synthesized via advanced polymerization techniques,[6–8] there were a few publications which dealt with cyclodetrix based polymer.

In our previous publications,[9–14] we reported a serial of novel controlled drug release systems—the cyclodextrin based polymers with both molecular inclusion ability, thermal, and pH sensitivities. In these studies, we designed and synthesized several functional copolymers in which poly(N-isopropylacrylamide) (PNIPAM) and β-cyclodextrin (β-CD) were used as the main components. The copolymers synthesized including hydrogels, interpenetrating networks and linear block polymers possess different macromolecular structures with distinct physical properties. We have studied the art of the copolymer's syntheses, and systematically characterized their fine macromolecular structures as well as their molecular inclusion and environment responsive behaviors. Besides, by incorporating some anti-cancer drugs into the matrixes of these copolymers, we found that all the samples present markedly controlled drug release functions via the volume phase change of copolymers at the various environment conditions. The researches also revealed that the β-CD can effectively modify the molecular interactions between the polymer matrix and the drug, as a result, control the drug release.

In this article, we reported another novel poly (acrylic acid-co-β-cyclodextrin- acrylate) based hydrogel with both molecular inclusion ability and environment sensitivity. It is well known that various polyacrylic acid based hydrogels with pH

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sensitivity have been synthesized and studied in recent years.[15–17] However, there are few reports about polyacrylic acid based hydrogels containing β-CD segments which not only possess pH sensitivity but also have molecular inclusion function. In previous studies,[9,11,14,18] the most of hydrogels were used by multifunctionalized CDs as crosslinker, and the few with monofunctional CDs as pendant groups. As we know, the hydrogel's property dependent on their structure. For the purperse of research on function of β-cyclodextrin included in different macromolecular structures hydrogels to the controlled drug release, two kinds of hydrogels poly(acrylic acid-co-β-cyclodextrin- acrylate) (AAc-β-CD-A) and poly {acrylic-co- [6-(2-acryloylaminoethyl) amino]-β-CD} (AAc-β-CD-6-EA) were synthesized using two kinds of β-CD modified monomers β-cyclodextrin acrylate (β-CD-A) and [6-(2-acryloylaminoethyl) amino]-β-CD (β-CD-6-EA). To clearly identify the molecular structures for both monomers and copolymers, FTIR, NMR measurements were employed to character the products. The pH sensitivities for the hydrogels were also studied via swelling experiments. Finally, the controlled drug release characters were investigated by loading chlorambucil (CHL), an anti-cancer drug able to form complexes with β-CD,[19] into the hydrogels via measuring the cumulative release of CHL at 6.8 pH values in aqueous solution.

EXPERIMENTAL

Materials

β-CD, a biochemical reagent, was obtained from Shan-Tou Chemical Factory in China, and purified two times by recrystallization from water before using. *p*-Toluensulfonyl chloride (*p*-TsCl) and *N*,*N*-methylene-bis(acrylamide) (BIS, crosslinker) were of chemical grade. Mono-6-OTs-β-CD used in the article was synthesized according to the method reported in the literature.[20] Dicyclohexylcarbodiimide (DCC) was purchased from Aldrich, USA (99% purity). CHL was from Fluka Chemie. Other reagents including ammonium persulfate (APS), sodium bisulfite (SBS), *N*,*N*-dimethylformamide (DMF), and acrylic acid were all analytical-grade made in China, and were used as received without further purification.

Synthesis of β-cyclodextrin acrylate (β-CD-A)

Calculated amount of β-CD and DCC were first dissolved in DMF, and then, stoichiometric amount of acrylic acid against DCC was added dropwise to the vigorously stirred β-CD solution at room temperature. After reaction for 30 min, the mixture was continuously heated for a short time, and then, the reaction was stopped. A solid precipitate, *N, N′*–dicyclohexylurea, was removed through filtration, and the coarse product was obtained via addition of acetone into the solution filtered before to make a precipitation. After being washed with dilute acetic acid, potassium bicarbonate solution and water, respectively, a fine product, β-CD-A, was finally obtained by adding acetone again to make a precipitation. The product was dried at room temperature for 1 day and 80°C for 3 days under the vacuum. The substitution degree (S.D.) of β-CD-A calculated by ^{1}H NMR and elementary analysis. The composition of β-CD-A was found to be $C_{48}H_{76}O_{37}{\cdot}5H_2O$ (Calcd. C 43.18, H 6.45; found: C 42.77, H 6.48) for S.D.2 and found to be $C_{51}H_{79}O_{38}{\cdot}4H_2O$ (Calcd. C 44.60, H 5.76; found: C 44.17, H 5.68) for S.D.3

Synthesis of [6-(2-acryloylaminoethyl) amino] -β-CD (β-CD-6-EA)

[6-(2-acryloylaminoethyl) amino]-β-CD (β-CD-6-EA) was synthesized by the reaction of primary-amino-containing β-CD (β-CD-6-E)[21] 2.0 g and acrylic acid with DCC 0.36 g as dehydrated reagent in DMF, and the low temperature 15°C and 8 h were performed this experiment. The purification was similar to β-cyclodextrin acrylate (β-CD-A)). The composition of β-CD-6-EA was found to be $C_{47}H_{78}N_2O_{35}{\cdot}7H_2O$ (Calcd. C 41.56, H 6.78, N 2.06; found: C 41.17, H 6.48, N 2.23).

Synthesis of poly(acrylic-co-β-cylodextrin acrylate) (AAc-β-CD-A) and poly {acrylic-co-[6-(2-acryloylaminoethyl) amino]-β-CD} (AAc-β-CD-6-EA) based hydrogels

The hydrogels AAc-β-CD-A and AAc-β-CD-6-EA were synthesized using the monomers of acrylic acid (AAc) with β-CD-A and β-CD-6-EA in aqueous solution at 20°C with a redox initiator system consisting of APS and SBS. Specifically, 0.3 g of β-CD-A and 0.7 g of AAc with stoichiometric calculation were dissolved in 3.0 mL of distilled water, and then, 10.6 mg of SBS solution was added. After bubbling with nitrogen gas for 20 min, 27.6 mg of APS solution was added. However, an additional explanation is necessary here: β-CD-6-EA is a monovinyl β-CD monomer, so the crosslinker BIS (1.5 wt % of total monomers) was required. The copolymerization was conducted at 20°C for 24 h, and then the hydrogel prepared was taken out from the bottle, cut into thin disks with 12 mm in diameter. The samples were immersed in distilled water that was changed for every 12 h, and lasted 5 days for removing the free monomer. Finally, samples were dried under an ambient temperature for 2 days, and 50°C for 48 h

TABLE I
Composition of Copolymers AAc-β-CD-A and AAc-β-CD-6-EA

Sample	Code		Feed ratio β-CD-A/β-CD-6-EA : AAc (g : g)	The content of β-CD in the copolymer (wt %)[a]
AAc-β-CD-A	**2**[b]	Ia	0.3 : 0.7	14.3
		Ib	0.4 : 0.6	18.8
	3[b]	IIa	0.3 : 0.7	23.6
		IIb	0.4 : 0.6	29.2
AAc-β-CD-6-EA	IIIa		0.1 : 0.9	11.5
	IIIb		0.2 : 0.8	16.9
	IIIc		0.3 : 0.7	18.5
	IIId		0.4 : 0.6	22.1

[a] Determined by colorimetric method[22]
[b] D.S. (substitution degree of β-CD-A) calculated by ^{1}H NMR and elementary analysis.

in a vacuum oven. The compositions of the hydrogels were listed in Table I.

Instrument analyses

^{1}H NMR measurements were conducted on a Varian Inova 400 spectrometer (Massachusetts) at room temperature with D_2O as a solvent. FT-IR spectroscopy experiments were preformed on a Specode WQF-310 model (Beijing, China). Elemental analyses were carried out on a Vario EL III instrument (Hanau, Germany). Ultraviolet–visible spectra were recorded on a UV-1200 spectrophotometer (Beijing, China). TGA measurements were used by Q50 TA Instruments (USA).

Swelling measurements

The swelling ratio (SR) of the hydrogels with an average mass of 60 mg, was measured in buffer solutions at 25°C. They were carefully taken out from the solution, wiped with a filter paper for the removal of the free water on the surface. SR (g/g) was calculated using the equation as follows: $SR = (W_t - W_0)/W_0$, where W_0 and W_t are the weights of dry and wet samples, respectively. When a sample reaches its swelling equilibrium state under a fixed condition, its SR is called ESR. $ESR = (W_\infty - W_0)/W_0$, where W_∞ is the weights of hydrogels at an equilibrium state. All SR and ESR measurements were triplicated for each sample.

Preparation of buffer solutions

Buffer solutions of NH_2CH_2COOH/HCl (pH 2.0-3.5); HAc-NaAc (pH 4.0-5.5); NaH_2PO_4/Na_2HPO_4 (pH 6.0-8.0) were prepared in this LAB. To obtain a solution with the constant ionic strength of 0.1mol/L, certain amount of NaCl or KCl was introduced into the buffer solution.

Drug loading

The completely dried AAc-β-CD-A and AAc-β-CD-6-EA xerogels, with an average mass of 60 mg, and an average size of 50 mm in diameter and 1.5 mm in thickness, were immersed in a mixture solution [V (acetone) : V (water) = 1 : 1] containing 0.88 wt % of CHL. At a certain time interval, the hygrogel loading with CHL were taken out, and the solution containing free drug on the sample surface was removed carefully with a filter paper, and then dried under an ambient temperature for 2 days and 50°C for 48 h in a vacuum oven. The amounts of drug loading were calculated as follows:

$$\text{Drug content (wt \%)} = (w_1 - w_0)/w_0\%$$

where w_0 and w_1 are the weights of drug unloading and drug loading samples, respectively, and listed in Table II.

Drug release study

The drug release experiments were conducted in 25 mL of aqueous NaCl solution of 0.1 mol/L at 37°C in pH 6.8 in a static state. A sample loaded with the

TABLE II
Results of the Drug-Loaded Hydrogels

Sample	PAAc	Ia	Ib	IIb	IIIa	IIIb	IIIc	IIId
Drug content (wt %)	6.29	5.23	5.61	4.83	5.33	5.30	6.03	6.12

drug was put into the solution by measuring the drug concentration of the solution for studying the drug release behavior. That is, at a certain time interval, 5 mL of the solution immersing with the drug loading samples was withdrawn, and the amount of the drug released was determined by measuring intensity of UV absorption of the drug in solution. The wavelength that used to determine the amount of drug released was 260 nm. After each measurement, the same amount of fresh solvent was put into the system to keep a constant volume.

It is necessary to establish a calibration curve at pH 6.8, and the linear fit for relationship between the concentrations of CHL and their absorbence in UV is $A = 2.64 \times 10^{-2} + 1.37 \times 10^{4}C$, Corr.coeff. $r^2 = 0.9974$ and λ (nm) = 260.

RESULTS AND DISCUSSION

Synthesis of β-cyclodextrin acrylate (β-CD-A)

Acrylic monomers (β-CD-A) containing β-CD can be prepared by esterification of β-CD and AAc using DCC as a condensation agent at a mild condition. The reaction mechanism is presented in Figure 1. Actually, this reaction can get different substitution extents by varying reaction conditions with relatively a higher yield. As can be seen from FT-IR spectra for β-CD-A in Figure 2, with the increase in substitution extent in β-CD, the absorption intensity at 1718 cm^{-1} assigned as C=O stretching vibration in carboxylic hydroxide increases; but the absorption band at 2938 cm^{-1}, representing the methylene C—H stretching vibration, does not change. By using the ratio of the intensities at 1718 cm^{-1} as a probing band, and at 2938 cm^{-1}as a reference band, a good linear relationship between the different substitution degree of β-CD acrylate is observed. Therefore, based on the reference,[23] the substitution extent of β-CD-A can be conveniently calculated by the ratio of $T\,\%_{1718}/\,T\,\%_{2938}$.

As shown in Table III, the samples A, B, and C was prepared using the same molar ratio (β-CD : AAc = 1 : 10) at different reaction temperatures for 37 h. The results indicate that their ratios of $T\,\%_{1718}/T\,\%_{2938}$ increase with the increase in temperature, because there exists a marked variation for

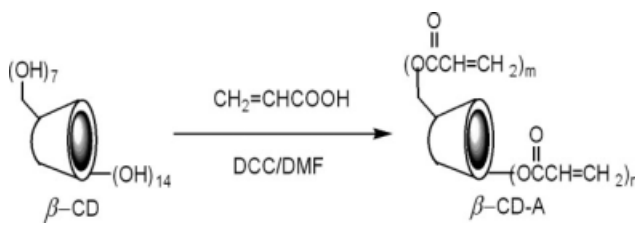


Figure 1 Reaction scheme for the synthesis of cyclodextrin-containing monomer β-CD-A.

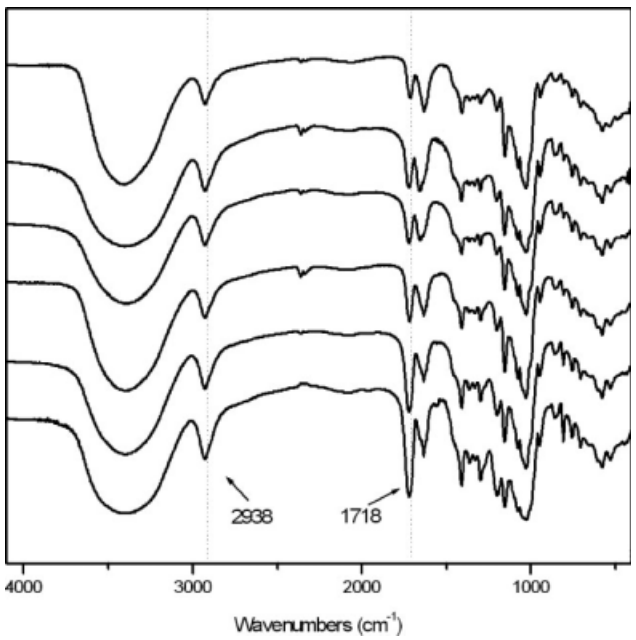


Figure 2 FT-IR spectra of β-CD-A with varying degree of substitution.

ratios of $T\,\%_{1718}/T\,\%_{2938}$ at 30–40 °C compared to the ratios at 20–30°C. In addition, it is found that, within 7–37 hours, the ratios of $T\,\%_{1718}/\,T\,\%_{2938}$ for samples D, E, F, and B increase gradually with the increase in reaction time, wheseas the ratios of $T\,\%_{1718}/T\,\%_{2938}$ for samples G, H, F, and I increase following the increase in the molar ratio of β-CD and AAc.

The stretching vibration for C=O group in β-CD-A is at around 1718 cm^{-1}, but it presents an intensity difference due to the different substitution extent. In general, C=C stretching vibration occurs at around 1640–1680 cm^{-1}, unfortunately this band in β-CD-A is difficult to be identified owing to the band's overlapping by surface inner bending vibration of O—H groups. However, ^{1}H NMR measurements can confirm the existence of C=C functional groups in β-CD-A shown in Table IV, where three chemical shifts ranging from 6.37 to 5.81 can be clearly observed. These chemical shifts are corresponding to CH_2=CH groups. Because of the effect of substitution groups, the chemical shifts of protons in β-CD (δ_H: 5.18–4.95) are partially downfield.

Synthesis of [6-(2-acryloylaminoethyl) amino]-β-CD (β-CD-6-EA)

Synthesis of monovinyl β-CD (β-CD-6-EA) is divided into two steps. The reaction mechanism is presented in Figure 3. Primary-amino-containing β-CD (β-CD-6-E) was obtained by the reaction of Mono-6-OTs-β-CD with ethylenediamine, and then it was acylated by acrylic acid using DCC as condensation agent according to the literature.[24,25] The results show that

TABLE III
Feed Composition and Effect of Reaction Temperature on $T\ \%_{1718}/T\ \%_{2938}$

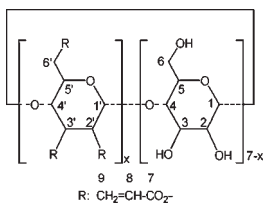
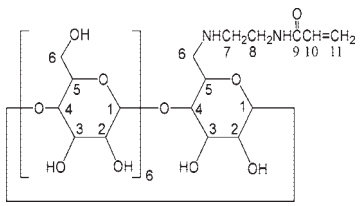
Code	Molar ratio β-CD : AAc	Reaction temperature(°C)	Reaction time (h)	$T\ \%_{1718}/T\ \%_{2938}$
A	1 : 10.10	20	37	0.990
B	1 : 10.10	30	37	1.018
C	1 : 10.10	40	37	1.235
D	1 : 11.05	30	7	0.9324
E	1 : 11.05	30	16	0.9613
F	1 : 11.05	30	25	0.9975
G	1 : 2.52	30	25	0.7835
H	1 : 5.05	30	25	0.9731
I	1 : 20.52	30	25	1.257

the only amino-group of primary-amino-containing β-CD was acylated by controlling the reaction conditions. The structure is confirmed by FT-IR and ^{1}H NMR measurements shown in Table IV. The absorptions at 1643 cm^{-1} and 1556 cm^{-1} assigned as C═O and C─N stretching vibration, N─H bending vibration in acylamino. The chemical shifts ranging from 5.99 to 5.54 are corresponding to protons of CH_2═CH groups.

Synthesis of poly(acrylic acid-co-β-cyclodextrin-acrylate) (AAc-β-CD-A) and poly {acrylic-co-[6-(2-acryloylaminoethyl) amino]-β-CD{ (AAc-β-CD-6-EA) based hydrogels

Copolymer hydrogels, Ia, Ib, IIa, IIb, and IIIa–IIId, are prepared by using β-CD-A and β-CD-6-EA monomers and AAc monomer. The feed compositions for copolymers are listed in Table I. The copolymer's FT-IR spectra are showed in Figure 4. It

TABLE IV
FT-IR and ^{1}H NMR Data of the β-CD-A and β-CD-6-EA

Sample	^{1}H NMR δ (D_2O)		FT-IR(cm^{-1})	
	1-H	5.18–4.95 (m)	ν_{O-H}	3375
β-CD-A	2-H, 4-H	3.48–3.39 (m)	$\nu_{(as)-CH2-}$	2938
	3-H, 5-H, 6-H	3.77–3.51 (m)	ν_{C-O}	1035
	8-H	6.37–6.32 (m)	$\nu_{C=C}$	1637
	9-H_1	6.06–6.02 (m)	$\nu_{C=O}$	1718
	9-H_2	5.85–5.81 (m)	–	–
	1-H	4.95 (s)	ν_{O-H}	3375
β-CD-6-EA	2-H, 4-H	3.55–3.41 (m)	$\nu_{(as)-CH2-}$	2928
	3-H, 5-H, 6-H	3.89–3.73 (m)	ν_{C-O}	1035
	7-H, 8-H	3.08–2.79 (m)	$\nu_{C=C}$	1643
	10-H	5.91 (d)	$\nu_{C=O}$	1643
	11-H_1	5.99 (d)	$\delta_{N-H} + \nu_{C-N}$	1556
	11-H_2	5.54 (d)	–	–

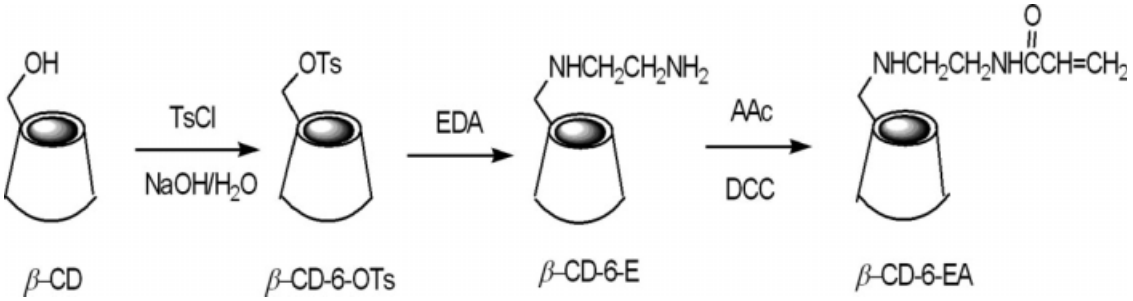


Figure 3 Reaction scheme for the synthesis of β-cyclodextrin containing acrylicmonomer β-CD-6-EA.

is found from Figure 4 that a strong broad band at 3480 cm^{-1}, which can be assigned as O—H stretching vibration in carboxylic hydroxide and in β-CD, is observed for all samples. And a band at 1028 cm^{-1}, which can be assigned as the C—O stretching vibration, can also be identified. Furthermore, the intensity of this band increases with the increase in β-CD's content in copolymers. The copolymer's thermal properties as showed in Figure 5 exhibit both Ia and IIb possess a higher decomposition temperature compared to a pure polyacrylic acid (PAAc), where the decomposition temperatures for Ia and IIb are 200°C and 218°C, and for pure PAAc is only 160°C. The results may suggest that incorporation of β-CD component can effectively enhance the thermal stability of copolymers.

Effect of pH value on equilibrium swelling ratio (ESR) of hydrogels

Figure 6 presents the effect of pH values on ESR of hydrogels (Ia, Ib, IIa, IIb, and IIIa-IIId) in different buffer solutions. Because the acidity constant (p*K*a) for acrylic acid is equal to 4.26,[26] therefore, the hydrogel's volume phase transition caused by pH's varying should be in this pH range. As can be seen, at the pH values less than 4, hydrogels are basically in a shrinkage state due to the hydrogen bonding from unionized carboxyl groups.[27–29] However, with the increase in pH, the carboxyl groups are getting ionized, as a result, causes a large difference in proton concentration among internal and external hydrogels. This can directly promote the increase in osmose pressure within hydrogel, and can result in its swelling. At the pH values higher than 4, due to the acceleration of ionization for carboxyl groups, the electrostatic repulsive interactions increase among ionic groups, and cause an abrupt enlargement of SR for hydrogel. However, because the increase in the network's deformation for hydrogel, the elastic tension also increases subsequently, these two kinds of opposed forces can be balanced so as to maintain the hydrogel's final equilibrium swelling state. It can also be observed from Figure 6(A) that samples Ia and Ib with less β-CD contents, less monomers substitution extent and smaller cross-linking densities present a marked volume phase transition region compared to samples IIa and IIb with

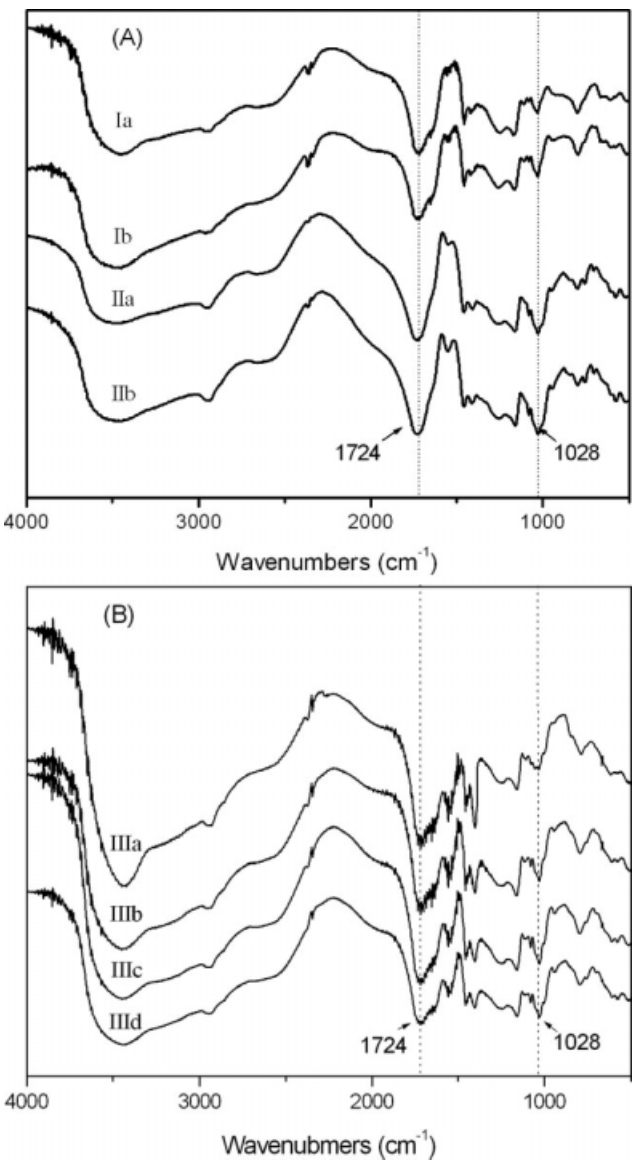


Figure 4 FT-IR spectra of AAc-β-CD-A (A) and AAc-β-CD-6-EA (B).

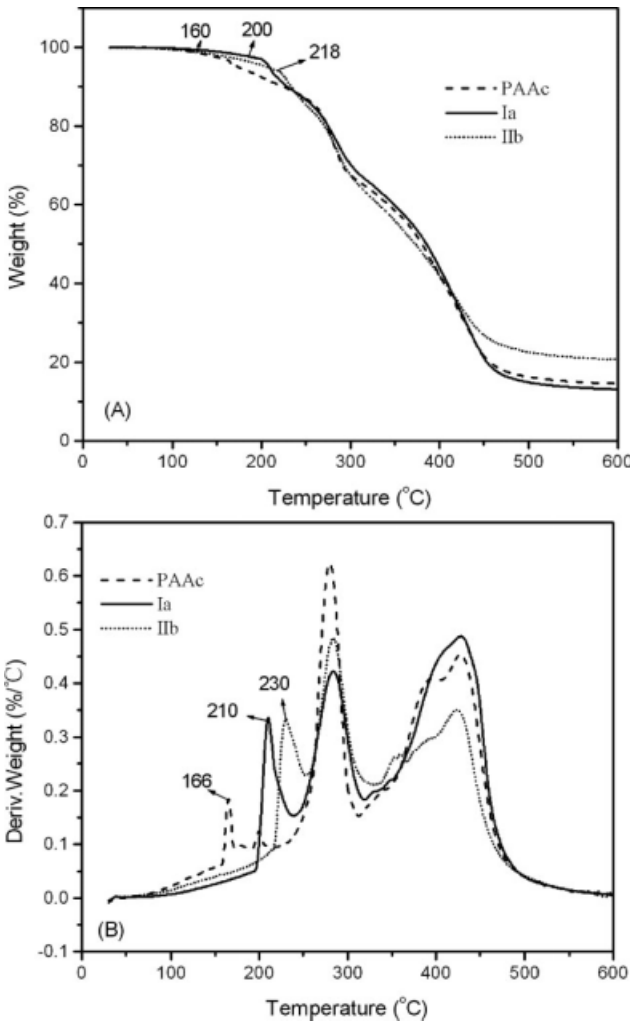


Figure 5 TGA (A) and DTG (B) thermograms of PAAc, Ia, and IIb.

relatively higher β-CD contents, monomer's higher substitution extent and higher cross-linking densities.

As clearly seen from Figure 6 (B), the equilibrium swelling of hydrogels IIIa-IIId follows the order IIIb > IIIc > IIId > IIIa at the pH values higher than 6. This indicates that for hydrogels, their swelling rates are not directly controlled by the β-CD contents in these hydrogels. The influence of β-CD to swelling rate has two aspects. However, β-CD monomer (β-CD-6-EA) posses lower reaction activity to compare with acrylic acid, thus make the hydrogel's density correspond to decrease, and their swelling rate enlarge. However, because of β-CD's rigidity and big volume that reduces the flexibility of networks. Therefore, the swelling behavior is controlled by the balance of the two aspects.

Dynamic analyses on hydrogel's swelling behavior

To further understand the detailed swelling process for hydrogels, the swelling dynamic studies are carried out by inspecting the variation of SRs of hydrogels versus time in buffer solutions at pH 6.8. Equation 1 proposed by Hariharan and Peppas[30] as showing below is employed to describe the water uptake and diffusion from hydrogels.

$$\frac{M_t}{M_0} = kt^n \tag{1}$$

$$\ln\frac{M_t}{M_0} = n\ln t + \ln k \tag{2}$$

where M_t is the water uptake at time t, M_0 is the weight of the dry polymer; k and n are the constants. Particularly, parameter n represents the mechanism of water uptake or diffusion from hydrogels during swelling process. If n equal to 0.5, the hydrogel's swelling may accord the classical Fickian's diffusion mechanism, and if the value of n is larger than 1.0, the water uptake or diffusion may be controlled by

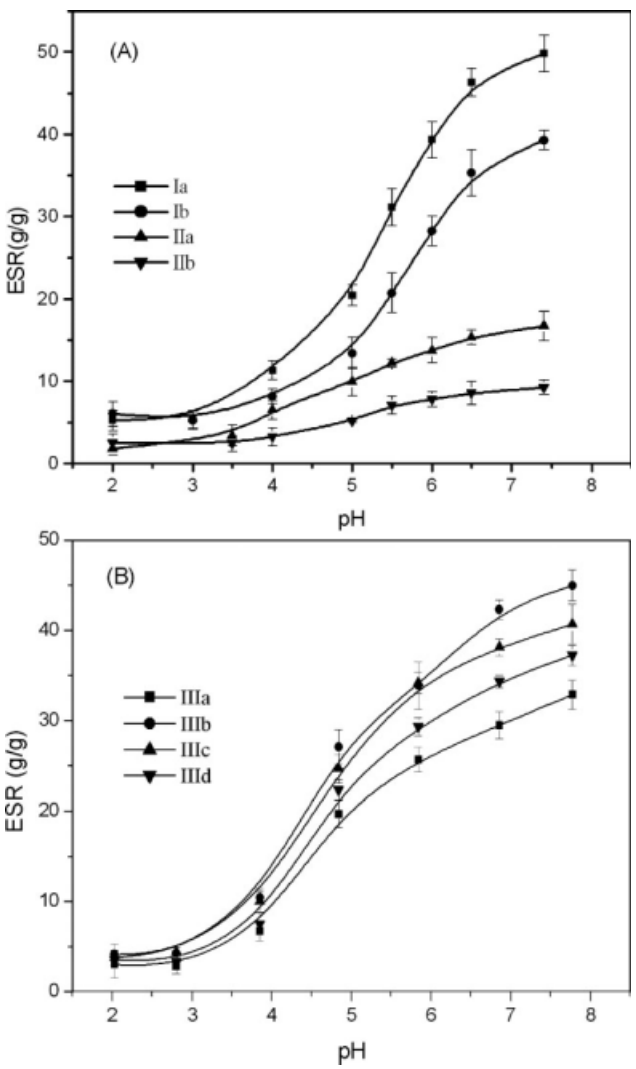


Figure 6 Influence of pH on ESR of hydrogels at 25°C. (A):Ia-IIb (B): IIIa-IIId.

TABLE V
Dymamic and Equilibrium Swelling Data of Copolymers PAAc and Ia–IIId in pH = 6.8 Buffered Solutions at 25°C

	Parameters corresponding to the eq. (1)			Parameters corresponding to the eq. (3)			
Sample code	Swelling exponent, n	K (min)	Corr. coeff. r	a	$b \times 10^2$	Corr. coeff. r	ESR[a]
PAAc	0.64	0.41	0.9961	10.88	1.63	0.9953	54.0
Ia	0.69	0.26	0.9963	9.37	1.51	0.9964	56.4
Ib	0.67	0.28	0.9954	11.95	2.06	0.9968	42.1
IIa	0.54	0.33	0.9840	12.32	6.25	0.9933	14.8
IIb	0.58	0.32	0.9855	12.98	10.98	0.9991	8.65
III a	0.53	0.49	0.9913	14.75	3.09	0.9955	28.9
III b	0.52	0.61	0.9908	8.87	2.11	0.9969	43.4
III c	0.58	0.48	0.9913	11.46	2.30	0.9985	39.0
III d	0.55	0.53	0.9906	11.68	2.61	0.9976	34.4

[a] Equilibrium swelling ratio.

the relaxation of hydrogel's network. For n in the range between 0.5 and 1, the swelling process may be affected by both the relaxation of the hydrogel network and diffusion of water.

For all samples prepared, their constants n and k values as well as other parameters for water uptake at pH values of 6.8 are listed in Table V. The first 86% of the water uptake data was used to evaluate these constants for Ia, Ib, and PAAc; 80% for IIa and IIb; 93% for IIIa-IIId. The n values vary between 0.52 and 0.69, indicating that the mechanism of water transport deviates from Fickian to non-Fickian, and their swelling mechanism is controlled by a cooperative process of water's diffusion and network's relaxation. But it can also be observed that the n values for Ia, Ib and PAAc are 0.64, 0.69 and 0.67, respectively, indicating that their water uptake mechanism is controlled primarily by relaxation of the polymer samples. However, for IIb, IIIa-IIId samples the swelling may be dominantly involved in the water's diffusion as shown by n values close to 0.5. These experimental phenomena may be related to the different cross-linking densities for the samples, because the increase in cross-linking density can result in a less flexible network structure, and in turn, can prohibit the relaxation of chain segments. For instance, the samples Ia and Ib possess lower cross-linking density due to their polymer chain including monomer β-CD-A with the lower substitution degree (S.D. = 2), and their network structure relaxation become easy, whereas, for IIa and IIb including monomer β-CD-A with substitution degree (S.D. = 3), leading to less flexible network. It is notable that though samples IIIa-IIId include a monovinyl β-CD monomer, the crosslinker BIS (1.5 wt % of total monomers) was used, their swelling mechanism is similar to IIa and IIb. Interestingly, the cross-linking density for pure PAAc is basically approaching the values of samples Ia and Ib, therefore, they should have the similar n values, and similar swelling mechanism. The results further demonstrate that the cross-linking density is a very crucial factor to determine the swelling behavior of the hydrogel.

Values of k did not show any systematic trend, because that the majority of the swelling kinetics of hydrogels inconsistent with Fickian's law, and the result is similar with Rudzinski et al.[31] Fickian's law assume that the diffusion coefficient of the diffusion agents and membrane thickness of matrix in the whole swelling process are regarded as constant, whereas the latter is obviously not constant. Schott[32] proposed a theoretical model for this swelling system, considering the swelling process can be described by the following relationship:

$$t/M_t = a + bt \tag{3}$$

where constants a and b were explained as follows: in a longer period of time during swelling, $bt >> a$, according to eq. 3, $b = 1/M_t$, that is, the reciprocal of absorption at the swelling equilibrium. In contrast, in the initial stage of swelling, $a >> bt$, therefore, intercept a is the reciprocal of the initial swelling rate. The constant a and b in Table V were obtained by fitting the data of the variation of SRs of hydrogels versus time with equation Eq.3. Comparison of a and b value for hydrogels Ia,Ib, IIa, and IIb, both all follow the order Ia < Ib < IIa < IIb, that is the changes of the initial swelling rate of hydrogels in trend coincide with the greatest degree of equilibrium swelling, which can explain their ESR follow the order—Ia > Ib > IIa > IIb. The similar results are in IIIa-IIId hydrogels. Therefore, the behaviors of the initial swelling rate and the greatest degree of equilibrium swelling of hydrogels depend primarily on their cross-linking density.

Controlled drug release behavior of hydrogels

Figure 7 presents the weight fraction of cumulative release of CHL from samples in buffer solution with

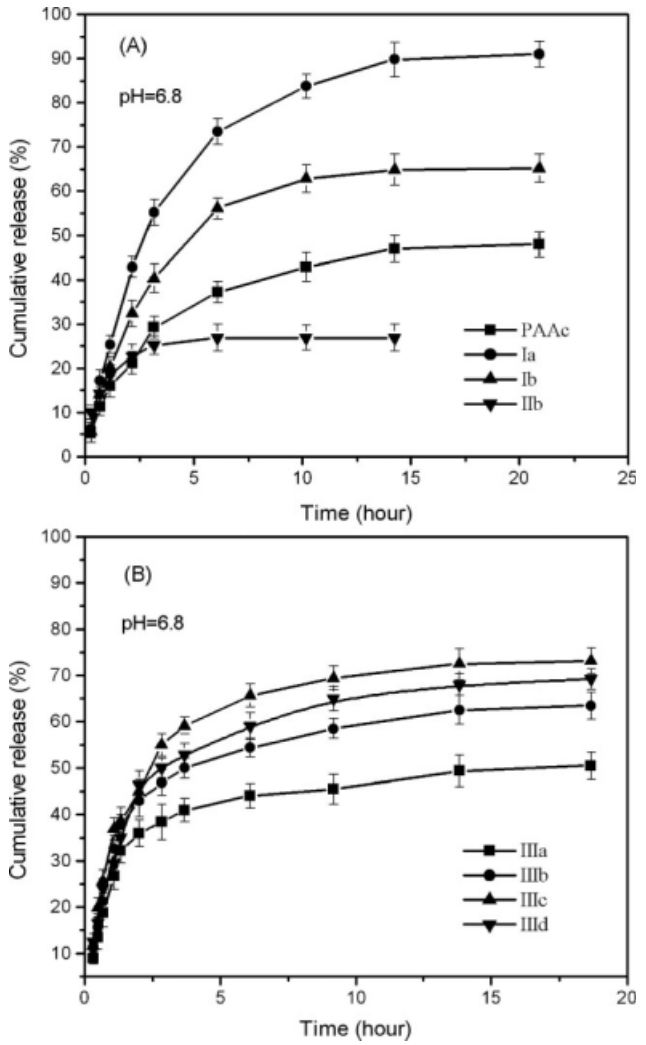


Figure 7 Cumulative release profiles of CHL from the Loaded hydrogels in buffered solutions at pH = 6.8 at 37°C. (A): PAAc and Ia–Ib (B): IIIa–IIId.

pH = 6.8 versus time. As AAc-β-CD-A and AAc-β-CD-6-EA hydrogels, including pure PAAc hydrogel, are all pH sensitive polymers owing to containing carboxyl groups, therefore, at the lower pH value (pH = 2), their SRs are accordingly very lower. Oppositely, at higher pH value (pH = 6.8), due to carboxyl group's ionization and producing strong electrostatic interactions, the sample's SRs are getting higher, and the drug release profile may follow a cooperative process of drug diffusion and the relaxation of hydorgel's network, causing larger amount of drug releasing from polymer matrix.

To understand the mechanism of two kinds of hydrgels with different structural characteristics, the cumulative release data from Figure 7 are used for kinetic analysis. The data have been fitted to the empirical equation proposed by Peppas and Peppas[33]:

$$\frac{M_t}{M_\infty} = kt^n \tag{4}$$

Here, M_t and M_∞ are the fraction of drug released at time t and at equilibrium, k is the release constant and n is the release index which characterizes the mode of transport of the drug outside the matrix. For $n = 0.5$, drug release is diffusion controlled and follows a Fickian mechanism. For $0.5 < n < 1$, an anomalous diffusion behavior is considered, the drug release is controlled by both the relaxation of matrix and diffusion of drug, and for $n > 1$, the drug release may be controlled by the relaxation of matrix.

The release parameters n and k calculated by using eq. 4 are showed in Table VI. The release index n value data indicate that for all samples except for IIb, n values are $0.5 < n < 1$, that is, the mechanism of drug release deviated from the Fickian diffusion by matrix relaxation and the diffusion of drugs collaborative control. But it should be noted that in the fitting Eq. 4, the first 90% of the drug release data were used to evaluate these constants for Ia, Ib, and PAAc but 70% for IIIa-IIId. This means that there are still larger differences of the drug release mechanism for two types of hydrogel. The experimental results show that controlled release mechanism of drugs depending on the hydrogel's network structure, this situation is related to the swelling mechanism of hydrogels.

However, it can be also seen from Figure 7(A) that at a certain time, the amount of drug release from polymer matrixes depends exactly on hydorgel's network structure. That is, the higher crosslinking density for hydrogels, the less amount of drug releasing from polymer matrixes. In stance, the use of a highly substituted monomer of β-CD causes an increase in the cross-linking density and in the stiffness of the hydrogel, with the consequent decrease in degree of swelling. However, by comparison, even the SRs for

TABLE VI
Analysis of Release Kinetics of the Loaded Hydrogels of PAAc and Ia–IIId in pH = 6.8 Buffered Solutions at 37 °C

Sample code	Rlease index, n	K (min) $\times 10^2$	Corr.coeff. r	Sample code	Rlease index, n	K (min) $\times 10^2$	Corr.coeff. r
PAAc	0.61	2.26	0.9928	III a	0.80	1.75	0.9846
Ia	0.73	1.33	0.9925	III b	0.78	1.78	0.9888
Ib	0.79	0.91	0.9895	III c	0.74	2.01	0.9695
Ib	0.38	13.09	0.9972	III d	0.72	2.16	0.9924

both PAAc and Ia are basically the same, the drug release rate for Ia is much fast than that of pure PAAc hydrogel. The result may indicate that cyclodextrin segments with the proper frame and concentration can effectively promote the drug release from the matrixes of hydrogels. This conclusion was further confirmed by drug release behavior of the hydrogels IIIa-IIId. The mechanism of the incorporation of cyclodextrins into polymeric matrices can modify drug release proposed in the literature,[34] that is by improving the aqueous solubility of drugs, or acting as channeling agents and promoting erosion of the matrix.

Figure 7(B) presents the release profiles of CHL from hydrogels IIIa-IIId. The cumulative release rate of CHL from hydrogels IIIa-IIId follows the order IIIc> IIId> IIIb> IIIa. It is found that the cumulative release of CHL from hydrogels is subjected to influence of hydrogel's swelling rate and β-CD content, and the cumulative release increase with the swelling rate and β-CD content. For example, hydrogel IIIa possess lowest cumulative release owe to its lowest swelling rate 28.92 and β-CD content 11.5 (*wt* %). For IIIc because of having largest swelling rate, the cumulative release rate of CHL from hydrogel is the largest. This result indicates the hydrogel's swelling rate is still domain factor. However, as shown in Figure 7, IIIb's swelling rate is larger than that of IIId, but the cumulative release of CHL from IIIb is lower compare with IIId. It is considered that this result is attributing to IIId having more β-CD content 22.1 (wt %). Therefore, we can conclude that β-CD can effectively promote the drug CHL release from the hydrogels.

CONCLUSION

We have synthesized and characterized polymer networks containing cyclodextrin. The effect of polymer structural characteristics such as the cyclodextrin as crosslinker or pendent groups and the content of cyclodextrin were studied on swelling and drug release properties of the polymer. The kinetics of transport of water into the polymer and drug CHL release were studied, the results show that the mechanisms of water uptake and drug release depend on the structure of polymer. In this system, properties of the polymer network can be modulated through an adequate selection of the proportion of both components, which makes them potentially useful as versatile vehicles of substances.

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