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Synthesis and properties of radiopaque polymer hydrogels II: copolymers of 2,4,6-triiodophenyl- or *N*-(3-carboxy-2,4,6-triiodophenyl)- acrylamide and *p*-styrene sulfonate ☆

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Abstract

In order to pursue a possibility of application of radiopaque polymer hydrogels to vascular embolization, studies were made on synthesis of iodine containing copolyanions and properties of their hydrogels with polycation via formation of polyion complexes (PIC). Acrylamide derivatives having triiodophenyl groups were synthesized and copolymerized with sodium styrene sulfonate (SS) under several conditions. It was found that *N*-(3-carboxy-2,4,6-triiodophenyl)-acrylamide (CIPA) and 2,4,6-triiodophenylacrylamide (TIPA) monomers are effectively copolymerized with SS, while *N*-allyl-2,3,5-triiodobenzamide (ATIBA) are hardly copolymerized. Hydrogels were prepared by mixing aqueous solutions of polyanions, i.e. the copolymers (PCIPA and PTIPA) and polyallylamine (PAAn). ^{13}C NMR spectra of PCIPA/PAAn and PTIPA/PAAn hydrogels gave peaks for both polyanion and polycation. This means that there remained free anionic and cationic monomer units, which did not form ion pairs because of spatial hindrance. Time dependence of ^{1}H T_2 showed quick increment and plateau for PSS/PAAn and gradual increments for PCIPA/PAAn. Therefore, PIC containing the radiopaque copolymer retains the hydrogel state for a long time. Embolization was examined by injection of PCIPA/PAAn hydrogels into the vein of a removed porcine kidney as a preliminary test for transcatheter arterial embolization (TAE). X-ray radiograms of the embolized organ were reasonably explained based on the structure and mobility of hydrogels.

Keywords: Polymer hydrogels; Polyion complexes; Transcatheter arterial embolization

1. Introduction

Recently, the transcatheter arterial embolization (TAE) has attracted attention as a treatment for hepatocellular carcinoma (HCC) [1]. The effectiveness of TAE treatment has been evaluated by the same methods for diagnosis of HCC as computed tomography (CT), magnetic resonance imaging (MRI),

☆ Dedicated to Professor Graham A. Webb on the occasion of his 65th birthday.

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angiography and so on. Of these methods, the angiography using radiopaque materials has been the predominant method for HCC. The angiography was achieved by introducing contrast media to the aimed vessel via catheter and successive monitoring of the embolizing state by X-ray radiogram. Requirements for radiopaque materials for TAE are (1) no damage to veins, (2) fluidity enough to pass through a catheter, (3) embolization of veins for a given period and (4) radiopacity to monitor embolization by X-ray radiography. So far, a mixture of lipiodol which is a commercial, hydrophobic, low molecular weight X-ray contrast medium and cisplatin [2], which is a gelatin sponge combined with lipiodol [3], and a polysaccharide solution with anticancer drugs [4] have principally been used. Microspheres of synthetic polymers with or without radiopacity were also used for embolization [5–8]. However, for long term analyses of embolizing states and continual treatments, the following difficulties are found; the introduced contrast medium overflows via blood flow to kidney and then to urinary bladder and finally expelled as urine out of the body and the handling of contrast media gives great burden to both patients and doctors.

We have anticipated that hydrogels of radiopaque polyion complexes (PIC) formed by mixing aqueous solutions of polycation and polyanion will be available by their transcatheter injection into feeding veins instead of hydrophobic lipiodol for embolic therapy, in order to embolize the target vessels or organs with easy handling and control. This is because such polymer hydrogels are so fluid as to flow in intravascular injection, while they are viscous enough to embolize peripheral veins without damaging the tissues.

As a preliminary study [9], we reported on a polymer hydrogel consisting of synthetic PIC, which was prepared by mixing a sodium poly(styrene sulfonate) (PSS) in an aqueous commercial X-ray contrast medium (Omnipaque 350) and that of polyallylamine hydrochloride (PAAn) in the same medium, where PSS and PAAn are not radiopaque polymers. The hydrogel thus prepared was transparent and so viscous like albumen that it has to be picked up with tweezers. It was found that the hydrogel was suitable for handling in transcatheter injection and flowed deep into the capillaries of the vein as was evident from the clearly contrasted X-ray radiogram of a removed porcine kidney. Although PIC hydrogel does not flow out through the capillaries to the peripheral tissues at all, a diffuse X-ray radiogram taken at 24 h after the injection, where the X-ray contrast in the region of capillaries disappeared, showed draining of the contrast medium into the peripheral tissues.

In the previous paper [10], we have adapted radiopacity to polymers by using triiodophenyl acrylamide as a monomer. Acrylamide derivatives having triiodophenyl and carboxyl groups were synthesized and copolymerized with sodium styrene sulfonate (SS) at various molar ratios of initiator to monomer and temperatures (PCIPA). The hydrogels prepared from the copolycation obtained under particular conditions gave high X-ray contrasts of the vein and remained there, though copolycations with low molecular weights had a tendency to drain out through the capillaries to the peripheral tissues.

In this paper, the effects of molecular weight and iodine content on the capability of embolization and radiopacity are examined based on the molecular mobility of water in the hydrogels as studied by NMR measurements.

2. Experimental section

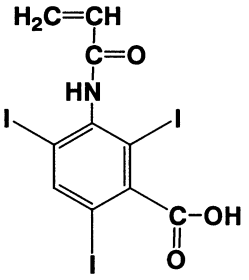
2.1. Materials

All chemicals obtained from commercial sources (Aldrich, Wako, Tokyo Kasei) were used without further purification, unless otherwise described. 2,2′-Azobisisobutyronitrile (AIBN) as an initiator was recrystallized from methanol solution before use. Tetrahydrofuran (THF) used in polymerization was distilled. Polyallylamine hydrochloride (PAAn) was also used without purification.

2.1.1. Synthesis of N-(3-carboxy-2,4,6-triiodophenyl) acrylamide (CIPA)

A mixture of 3-amino-2,4,6-triiodobenzoic acid (10 g, 18.4 mmol) and acryloyl chloride (25 ml, 30.7 mmol) was reacted with stirring at 80°C for 90 min. After cooling, the resultant precipitate collected by filtration was washed with diethyl ether and recrystallized from ethanol solution (yield: 70.8%). Chemical shift δ (ppm) of ^{1}H NMR: 5.80,

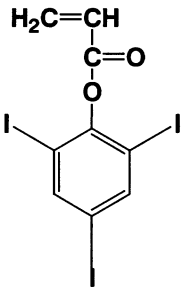
6.24 (d,2H,=CH_2), 6.41(q,1H,=CH), 8.36 (s,1H,Ar–H), 10.12 (s,1H,–OH).



CIPA

2.1.2. Synthesis of 2,4,6-triiodophenyl acrylate (TIPA)

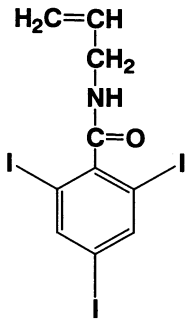
Acryloyl chloride (1.9 ml, 22 mmol) dissolved in dichloromethane (70 ml) was added dropwise in 30 min to a mixture of 2,4,6-triiodophenol (10 g, 19 mmol) and triethylamine (2.64 ml, 19 mmol) dissolved in dichloromethane (100 ml) with stirring below room temperature and kept for 3 h. The resultant TIPA was collected from the organic and water phases, extraction being carried out from the latter phase with cyclohexane. TIPA obtained from the cyclohexane extract was washed with 10 wt% aqueous citric acid, 10 wt% aqueous sodium bicarbonate and 10 wt% aqueous sodium chloride for three times and then dried over anhydrous sodium sulfate (yield: 73.3%). Chemical shift δ (ppm) of ^{1}H NMR: 6.28, 6.65 (d,2H, =CH_2), 6.47 (q,1H, =CH), 8.20 (s,1H, Ar)



TIPA

2.1.3. Synthesis of N-allyl-2,3,5-triiodobenzamide (ATIBA)

Thionyl chloride (1.4 ml, 20 mmol) was added dropwise to a solution of 2,3,5-triodobenzamide (5 g, 10 mmol) in THF (200 ml) and the mixture was stirred at 80°C for 2 h. Then the reaction mixture was concentrated under a reduced pressure. After diluting with THF, triethyl amine solution in THF was added to the solution to remove HCl as triethylamine hydrochloride. Allylamine (7.6 ml, 10 mmol) was added to the filtrate, stirring the mixture at room temperature for 1 h. Product ATIBA thus obtained was recrystallized from water (yield: 71.6%).



ATIBA

2.2. Copolymerization of radiopaque monomers (CIPA, TIPA and ATIBA) and sodium styrene sulfonate (SS)

Copolymerizations of radiopaque monomers (CIPA, TIPA and ATIBA) and SS were carried out, initiated by AIBN in dimethyl sulfoxide (DMSO) with stirring at 80°C for 20 h in a glass ampule sealed in vacuo. The reaction mixture was poured into acetone/methanol (9/1) mixture. The precipitate was filtered, washed with acetone and dried. Copolymers of CIPA, TIPA and ATIBA with SS are abbreviated as PCIPA, PTIPA and PATIBA, respectively.

2.3. NMR measurements

^{1}H NMR spectra PSS and PAAn solutions and hydrogels of PSS and copolymers with PAAn were measured with a JEOL Alpha 500 NMR spectrometer

using DMSO-d_6 either as a solvent or as internal reference. ^{13}C NMR spectra were recorded with a JEOL EX-270W NMR at room temperature using deuterated oxide as a solvent. ^{1}H T_2 measurements were carried out in a JEOL MU-25 NMR at room temperature by CPMG pulse sequence for the hydrogels as a function of time after mixing the aqueous solutions of polycation and polyanion, each concentration being 15 wt %.

2.4. Outflow time measurement

Time for outflow of the hydrogels through a glass tube with a size of inner diameter of 3 mm and length of 60 mm was measured under atmospheric pressure as a function of aging time to estimate a change in hydrodynamic properties of the gels in which the concentration of polyanion and polycation was 15 wt% each.

2.5. Embolization

Prior to embolization experiment, we examined the texture of the PIC hydrogels prepared by mixing 10 or 30 wt% of aqueous solutions of the copolymer and polyallylamine hydrochloride (PAAn) in a glass vessel. Polyanion and polycation were mixed under a condition that the number of cation is equal to that of anion. Embolization experiments were made by injecting the gel prepared from the 30 wt% solutions through a catheter into the vein of a removed porcine kidney. X-ray radiograms were taken immediately and 24 h after the injection.

3. Results and discussion

3.1. Molecular properties of radiopaque copolymers and their hydrogels

In Table 1 are shown conversion of the copolymerization of radiopaque monomer and SS, copolymer composition as the molar ratio of radiopaque monomer to SS, and iodine content, solubility in water and relative viscosity of the copolymer. Copolymer composition of PCIPA-1 and PTIPA was 1/3.2 and 1/3.5, respectively. Since ratios of radiopaque monomer to SS and AIBN to monomer in feed are 1/4 and 1/100, respectively, for both polymers, the reactivities of CIPA and TIPA with SS seem to be similar. Conversion of both polymers was 98%, indicating that these two radiopaque monomers almost completely copolymerized with SS. Iodine contents of these polymers are more than 300 mg/g-polymer.

Assuming a radiopaque hydrogel from 30 wt% polyanionic and polycationic solutions, where the concentration of the resultant polyanion is 15 wt%, the iodine content will be 45 mg/g in the gel. Compared with the iodine concentration of commercial radiopaque compounds, in the range of 24–500 mg/g, the above estimated concentration of 45 mg/g in solution is in the low level range. Therefore, these polymers may give radiopacity for TAE.

In comparison with PCIPA and PTIPA, the copolymer composition and iodine content of PATIBA was 1/27.7 and 61 mg/g-polymer, respectively. These values are extremely lower than those of PCIPA-1 and PTIPA. Conversion was also as low as 56%. Inspite of the same copolymerizaiton condition as for PCIPA-1 and PTIPA, the reactivity of ATIBA with SS was so low that only SS seems to polymerize. This is consistent with a fact that PATIBA is very soluble in water, though the monomer, ATIBA is hydrophobic.

Although conversion of PCIPA-2 was 69% which is lower than those of PCIPA-1 and PTIPA, copolymer composition of PCIPA-2 was the same as the monomer composition in feed (Table 1). Therefore, CIPA is effectively copolymerized with SS even at a monomer ratio of one. As a result, this polymer has the highest iodine content (508 mg/g) of all the CIPA polymers, being expected to give good X-ray contrast. Water solubility of this polymer, however, was lower than the others, probably due to lower SS content in the copolymer chain.

PCIPA-3 was obtained by copolymerization with SS at CIPA/SS of 1/4 and AIBN/monomer ratio of 1/1000. Copolymer composition of this polymer was also comparable to the molar ratio in monomer feed. It is evident that this polymer has the highest molecular weight of all the PCIPAs as estimated from relative viscosity.

It was also found that PTIPA has a copolymer composition close to that of the charged monomers and a relatively high viscosity. It is, therefore, expected that both PCIPA and PTIPA can give PIC hydrogels with PAAn.

Table 1
Copolymerization and properties of the resultant copolymers

	Radiopaque monomer (mmol)	SS (mmol)	AIBN	Conversion (%)	Composition[a]	Iodine content (mg/g-polymer)	Water solubility[b]	Relative viscosity	Relaxation time (ms)
PCIPA-1	4	16	1/100	98	1/3.2	317	A	1.38	1280
PCIPA-2	8	8	1/100	69	1/1.0	508	B	1.19	614
PCIPA-3	4	16	1/1000	72	1/3.4	306	A	3.58	714
PTIPA	4	16	1/100	98	1/3.5	305	B	1.58	1630
PATIBA	4	16	1/100	56	1/27.7	61	A	1.43	978

[a] Copolymer composition as a mole ratio of radiopaque monomer/SS. Determined by ^{1}H NMR.
[b] Soluble at room temperature (A) and 80°C (B).

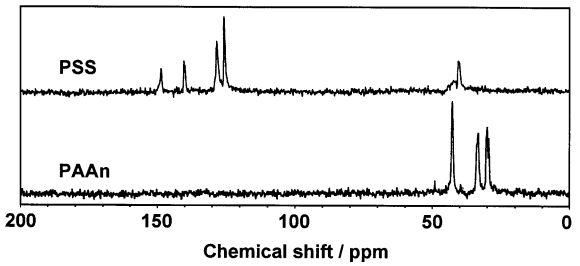


Fig. 1. ^{13}C NMR spectra of PSS and PAAn in D_2O solutions.

3.2. Structure of radiopaque copolymer hydrogels as measured by ^{13}C NMR

In order to characterize the structure of the PICs, ^{13}C NMR spectra of aqueous solutions of the copolymers and their PIC hydrogels were measured. In Fig. 1 is shown ^{13}C NMR spectra of aqueous PSS and PAAn solutions (15 wt%) as reference data prior to mixing. Peaks for PSS between 120 and 150 ppm are assigned to phenyl carbons. Methylene and methine carbons of PSS appeared at about 45 and 40 ppm, respectively. Peaks at 42, 33 and 29 ppm for PAAn are assigned to NCH_2, CH and CH_2 carbons, respectively. Sharp peaks for all the carbons mean that PSS and PAAn chains have enough mobility to average out the dipolar interaction in aqueous solutions.

Fig. 2 shows ^{13}C NMR spectra of PIC hydrogels as measured soon after mixing the solutions where the molar ratios of SS/AAn are all 4/1. Fig. 2(a) is a ^{13}C NMR spectrum of PIC prepared from PSS and PAAn.

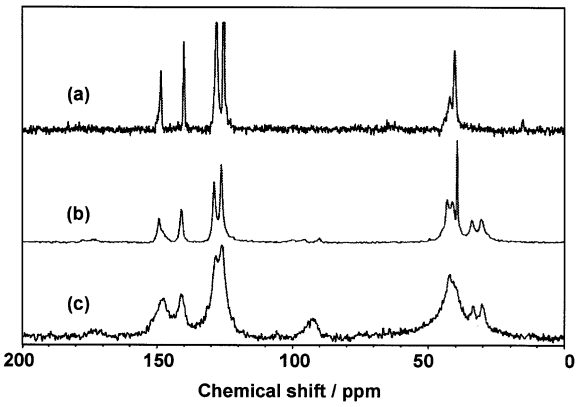


Fig. 2. ^{13}C NMR spectra of PIC hydrogels with monomer mole ratios SS/AAn of 4/1: (a) PSS/PAAn, (b) PCIPA-1/PAAn and (c) PTIPA/PAAn.

In this figure, all the peaks are assigned to PSS and no signals due to PAAn were found, indicating very low chain mobilities of PAAn. Since the monomer ratio of SS/AAn is 4/1, i.e. the amount of AAn is lean in the PCI, PAAn is thought to be almost incorporated in ion pairs. On the other hand, excess SS units have enough mobility to give NMR peaks with intensities similar to those for PSS solution.

Fig. 2(b) is a ^{13}C NMR spectrum of the PIC gel prepared from PCIPA-1 and PAAn. In this figure, very weak signals assigned to CIPA units appeared at about 170–180 ppm (C=O) and 90–100 ppm (C–I), while SS and AAn peaks are all strong, though they are boarder than those shown in Figs. 1 and 2(a). Existence of SS and AAn peaks means that some SS and AAn units, which do not form ion pairs are so mobile to give strong NMR peaks. However, the line widths of the SS and AAn peaks are larger than those in Figs. 1 and 2(a), suggesting that these SS and AAn groups are less mobile than those in the solution state. The low mobility of AAn groups may be accounted for, by a weak interaction to be formed between the carboxyl group of CIPA unit and the free amino group of PAAn. On the other hand, the low mobility of SS units may be due to a restriction in chain mobility in their vicinity where ion pairs and/or weak interchain interactions are formed.

A similar trend was observed for PTIPA PIC gel (Fig. 2(c)). Comparing Fig. 2(b) and (c), peaks in Fig. 2(c) are much broader than those in Fig. 2(b). The broad signals of both SS and AAn units in the PTIPA PIC gel are thought to be due to the nature of TIPA unit, which has no polar side groups and accordingly is insoluble in water. Therefore, a hydrophobic interaction between spatially close TIPA groups should decrease the chain mobility, giving rise to more broadening of the NMR signals.

Fig. 3 shows ^{13}C NMR spectra of PIC hydrogels as measured soon after mixing the solutions in which molar ratios of SS/AAn are all 1/1. Fig. 3(a) is a spectrum of PIC gel prepared from PSS and PAAn. Sharp signals for both PSS and PAAn appeared as compared with that in Fig. 2(a), where the SS/AAn ratio was 4/1. The appearance of sharp peaks of both SS and AAn units may indicate that these free units are rather mobile in the gel state and accordingly that the fraction of the ion-paired SS and AAn units are rather small.

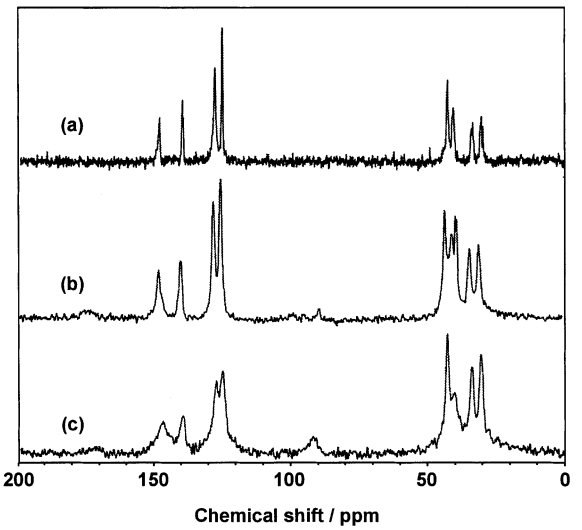


Fig. 3. ^{13}C NMR spectra of PIC hydroges with monomer mole ratios SS/AAn of 1/1: (a) PSS/PAAn, (b) PCIPA-1/PAAn and (c) PTIPA/PAAn.

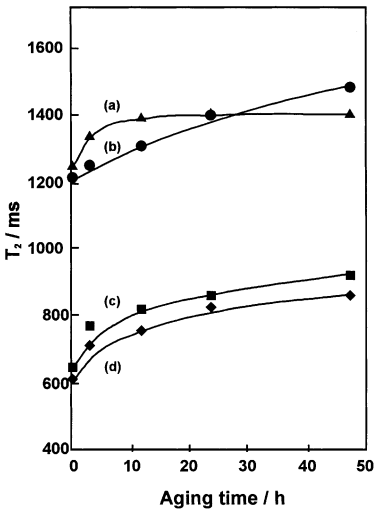


Fig. 4. Dependence of ^1H relaxation time T_2 for PIC hydrogels on aging time after preparation. (a) PSS/PAAn, (b) PCIPA-1/PAAn, (c) PCIPA-2/PAAn and (d) PCIPA-3/PAAn.

Fig. 3(b) and (c) shows spectra for PCIPA-1/PAAn and PTIPA/PAAn gels. It is of interest that the relative peak intensities for PAAn in these gels are higher than that in Fig. 3(a), while those of PSS are lower. This may indicate that the mobility of SS units decrease probably due to hydrophobic interactions of CIPA or TIPA units in the vicinity of the SS units. It is also noted that the line width broadening for these gels is a similar tendency in the case of SS/AAn of 4/1 (Fig. 2(b) and (c)).

3.3. Relaxation time ^1H T_2 of hydrogels

When the polycation and polyanion solutions are mixed, a large fraction of ionic units did not form ion pairs and these residual, free ionic groups may contribute to swelling in water, though the network structure of the gel is formed (primary complex formation) [11]. It is anticipated that the free SS and AAn units tend to form ion pairs by their mutual collision with time due to chain mobility in the gel state (secondary complex formation). As the spectra in Fig. 3 show the initial stage of PIC gels, most SS and AAn units with no ion pairs maintain high chain mobilities. This should arise from a spatial hindrance of these units to collide with each other. It is of interest to pursue the rate of the secondary complex formation in relevant to application of the PIC gels to TAE. ^1H T_2 measurements were carried out to estimate a change in chain mobility with time after mixing the polycation and polyanion solutions.

Fig. 4 shows a dependence of ^1H T_2 for PIC hydrogels on aging time after their preparations. T_2 for PSS/PAAn increased rapidly with time and became almost constant after about 12 h. On the other hand, T_2 increased gradually with aging time for the other PIC hydrogels. The increament of T_2 indicates an increase in mobility of water molecules. When polycation and polyanion are mixed, the network gel structure of PIC is thought to grow with time.

First, the primary complex is formed by ion pairings between cation and anion units which are spatially close to each other soon after the mixing. In this stage, the complex will be formed at the interface of the polycation and polyanion phases which are thought to be dispersed heterogeneously just after mixing the solutions. As this structure should be a metastable state, complex formation gradually proceeds via mutual diffusion of the polymer chains through the interface to attain to a thermodynamically stable state, i.e. the secondary complex formation. This process may accompany changes in polymer chain conformation such that neutralization of the

charged SS and AAn units gives rise to a contraction of the initial, expanded polymer coils.

Many polycation (or polyanion) chains should be mutually interpenetrated or entangled, based on random coil concept, in such a concentrated solution before mixing as used in this study. Water molecules in the concentrated polymer solution are in a low entropy state, irrespective of their hydration to ionic groups of polymer chains, as compared with those in its pure liquid where they have a high mobility. When ion pairings take place between the oppositely charged polymer chains and subsequently the chains are contracted, the interaction between water molecules and polymer chains decreases. This gives rise to an increase in molecular motion of water and hence an increase in ^{1}H T_2 value [12].

T_2 values were much larger for PSS/PAAn and PCIPA-1/PAAn than for PCIPA-2/PAAn and PCIPA-3/PAAn. The difference in T_2 values between the two groups was far beyond each T_2 change over the whole range of measuring time. It is worthy to compare T_2 values in these mixtures with those for the polyanion solutions before mixing. T_2 value was 1280, 614 and 714 ms for PCIPA-1, PCIPA-2 and PCIPA-3 solutions, respectively. These values are very close to those measured just after mixing (at time = 0 h in Fig. 4) for the corresponding mixtures. It can be said, therefore, that the molecular motion of water is more restricted in the concentrated PCIPA-2 and PCIPA-3 solutions than in PCIPA-1 one.

T_2 value for PSS solution itself was 978 ms which is much lower than 1250 ms for PSS/PAAn just after mixing (Fig. 4(a)). This indicates that the mobility of water molecules is restricted to some extent in PSS solution and abruptly increases as soon as the PSS solution is mixed with PAAn solution. This can be accounted for by a high rate of ion pair formation between SS and AAn units in case of PSS/PAAn as compared with the cases of the copolymers/PAAn, the SS content being as low as ca. 76 mole% in the copolymers. The relative viscosity of 1.43 in DMSO for PSS, which is comparable to that for PCIPA-1 may support a high mobility of PSS chains so that they can easily undergo their conformational change and diffusion when being mixed with PAAn solution.

Taking into consideration the molecular properties of PCIPA-1 with a SS content of ca. 76 mol% and a low viscosity as compared with PCIPA-2 (SS content of 50 mol%) and PCIPA-3 (a high relative viscosity of 3.58) (Table 1), respectively, the PCIPA-1 molecules should have a less interchain interaction due to repulsive forces among SS units and a high molecular chain mobility. This gives rise to a high molecular mobility of water occluded in interstices of entangled PCIPA-1 chains and accordingly T_2 value as high as 1280 ms.

On the other hand, PCIPA-2 chains seem to have a high interchain interaction due to a comparable hydrophobic interaction between CIPA units (because of a low SS content). This should decrease the chain mobility and subsequently the mobility of water occluded therein, giving rise to a low T_2 value (614 ms). Although the solution viscosity of PCIPA-2 was lowest of all, the interchain interaction between CIPA units is thought to play a role in restriction of chain mobility. The low T_2 value for PCIPA-3 can be interpreted by its high molecular weight as estimated by the highest solution viscosity. This is because the higher the chain length is, lower the molecular mobility is, due to a large amount of crosslinks which arise from chain entanglements.

T_2 value for PSS/PAAn increased up to ca. 12 h and then leveled off. This indicates that the mutual diffusions of PSS and PAAn chains and maximum ion pairings were accomplished within 12 h. No further PIC formation is thought to take place thereafter. On the other hand, T_2 for PCIPA-1, 2 and 3 increased gradually with time and did not become constant even after 40 h. The gradual increase of T_2 within the time range measured means that PIC formation proceeded for a very long time during which conformational changes of these copolymer chains due to a change in interchain interactions of the CIPA groups took place.

3.4. Hydrodynamic properties of hydrogels

In order to examine the hydrodynamic properties of PCIPA hydrogles, outflow time of PIC hydrogels, where they flow out through a glass tube (3 mm diameter and 6 cm long) under atmospheric pressure, was measured as a function of aging time after preparation. Fig. 5 shows the time dependence of outflow time for the PIC hydrogels. It is found that outflow time increased with aging time in all the cases. This indicates that the outflow time is consistent with hydrogel viscosity. Namely, the network structure of PCIPA hydrogel developed with aging

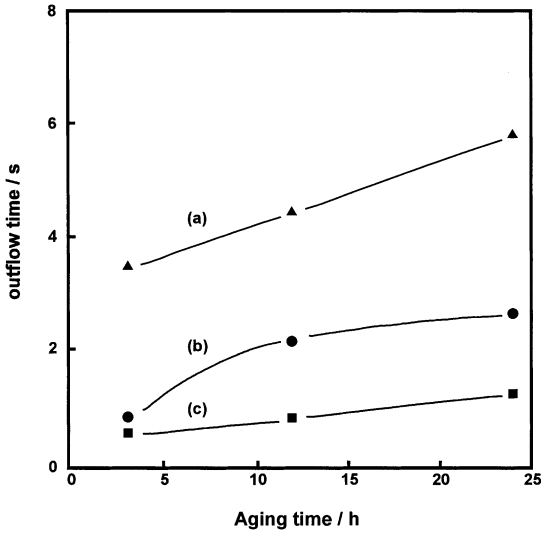


Fig. 5. Time dependence of outflow time of PIC hydrogels through a glass tube with a diameter of 3 mm and a length of 60 mm under atmospheric pressure: (a) PCIPA-3/PAAn, (b) PCIPA-1/PAAn and (c) PCIPA-2/PAAn.

time. The outflow time at a given aging time was in the order PCIPA-3/PAAn > PCIPA-1/PAAn > PCIPA-2/PAAn. This tendency is in accord with the relative viscosities of the copolymers: PCIPA-3 > PCIPA-1 > PCIPA-2. This indicates that three-dimensional networks of polyion complexes developed with aging time. It is also found that the mobility of water molecules occluded in the gel networks is not dependent on the gel viscosity but on the local interchain interactions.

As for the fluidity of the hydrogels, it is noted that they did not flow at all through a glass tube with a diameter less than 1 mm which is much larger than the diameter of capillaries of veins. This suggests that the hydrogels prepared in this study do not flow out through the capillaries of veins but reach there through a catheter under a moderate pressure. In addition, polyion complexes did not precipitate over the whole range of measurement. This behavior means that the hydrogels from PCIPA copolymers are stable and suitable for TAE.

3.5. Embolization by radiopaque hydrogels as studied by X-ray radiogram

All the hydrogels used for embolization experiments were prepared by mixing 30 wt % aqueous solutions of PCIPA-1, 2 and 3 and that of PAAn. Fig. 6 shows X-ray radiograms of a removed porcine kidney, into the vein of which a radiopaque hydrogel prepared from PCIPA-1 and PAAn was injected through a catheter. In Fig. 6(a), the hydrogel introduced into the vein is clearly seen and a weak, wide-spread and gradational X-ray absorption contrast is also seen due to the thickness of the kidney. As capillaries of the vein are slightly seen in the periphery of the kidney, the hydrogel seems to be introduced deep into capillaries. This PIC hydrogel has enough fluidity to be introduced into both thick branches and capillaries. The X-ray contrast of the

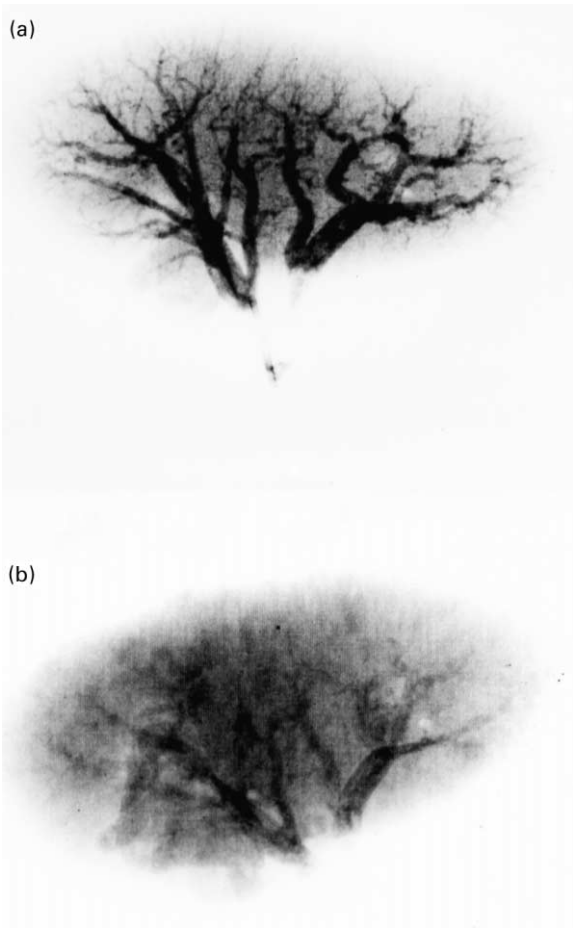


Fig. 6. X-ray radiograms of a removed porcine kidney embolized with a PIC hydrogel prepared by mixing 30 wt % aqueous solutions of PCIPA-1 and PAAn: Immediately (a) and 24 h (b) after injection.

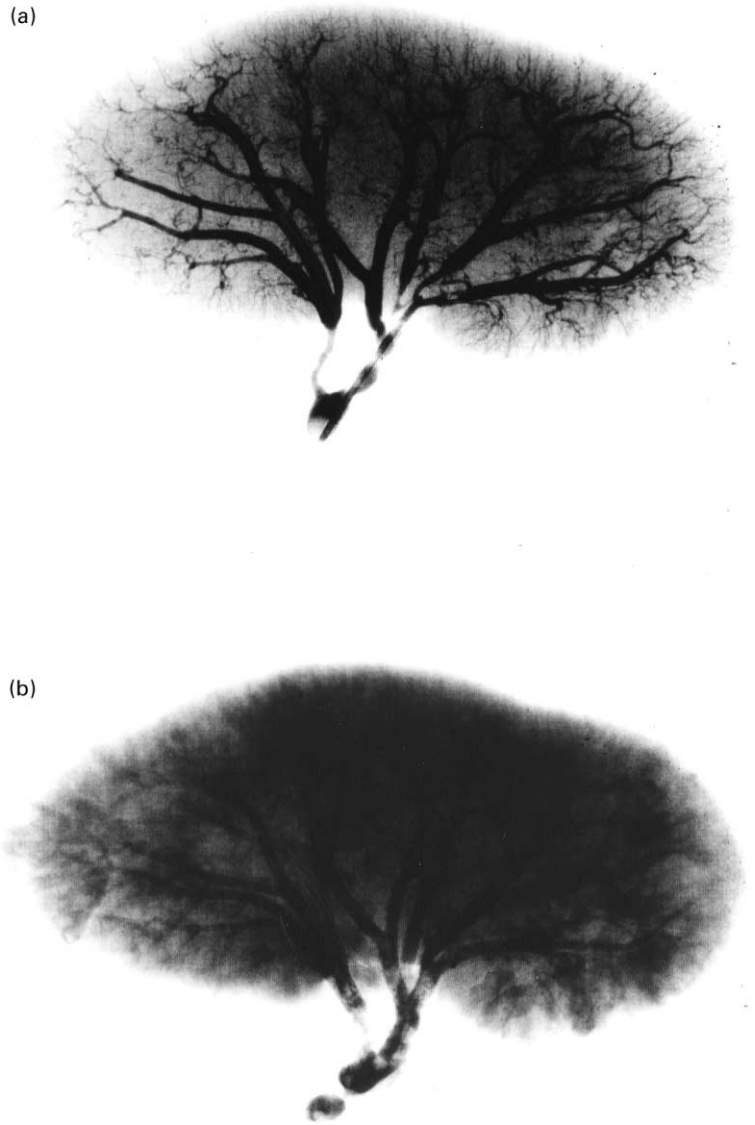


Fig. 7. X-ray radiograms of a removed porcine kidney embolized with a PIC hydrogel prepared by mixing 30 wt % aqueous solutions of PCIPA-2 and PAAn: Immediately (a) and 24 h (b) after injection.

thick branches and capillaries are deteriorated 24 h after injection (Fig. 6(b)). The X-ray contrast of the capillaries completely disappeared, though that of the thick branches remained. The change in X-ray contrast with aging time can be accounted for by draining of radiopaque, low molecular weight copolymers, which were not incorporated via ionic bonds in the three dimensional network gel, through the capillaries to the peripheral tissues.

Fig. 7 shows the corresponding X-ray radiograms for PIC hydrogel prepared from PCIPA-2 and PAAn. As seen in Fig. 7(a), a clear X-ray contrast was obtained not only in the thick vein but also in the capillaries just after injection of the hydrogels, where a relatively weak, wide-spread, gradational X-ray contrast due to thickness of the organ is also seen. Contrast of capillaries is enhanced compared with Fig. 6(a). As the iodine content of PCIPA-2 is

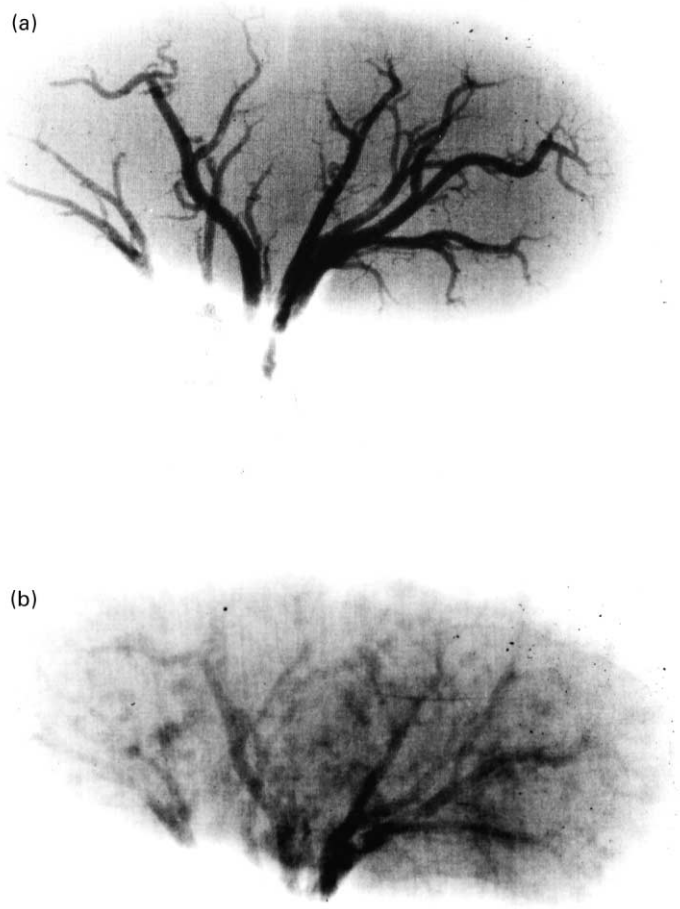


Fig. 8. X-ray radiograms of a removed porcine kidney embolized with a PIC hydrogel prepared by mixing 30 wt % aqueous solutions of PCIPA-3 and PAAn: Immediately (a) and 24 h (b) after injection.

500 mg/g-polymer, highest of all the copolymers, details of capillaries are clearly observed. This result indicates that the contrast of radiogram increases with iodine concentration. The X-ray contrast of both the vein and the capillaries turned obscure to some extent at 24 h after the injection (Fig. 7(b)). This shows draining of some radiopaque copolymer molecules through the capillaries to peripheral tissues, similarly to the case of PCIPA-1/PAAn hydrogel.

Fig. 8 shows the corresponding X-ray radiograms for PCIPA-3 which has the highest molecular weight. As is seen in Fig. 8(a), X-ray contrast immediately after hydrogel injection was clearly seen in thick branches but not in the capillaries compared with those for PCIPA-1 and 2. The very slight X-ray contrast in the capillaries is due to a low fluidity of the hydrogel which may arise from a difficulty of change in gel texture to be deformed into small size of 5–10 μm. The X-ray contrast was found to be kept to a large extent 24 h after injection as is evident from Fig. 8(b). This indicates that most radiopaque PCIPA-3 remained in the vein in the form of hydrogel, but a small amount of the copolymer which did not join three-dimensional network of the gel drained out through the capillaries. As is anticipated from the highest molecular weight and the longest outflow time of PCIPA-3, it is said that its three dimensional

gel network with PAAn is well grown to be suitable for embolization.

4. Conclusion

In order to design the radiopaque embolizing materials which flow through a catheter and reach the vein capillaries, polycations consisting of radipaque monomers and anionic styrene sulfonate (SS) groups were parepared and their concentrated aqueous solutions were mixed with that of polyallylamine (PAAn), i.e. a polycation. It was found that a stable hydrogel was obtained by a formation of polyion complex just after mixing. A structural study by NMR revealed that the radiopaque hydrogel is formed by a strong interchain interaction between SS and AAn groups, accompanying a decrease in molecular mobility of the polymer chains and an increase in mobility of water molecules occluded in the polymer coils. Viscosity data revealed that the present hydrogel has a fluidity, enough to pass through a thick catheter and veins but not through the thin capillaries. From the embolization experiments, it is concluded that radiopaque copolymer with SS groups which contains an iodine content higher than 300 mg/g-polymer and a high molecular weight can give a radiopaque hydrogel with a high contrast of X-ray radiograms and a long retention in veins.

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