Synthesis and Properties of Radiopaque Polymer Hydrogels: Polyion Complexes of Copolymers of Acrylamide Derivatives Having Triiodophenyl and Carboxyl Groups and *p*-Styrene Sulfonate and Polyallylamine

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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. Acrylamide derivatives having triiodophenyl and carboxyl groups were synthesized and copolymerized with sodium styrene sulfonate at various molar ratios of initiator to monomer and temperatures. Hydrogels were prepared by mixing aqueous solutions of the obtained radiopaque copolyanions and polyallylamine. Embolization was examined by injection of these hydrogels into vein of a removed porcine kidney as a preliminary test for transcatheter arterial embolization (TAE) for hepatocellular carcinoma. It was found that the hydrogels prepared from the copolycation obtained under particular conditions give high X-ray contrasts of the vein and remained there, though copolycations with low molecular weights had a tendency to drain through the capillaries to the peripheral tissues. It is therefore concluded that the hydrogels examined in the present study are promising for vascular embolization.

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Introduction

Transcatheter arterial embolization (TAE) using radiopaque materials has been the predominant method for hepatocellular carcinoma[1]. Requirements of radiopaque materials for TAE are 1) no damage to veins, 2) fluidity to pass through a catheter, 3) embolization of veins for a given period and 4) radiopacity to monitor embolization by X-ray radiography. There have been used no polymer hydrogels but a mixture of lipiodol which is a commercial, hydrophobic low molecular weight X-ray contrast medium and cisplatin[2], gelatin sponge combined with lipiodol[3], polysaccharide solution with anticancer drugs[4] and so on. This indicates that embolizing materials presently used for TAE are principally mixtures of water soluble natural polymers and lipiodol. Microspheres of synthetic polymers with or without radiopacity were also used for embolization[5-8].

We have anticipated that hydrogels of radiopaque polyion complexes (PIC) formed by mixing aqueous solutions of polycation and polyanion will be available instead of hydrophobic lipiodol for embolic therapy by their transcatheter injection into feeding veins, 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 for intravascular injection, while they are viscous enough to embolize peripheral veins without damaging tissues.

As a preliminary study[9], we reported on a polymer hydrogel consisting of synthetic PIC, which was prepared by mixing a solution of 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 PIC hydrogel thus prepared was transparent and so viscous like albumen as to be picked up with tweezers. It was injected through a catheter into the vein of a removed porcine kidney, which was used because of an easy handling for the preliminary experiment. It was found that the hydrogel was suitable for handling

the clearly contrasted X-ray radiogram of the kidney. This indicates that the hydrogel does not flow out through the capillaries to the peripheral tissues at all. However, a diffuse X-ray radiogram taken at 24 h after the injection, where the X-ray contrast in the region of capillaries disappeared, showed a draining of the contrast medium into the peripheral tissues. Taking into consideration the structure

of the PIC gel itself which are not decomposed into molecularly isolated, fluidal polymers but stable via

due to the water soluble contrast medium as a low molecular compound which is so small in molecular size to easily pass through the blood capillaries with a diameter of 5 - 10 μm.

We also reported in the previous paper[9] on synthesis of a radiopaque polyanion having carboxylated triiodophenyl groups, PCIPA (polymer of CIPA monomer as will be mentioned below) and its PIC hydrogel with PAAn which was prepared by mixing their aqueous solutions without using Omnipaque 350. As the hydrogel of PCIPA and PAAn was found to be unstable and precipitated from the system, we examined a ternary system consisting of aqueous solutions of PSS, PCIPA and PAAn to avoid the precipitation of the polymers. As a result, the X-ray contrast of vein of a removed porcine kidney at 24 h after the gel injection was much improved as compared with the previous case of PSS/PAAn hydrogels in Omnipaque 350. However, the X-ray contrast was found to be deteriorated due to a partial draining or flow of PCIPA through the capillaries. It can be said that a hydrogel prepared from radiopaque polyion in aqueous solution is useful in embolization but a polyanion having carboxylate groups, which does not give a strong, stable ionic bonds with polycation, gradually flows to drain to the peripheral tissues, though polyanion with carboxylate groups are occluded in the PSS/PAAn gel network.

In this paper, we will report on the synthesis of a radiopaque copolyanion having the carboxylated triiodophenyl groups and sulfonate groups in the chain and the embolization of the vein of a removed porcine kidney by its hydrogel with PAAn in order to avoid draining through the capillaries. A study was also made on the synthesis and hydrogel of copolyanion having higher iodine content in the monomer.

Experimental

Materials

All chemicals obtained from commercial sources were used without further purification, unless otherwise noted. Tetrahydrofuran (THF) was distilled over sodium. 2,2'-Azobisisobutyronitrile (AIBN) as initiator was recrystallized from methanol.

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

A mixture of 3-amino-2,4,6-triiodobenzoic acid (1.94 mmol), acryloyl chloride (30.7 mmol) and 2,4-di-*t*-butylphenol (0.12 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 methanol solution. Chemical shift δ (ppm) of ^{1}HNMR: 5.80 (1H), 6.23 (1H), 8.00 (1H), 8.28 (1H)

and 10.11 (1H).

Place Scheme 1 here

Synthesis of N-[3-(carboxy-2,4,6-triiodophenylcarbamoyl) 2,4,6-triiodophenyl] acrylamide (CIPCIPA)

In order to increase the iodine content in monomer, CIPCIPA was synthesized from CIPA by the dicyclohexylcarbodiimide (DCC) method. To a mixed solution of CIPA (2 mmol) and N-hydroxysuccinimide (2 mmol) in THF (20 mL), 3-amino-2,4,6-triiodobenzoic acid (2 mmol) and DCC (2 mmol) were added and the reaction was carried out with stirring at room temperature for 12 h. After filtering the reaction mixture, the solvent was evaporated from the filtrate. The residual precipitate was dissolved in chloroform and washed with aqueous solutions of citric acid, sodium bicarbonate and sodium chloride three times each. The organic phase was dried over sodium sulfate. CIPCIPA was isolated by adding petroleum ether to the dried organic solution. Chemical shift δ (ppm) of ^{1}H NMR: 5.80 (1H), 6.23 (1H), 6.40 (1H), 8.15 (1H), 8.30 (1H), 8.52 (1H) and 10.20 (1H).

Copolymerization of CIPA or CIPCIPA and sodium styrene sulfonate (SSNa)

Copolymerization of radiopaque monomer (CIPA or CIPCIPA) and SSNa was carried out initiated by AIBN at the molar initiator/total monomer ratio of 1/100 and the total monomer concentration of 0.8 mol/L in dimethyl sulfoxide (DMSO) with stirring at 80^{o}C for 20 h in a glass ampule sealed in vacuo. Copolymerization was also carried out over a wide range of temperature. The

for all the copolymerization. The reaction mixture was precipitated by adding acetone/methanol (9/1) mixture, the resultant precipitate being further filtered, washed with acetone and dried.

NMR measurement

^{1}H NMR spectra were recorded in a JEOL Alpha 500 NMR spectrometer at room temperature using DMSO-d$_6$ either as a solvent or as internal reference.

Viscometry

Relative viscosity of the copolymer was measured at 25^{o}C as the ratio of flow time of solution to that of solvent at a polymer concentration of 0.1 g/100 mL in DMSO using an Ubbelohde viscometer.

ESCA measurement

Electron spectroscopy for chemical analysis (ESCA) was carried out in a Perkin Elmer ESCA PHI-5600 spectrometer to estimate iodine and comonomer contents in the copolymer from the ratio of iodine to sodium and the ratio of iodine and sulfur, respectively.

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. Embolization experiments were made by injecting the gel prepared from the 30 wt % solutions through a catheter into vein of a removed porcine kidney. X-ray radiograms were taken immediately and 24 h after the injection.

Results and discussion

Copolymers of CIPA and SSNa: P(CIPA-co-SS)

In Table 1 are listed conversion of the copolymerization of CIPA and SSNa, copolymer composition as the molar ratio of CIPA to SS, solubility of the copolymer P(CIPA-co-SS) in water and stability of the gel formed by mixing aqueous solutions of the copolymer and PAAn as a function of molar ratio of initiator to total comonomers charged in the polymerization system. It is noted that all the copolymerizations proceeded to conversions as high as more than 70 %. The resultant copolymers were all readily soluble in water. The highest CIPA, i.e., iodine content in the copolymer was obtained at initiator/monomer ratio of 1/100. The copolymers synthesized at the initiator/monomer ratio lower than 1/400 gave rather stable hydrogels which was able to be picked up with tweezers when a 10 wt % solution of these copolymers was mixed with a corresponding solution of PAAn, while those synthesized at the ratio higher than 1/300 gave stable hydrogels which seemd to be applicable to embolization.

Place Table 1 here

In order to pursue a better polymerization condition, copolymerization was carried out at various temperatures at a fixed initiator/monomer ratio of 1/100, where the highest iodine content, which is an important factor of X-ray contrast in embolization, was attained at 80^{o}C. As is listed in Table 2, both the conversion and the iodine content were highest for the copolymers synthesized at 70 - 90^{o}C. The solubility in water and gel stability for these copolymers were also found to be acceptable for embolization.

The polymerization at high temperatures above 100^{o}C seems to be accompanied by a side reaction of elimination of bulky iodine atoms from the monomer or the polymer, probably giving rise to a hydrogel with less X-ray contrast. This is because the content of CIPA in the copolymer decreased with decreasing polymerization temperature. The CIPA/SS ratio of the copolymer obtained at 30^{o}C was as low as 1/147. In addition, this polymer did not give a stable hydrogel with PAAn but powder precipitates. The very low CIPA/SS value and the formation of powder

precipitates indicate that the polymerization itself hardly proceeded at 30oC. It can be said that the copolymers obtained at 70 - 90oC have molecular weights and iodine contents suitable for embolization.

Place Table 2 here

Relative viscosity of aqueous P(CIPA-co-SS) solution is plotted against copolymerization temperature in Fig. 1. The relative viscosity, as a measure of molecular weight, increased with increasing polymerization temperature, attained to a maximum at 50oC and decreased thereafter. In comparison with the copolymer composition listed in Table 2, it may be suggested that polymerization of SSNa predominantly took place around 50oC. On the other hand, the reactivity of CIPA increased with increasing temperature, while that of SSNa decreased, giving rise to a high iodine content in the copolymers which may have molecular weights enough to form hydrogel for embolization.

Place Fig. 1 here

Copolymers of CIPCIPA and SSNa: P(CIPCIPA-co-SS)

In order to pursue a possibility of raising the content of iodine in the copolymer, we carried out synthesis of CIPCIPA having two triiodophenyl groups in the monomer unit and its copolymerization with SSNa at various temperatures. Compared with the case of P(CIPA-co-SS) (Table 2), a similar tendency was found that the conversion increased with polymerization temperature, attained to a maximum at 60oC and decreased thereafter. It is also noted, however, that the conversion at 60oC was as low as ca. 60 % at highest. From very low values of the molar CIPCIPA/SS ratio and no stable hydrogel formation for polymerization temperature of 30 and 40oC, it is said that the reactivity of CIPCIPA and the molecular weight of resultant copolymers are very low. It is also found that the copolymerization at temperatures higher than 90oC gave lower conversions and iodine content in the resultant copolymers, being similar to the corresponding case of P(CIPA-co-SS). This is probably due to a steric hindrance of the bulky side group of CIPCIPA monomer and side reactions such as elimination of iodine from the monomer or the copolymer and/or hydrolysis of the amide bond of the CIPCIPA unit during polymerization at high temperatures. As a result, it can be said that the highest iodine content was obtained at 80oC.

Place Table 3 here

Relative viscosity of the copolymers P(CIPCIPA-co-SS) is also plotted in Fig. 1, indicating a very similar tendency to that for P(CIPA-co-SS). The fact that hydrogels prepared from 10 wt % aqueous solutions of P(CIPA-co-SS) or P(CIPCIPA-co-SS) and PAAn were stable except for the low polymerization temperatures suggests that very high molecular weight copolymers are not

always necessary but copolymers having relative viscosity in DMSO higher than ca. 1.2 seem to be available for stable hydrogel formation. It is also said that copolymers with moderate relative viscosity are preferable, because hydrogel can contain higher copolymer content, which provides high X-ray contrast, keeping its fluidity to pass through a catheter.

Iodine content of P(CIPA-co-SS) and P(CIPCIPA-co-SS)

It is of interest to compare the iodine content of the copolymers to that of a commercial low molecular weight X-ray contrast medium, Omnipaque 350 which contains 350 mg iodine per mL of solution. Fig. 2 shows polymerization temperature dependences of iodine content of P(CIPA-co-SS) and P(CIPCIPA-co-SS) in mg iodine per g of copolymer. The iodine content was very low in the copolymers obtained at polymerization temperature of 30 and 40oC and still as low as less than 200 mg/g at 50oC, at which the highest conversion was obtained for both copolymers. The iodine content reached more than 300 mg/g at temperatures from 60 to 90oC for P(CIPA-co-SS) and ca. 440 mg/g at 80oC for P(CIPCIPA-co-SS) and then decreased down to a level of ca. 200 mg/g with increasing polymerization temperature.

Omnipaque 350 is an aqueous solution of X-ray contrast molecule iohexol. As we have chosen 30 wt % aqueous solutions of the copolymers and PAAn to prepare hydrogels for embolization, the resultant iodine contents in their hydrogels are nearly 1/10 of the corresponding values in mg/g of copolymer mentioned above.

Place Fig. 2 here

Embolization by PIC hydrogels

All the hydrogels used for embolization experiments were prepared from 30 wt % aqueous solutions of the copolymer having a high iodine content, which was obtained at 80oC, and PAAn. P(CIPA-co-SS) obtained at 50oC was also subjected to embolization experiment in order to investigate the effect of its higher molecular weight and lower iodine content on the radiopacity.

Fig. 3 shows X-ray radiograms of a removed porcine kidney, into the vein of which a hydrogel prepared from P(CIPA-co-SS) with a comparatively high molecular weight obtained at 50oC and PAAn was injected. It is noted here that the hydrogel was introduced into only one of the vein branches and that a weak, wide-spread and gradational X-ray absorption is due to the thickness of the kidney. In Fig. 3(a), X-ray contrast immediately after hydrogel injection was rather clearly seen in thick branches but not in the capillaries as compared with the case of PSS/PAAn hydrogel in Omnipaque 350. The very slight X-ray contrast in the capillaries is due to a low fluidity of the hydrogel

5 - 10 μm. The X-ray contrast was found to be kept to a large extent at 24 h after injection as is

evident from Fig. 3(b). This indicates that most radiopaque P(CIPA-co-SS) 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 a result, this PIC hydrogel can be applied to embolization, though the iodine content and accordingly the X-ray contrast was not so high.

Place Figs. 3 and 4 here

Fig. 4 shows the corresponding X-ray radiograms in case of P(CIPA-co-SS) obtained by polymerization at 80oC which has the highest iodine content but has a molecular weight lower than that for 50oC. As is seen in Fig. 4(a), a clear X-ray contrast was obtained not only in the thick vein but also in the capillaries just after the hydrogel injection, where a relatively weaker, gradational X-ray contrast due to thickness of the organ is also seen. The X-ray contrast of both the vein and the capillaries was deteriorated to a large extent at 24 h after the injection (Fig. 4(b)). This can be accounted for by draining of radiopaque copolymer molecules, which were not incorporated via ionic bonds in the three dimensional network gel, through the capillaries to the peripheral tissues.

Fig. 5 shows the X-ray radiograms of a removed porcine kidney, into the vein of which the hydrogel prepared by mixing 30 wt % aqueous solutions of P(CIPCIPA-co-SS) polymerized at 80oC and PAAn was injected. The X-ray contrast of the capillaries of the vein just after the injection (Fig. 5 (a)) seems more or less clearer than that for P(CIPA-co-SS) (Fig. 4(a)). Similarly to the case of P(CIPA-co-SS) (Fig. 4(b)), the X-ray contrast was highly deteriorated at 24 h after the injection (Fig. 5(b)), though the contrast of the capillaries remained to some extent.

This may be also due to draining of some radiopaque copolymer molecules as in the case of P(CIPA-co-SS).

Place Fig. 5 here

Conclusion

The X-ray radiograms of the above mentioned radiopaque hydrogels injected into vein of removed porcine kidney show that the gel prepared from P(CIPA-co-SS) obtained at 50oC remained stable at 24 h after the injection, though the contrast was not high due to the low iodine content. On the other hand, a considerable amount of gels prepared from both copolymers obtained at 80oC did not remain but drained to the peripheral tissues. It can be said that lower molecular weight fractions contained in the copolymers obtained at 80oC did not form stable gel with PAAn but were soluble in the aqueous medium and accordingly drained through the capillaries with diameter of 5 - 10 μm which is much larger than the molecular size of the polymers.

It is therefore thought that P(CIPA-co-SS) and P(CIPCIPA-co-SS) obtained by polymerizations at 60 and 70oC are promising because they have relative viscosities higher than those for 80oC and

iodine contents higher than that for 50oC. Taking into consideration a possibility that the copolymers for 60 and 70oC may also contain low molecular weight fractions, fractional precipitation of the copolymers from the DMSO solution will give hydrogels which do not drain through the capillaries but are available for a stable embolization and a high X-ray contrast of both the vein and its capillaries. In other words, it can be concluded that the radiopaque PIC hydrogels from the present copolyanion and polycation will be promising materials for TAE.

References

1) R. Yamada, M. Sato, M. Kawabata, H. Nakatsuka, K. Nakamura, S. Takashima, *Radiology*, **148**, 397 (1983)
2) A. Kawakami, H. Yoshioka, A. Ohkusa, T. Okafuji, Y. Ono, H. Shindo, S. Arita, O. Ishida, Y. Yamazoe, H. Matsuoka, S. Ishida, *J. Jpn. Soc. Cancer Ther*., **28**, 794 (1993)
3) Y. Suzuki, S. Hirota, M. Sako, *J. Jpn. Soc. Cancer Ther*., **30**, 1908 (1995)
4) T. Shimizu, M. Sako, S. Hirota, H. Watanabe, M. Hasegawa, K. Okuda, M. Hase, K. Tanaka, M. Kono, K. Sakamoto, *J. Jpn. Soc. Cancer Ther*., **23**, 673 (1988)
5) D. Horak, M. Metalova, F. Svec, J. Drobnik, J.Kalal, M. Borovicka, A. Adamyan, O. S. Voronkova, K. Z. Gumargalieva, *Biomaterials*, **8**, 142 (1987)
6) D. Horak, E. Guseinov, A. Adamyan, M. Titova, M. Danilov, N. Trostenyuk, O. Voronkova, K. Gumargalieva, *J. Biomed. Mater. Res*., **33**, 193 (1996)
7) Y. M. Wanga, H. Sato, I. Horikoshi, *J. Control. Rel*.., **49**, 157 (1997)
8) P. Flandroy, Ch. Grandils, B. Daenen, F. Snaps, R. F. Dondelinger, R. Jerome, R. Bassleer, E. Heinen, . *Control. Rel*.., **44**, 153 (1997)
9) T. Komoto, N. Shiobara, M. Manaka, M. Okamura, T. Yamanobe, S. Hosoi, "Synthesis and Vascular Embolization of Radiopaque Polymer Hydrogels", in "Advances in Polymeric Biomaterials Science", ed. T. Akaike, T. Okano, M. Akashi, M. Terano, N. Yui, CRC (1997) 657

Figure captions

Fig. 1 Polymerization temperature dependence of relative viscosity for P(CIPA-co-SS) (●) and P(CIPCIPA-co-SS) (□). Relative viscosity was measured at 0.1 g/100mL in DMSO.

Fig. 2 Polymerization temperature dependence of iodine content for P(CIPA-co-SS) (●) and P(CIPCIPA-co-SS) (□). Iodine content was measured by ESCA.

Fig. 3 X-Ray radiograms of a removed porcine kidney embolized with a PIC hydrogel prepared by mixing 30 wt % aqueous solutions of P(CIPA-co-SS) polymerized at 50°C and PAAn. Immediately (a) and 24 h (b) after the injection.

Fig. 4 X-Ray radiograms of a removed porcine kidney embolized with a PIC hydrogel prepared by mixing 30 wt % aqueous solutions of P(CIPA-co-SS) polymerized at 80°C and PAAn. Immediately (a) and 24 h (b) after the injection.

Fig. 5 X-Ray radiograms of a removed porcine kidney embolized with a PIC hydrogel prepared by mixing 30 wt % aqueous solutions of P(CIPCIPA-co-SS) polymerized at 80°C and PAAn. Immediately (a) and 24 h (b) after the injection.

Table 1 Effect of initiator concentration on conversion, copolymer composition and properties of P(CIPA-co-SS)

Initiator/Monomer[a]	Conversion(wt%)	CIPA/SS[b]	W.S.[c]	Gelation[d]
1/ 50	87.6	1/4.6	◎	○
1/ 100	88.3	1/2.8	◎	○
1/ 150	97.8	1/4.2	◎	○
1/ 200	83.9	1/4.9	◎	○
1/ 300	76.6	1/ 16	◎	○
1/ 400	93.8	1/4.8	◎	◎
1/ 600	72.6	1/ 11	◎	◎
1/ 800	79.6	1/7.5	◎	◎
1/1000	70.8	1/ 22	◎	◎

a) Molar ratio of initiator to total monomers in copolymerization of CIPA and SS at 80℃, initiated by AIBN. Total monomer concentration: 0.8 mol/L in DMSO.

b) Copolymer composition as molar ratio of CIPA to SS, measured by ESCA.

c) Solubility of copolymers in water: readily soluble (◎).

d) Stability of hydrogel prepared by mixing 10 wt % aqueous solutions of the copolymer and PAAn: albumen-like gel which can be picked up with tweezers (◎) and albumen-like gel which is, however, broken when being picked up with tweezers (○).

Table 2 Effect of copolymerization temperature on conversion, copolymer composition and properties of P(CIPA-co-SS)

Copolymerization temp.(°C) [a]	Conversion(wt%)	CIPA/SS [b]	W.S. [c]	Gelation [d]
30	40.9	1/147	◎	△
40	51.8	1/ 65	◎	○
50	67.9	1/ 14	◎	◎
60	64.7	1/ 3.3	◎	◎
70	84.7	1/ 2.5	◎	◎
80	84.9	1/ 2.9	◎	◎
90	87.8	1/ 2.8	◎	○
100	81.0	1/ 3.7	◎	○
110	76.9	1/ 5.0	◎	○
120	70.8	1/ 5.2	◎	○

a) Copolymerization of CIPA and SS at molar ratio of initiator to total monomer of 1/100, initiated by AIBN. Total monomer concentration: 0.8 mol/L in DMSO.

b) Copolymer composition as molar ratio of CIPA to SS, measured by ESCA.

c) Solubility of copolymers in water: readily soluble (◎).

d) Stability of hydrogel prepared by mixing 10 wt % aqueous solutions of the copolymer and PAAn: albumen-like gel which can be picked up with tweezers (◎), albumen-like gel which is, however, broken when being picked up with tweezers (○) and precipitation (△).

Table 3 Effect of copolymerization temperature on conversion, copolymer composition and properties of P(CIPCIPA-co-SS)

Copolymerization temp.(°C)[a]	Conversion(wt%)	CIPCIPA/SS[b]	W.S.[c]	Gelation[d]
30	21.5	1/ 131	◎	×
40	33.3	1/87.0	◎	△
50	50.5	1/13.6	○	○
60	60.5	1/ 6.5	○	◎
70	44.1	1/ 7.2	◎	○
80	54.1	1/ 2.9	◎	◎
90	53.5	1/ 6.1	◎	◎
100	46.2	1/13.6	◎	◎
110	45.2	1/13.9	◎	○
120	43.0	1/13.0	◎	◎

a) Copolymerization of CIPCIPA and SS at molar ratio of initiator to total monomer of 1/100, initiated by AIBN. Total monomer concentration: 0.8 mol/L in DMSO.

b) Copolymer composition as molar ratio of CIPCIPA to SS, measured by ESCA.

c) Solubility of copolymers in water: readily soluble (◎) and soluble (○).

d) Stability of hydrogel prepared by mixing 10 wt % aqueous solutions of the copolymer and PAAn: albumen-like gel which can be picked up with tweezers (◎), albumen-like gel which is, however, broken when being picked up with tweezers (○), precipitation (△) and neither hydrogel formation nor precipitation (×).

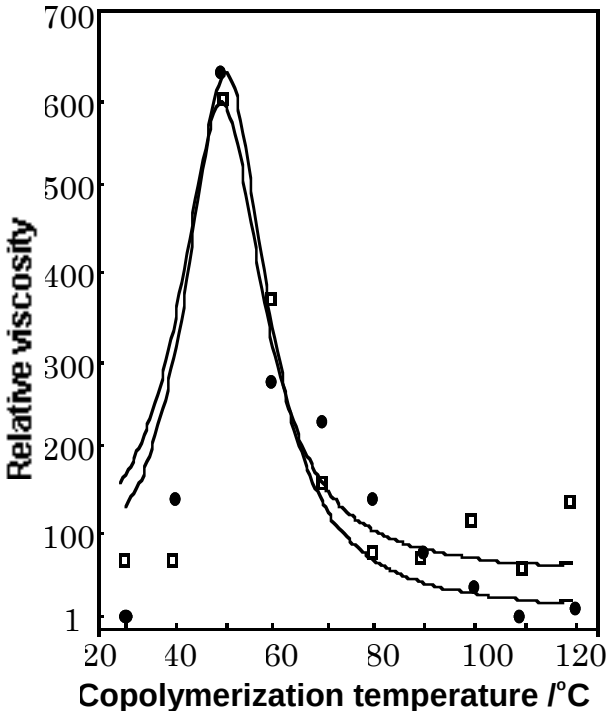

Figure 1. Relative viscosity vs. copolymerization temperature.

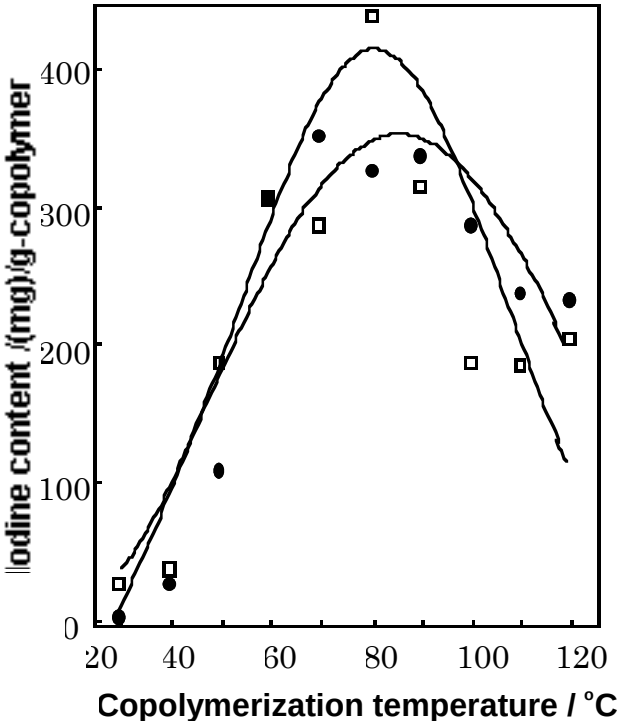

Figure 2. Dependence of iodine content on copolymerization temperature.

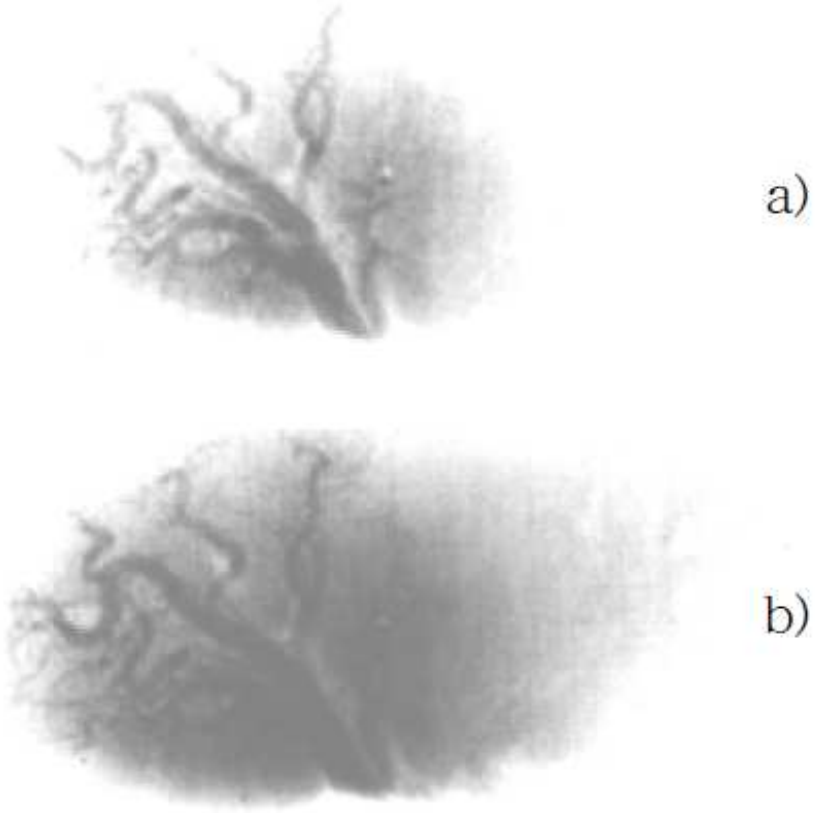

Fig.3. X-Ray radiograms of a removed porcine kidney embolized with a PIC hydrogel preparedby mixing 30 wt % aqueous solutions of P(CIPA-co-SS) polymerized at 50°C and PAAn. Immediately (a) and 24 h (b) after the injection.

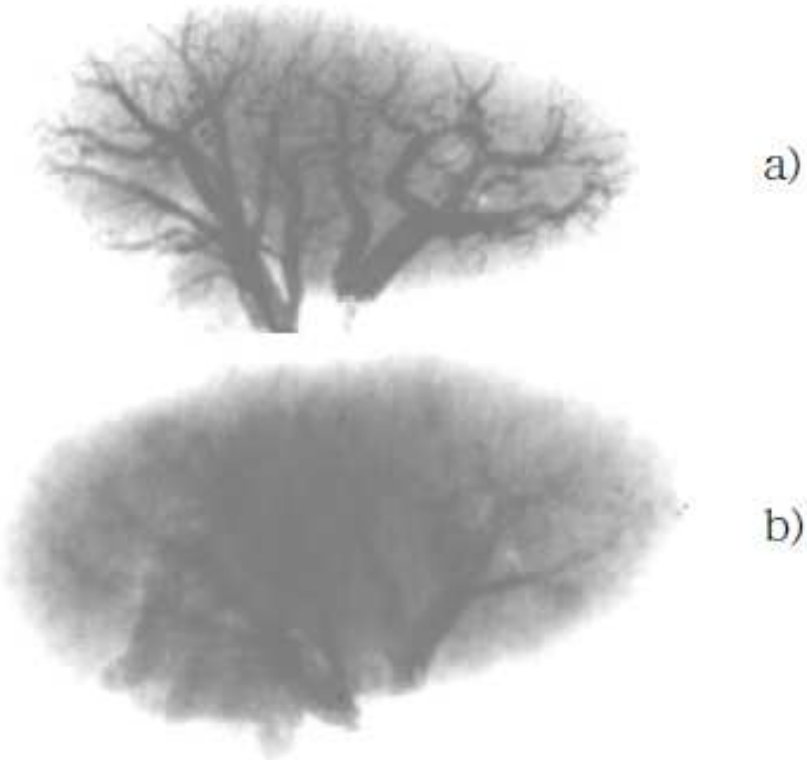

Fig.4. X-Ray radiograms of a removed porcine kidney embolized with a PIC hydrogel prepared by mixing 30 wt % aqueous solutions of P(CIPA-co-SS) polymerized at 80°C and PAAn. Immediately (a) and 24 h (b) after the injection.

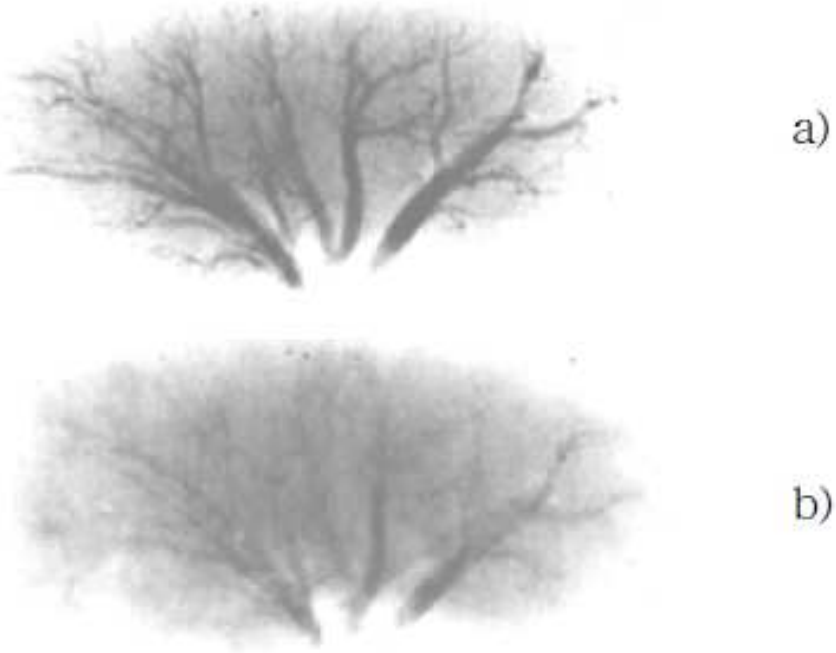

Fig.5. X-Ray radiograms of a removed porcine kidney embolized with a PIC hydrogel prepared by mixing 30 wt % aqueous solutions of P(CIPCIPA-co-SS) polymerized at 80oC and PAAn. Immediately (a) and 24 h (b) after the injection.