Preparation of Monodisperse Poly(vinyl alcohol) Microspheres by Heterogeneous Surface Saponification and Iodine Complex Formation

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ABSTRACT: Monodisperse poly(vinyl acetate) (PVAc) microspheres with high molecular weight obtained by suspension polymerization of vinyl acetate were saponified in alkaline aqueous solution to keep their spherical structure. The saponification was restricted on the surface of the PVAc microspheres and obtained particles had skin/core structure. Various poly(vinyl alcohol) (PVA) microspheres with different diameters and degrees of saponification (DSs) were obtained. The conversion of PVAc to PVA during the heterogeneous surface saponification time were examined by nuclear magnetic resonance spectroscopy and after 72 h hydrogel type PVA microspheres completely saponified were obtained. The crystal melting temperatures of the microspheres obtained by the saponification were measured a constant value of 238°C irrespective of varying DS, and the peaks became enlarged as reaction time. Iodine complexes were formed in saponified microspheres with DS of 41% and 99% by immersing them in I_2/KI aqueous solution and decomposed by the reduction of I_2 in the complexes to $2I^-$ using sodium sulfite to confirm whether the skin formed through the saponification was composed of PVA with high VA content. Obviously, characteristic blue color developments owing to I_5^--PVA complexes were observed in both saponified regions and a red in the PVAc core. Consequently, it was concluded that the PVA skins formed by heterogeneous surface saponification had high DSs. Such complexes endowed polymeric microspheres a good radiopacity which would be useful in clinical treatment of vascular diseases and were examined by X-ray irradiation image. © 2007 Wiley Periodicals, Inc. J Appl Polym Sci 107: 1701–1709, 2008

Key words: PVA microsphere; heterogeneous surface saponification; skin/core structure; iodine complex

INTRODUCTION

Recently, there has been much interest in various polymeric particles applicable to biomedical or environment-friendly fields where it is necessary to design chemical structure of polymer considering its properties like hydrophilicity, sorbability, bioaffinity, and biodegradability and to produce particles with proper size, distribution, and morphologies.[1–4] Especially, spherical particles has been widely used because they could be easily separated to various sized particles with narrow distribution owing to one dimensional criterion, ''diameter,'' furthermore, all results are more predictable than ones with broad distribution.

Various preparation methods for monodisperse polymeric spheres have been tried. Emulsion or suspension polymerizations are the typical and traditional methods, but obtained particles have broad size distribution and it is very difficult to make them separated and monodisperse owing to the aggregations between particles and the static electricity on the surface.[5] Lately, there have been some reports on the preparation of monodisperse poly(vinyl acetate) (PVAc) and poly(vinyl pivalate) (PVPi) as precursors for PVA through low temperature suspension polymerization of vinyl acetate (VAc) and vinyl pivalate (VPi).[6] Other methods in which polymer solution as discontinuous phase is dispersed or emulsified in continuous phase and then particles are obtained by solidification have also been tried.

Poly(vinyl alcohol) (PVA) obtained by the saponification of poly(vinyl ester) like a poly(vinyl ester), such as PVAc or PVPi.[7–14] Furthermore, PVA hydrogels have been concerned greatly and beneficial for various applications because of easy preparation, excellent chemical resistance and physical properties, biocompatibility, biodegradability, and a low price. Furthermore, the high water content and elastic properties make PVA hydrogels advantageous for many biological applications, including wound dressings, bioreactors, controlled release matrices, and bioadhesives.[15–18]

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Especially, PVA particle swelling in an aqueous contrast medium have been used in embolization. Embolization is a noninvasive procedure that occludes an abnormal artery or vein (blood vessel) through the injection of a special embolic material through a catheter. This closes the blood vessel and stops or prevents bleeding. For nearly 30 years, this embotherapy has been used as a means of stopping uncontrollable bleeding from the uterus due to cancer, blood vessel malformations, and traumatic rupture of blood vessels. Many different polymeric materials have been used to occlude vessels. PVA has good biocompatibility, few foreign-body reactions *in-vivo*, high blocking efficiency due to good binding properties, and ease of treatment,[19–21] which are the reasons why PVA among various particular embolic materials, is preferred and extensively used for the selective embolization of vascular lesions.

The irregularity of the particle size and the shape of PVA, however, have caused inflammatory reactions in the walls of embolized vascular tissues and made it difficult to occlude targeted blood vessels selectively.[20–23] Therefore, the regulation of the particle size homogeneity, spherical morphology, and stability to human blood is required. Until now, there have been few results on the preparation of PVA microspheres with uniform diameters and blood stabilities.

It was reported that PVAc microspheres were saponified in aqueous alkali solution containing sodium hydroxide, sodium sulfate, and methanol and converted to PVA from the surface resulting PVA/PVAc skin/core type microspheres.[5,24,25] This heterogeneous surface saponification restricted the reaction on the surface of PVAc microspheres dispersed in aqueous alkali solution and was feasible to preserve the spherical structure of PVAc prepared by suspension polymerization. It is famous that in general preparation method to obtain fully saponified PVA, an autocatalytic acceleration of the reaction may occur. Thus, the hydroxyl groups produced as the reaction progresses are not distributed randomly but rather in blocks along the polymer chain.[26] It may be interesting and important for a bioapplication to investigate the characteristics of PVA skin on microspheres obtained by the heterogeneous surface saponification.

Iodine/PVA complexation occurs both in an aqueous solution and in a swollen gel state of PVA. For example, the amount of complex increases with increasing concentrations of PVA, iodine, and boric acid.[27] Investigations of PVA/iodine complex formation have revealed the influence of the molecular parameters of PVA, such as stereoregularity,[28–32] 1,2-glycol bonds,[33] short branches,[34] degree of saponification (DS),[35,36] and degree of polymerization.[31] This phenomenon has been widely used for preparation of polarizing film in which PVA molecules form a complex with oligo iodide ions orienting parallel to the drawing direction to give a polarizing effect.[37,38] Iodine complexes have characteristic color according to the length of oligo iodide. As longer the complex, its color turns from red to blue. Especially the blue complex is observed in PVA with high DS. Most of all, Hayashi et al. studied extensively on the red iodine complexation of PVAc with the absorption maximum of 510 nm on which effects of temperature[39,40] and iodine/iodide concentration[41,42] were investigated and suggested iodine complexation method for the analysis of sequence distribution of poly(vinyl alcohol-*co*-vinyl acetate) (P(VA-*co*-VAc)).[43,44] It is difficult to detect most polymeric materials by X-ray because they are relatively radiolucent. Iodine[45] or iodide attached to a compound by covalent bonding[46] do not allow X-ray to pass and have been used to impart radiopacity to polymeric biomaterials, which is a very important characteristic for embolic materials for the minute positioning control of materials in human organs.[47]

In this study, high molecular weight PVAc microspheres obtained by suspension polymerization of VAc using 2,2′-azobis(isobutyronitrile) (AIBN) at 50°C was saponified in heterogeneous system at various conditions to establish a stable reaction conditions for PVA microspheres, and then monodisperse PVAc microspheres of different diameters without any satellite particles or aggregates were converted to PVA/PVAc skin/core microspheres through the heterogeneous surface saponification. To make an inspection of a nature of PVA, crystal melting temperatures (T_m) of saponified microspheres according DSs were analyzed using differential scanning calorimeter skin and color developments of iodine complexes were observed during formation and decomposition of them using I_2/KI and Na_2SO_3 aqueous solution. Finally, the surface morphology and radiopacity of PVA/PVAc skin/core type microspheres complexed with iodine were investigated.

EXPERIMENTAL

Materials

VAc purchased from Shin-Etsu, was washed with an aqueous solution of $NaHSO_3$, and with water, was dried over anhydrous $CaCl_2$, and was then distilled under a reduced pressure of nitrogen. The initiator AIBN (Wako, 99%) was recrystallized twice from absolute methanol before use. PVA with a number-average molecular weight of 127,000 and a DS of 88% (Aldrich), was used as a suspending agent. Other extra-pure-grade reagents were used without further purification. The water used for all the procedures was deionized.

Suspension polymerization of VAc

Suspending agent (1.5 g) was dissolved in 100 mL water under a nitrogen atmosphere and constant stirring in a 250 mL reactor fitted with a condenser. After degassing, VAc monomer (50 mL) along with AIBN (0.0001 mol/mol of VAc) was added simultaneously at polymerization temperature of 50°C. The polymerization was conducted at a stirring rate of 300 rpm. After 4 h, the reaction mixture was cooled and kept for 1 day to effectively separate and to sink spherical PVAc particles. To eliminate residual VAc and suspending agent, PVAc particles was filtered and washed with warm water. The washed PVAc microspheres were dried in a vacuum oven at 40°C for 24 h.

PVAc microspheres suspension-polymerized were separated into individual microspheres having uniform size and distribution by milling with sodium sulfate as a dispersion and antistatic agent and then sieving with standardized mesh sieves.[48]

Heterogeneous surface saponification of PVAc microspheres

In a flask equipped with a reflux condenser, and a thermocouple, a dropping funnel, and a stirring device, 150 mL alkali solution (sodium hydroxide/inorganic salt/methanol/water) was made. Monodisperse PVAc microspheres (0.75 g) were slowly added to the flask during stirring. After reaction, the reaction mixture was poured into cold water and kept for 1 day to separate and to eliminate reactant from saponified microspheres. The solid saponification product was filtered and washed several times with water and was dried in vacuo at 40°C for 1 day. PVA/PVAc microspheres, with a skin/core structure, were obtained through the control of the saponification time. The detailed saponification conditions are listed in Table I.

Iodine complex formation and decomposition

Saponified microspheres (0.5 g) were immerged in 50 mL aqueous I_2/KI solution with concentration of I_2 2×10^{-3} mol/L and KI 4×10^{-3} mol/L for 48 h at room temperature and then were washed in water for 1 h at room temperature to wash off the adhesive iodine. Iodinated PVA microspheres were dried at room temperature without vacuum to prevent the sublimation of iodine. To identify the skin of saponified microsphere in heterogeneous system, its color changes were observed using optical microscope during formation and decomposition of iodine complexes. By reduction of iodines using Na_2SO_3 the complexes in microspheres were decomposed.[41] Whole procedures proceeded on the slide glass *in-situ*.

TABLE I
Heterogeneous Saponification Conditions of PVAc Microspheres

Alkali aq. solution	Sodium hidroxide: 100 g/L, Methanol: 100 g/L, Sodium sulfate: 100 g/L
PVAc microspheres	0.5 g/dL
Temperature	40°C
Time	2, 4, 8, 16, 72 h

Characterization

The number-average degree of polymerization (P_n) of PVAc was calculated by using following equation,[49]

$$[\eta] = 8.91 \times 10^{-3}[P_n]^{0.62} \text{ (in benzene at 30°C)}$$

where [η] is the intrinsic viscosity.

The particle size and size distribution were measured with a Horiba LA-910 laser scattering particle size distribution analyzer (the range of operational measurement was 20 to 1200 μm). The mean diameter, from the data analysis of the Horiba LA-910, was based on the volume-average diameter (D_{vad}). The particle diameters of some samples were also measured directly with scanning microscope (SEM). Before the SEM examination, the samples were dried at room temperature and coated with a thin layer of gold with a JEOL JFC-1100 ion-sputter coating machine. The number–average diameter (D_n) and weight-average diameter (D_w) were calculated with the following equation.[50] At least 300 particles [number of added particles (N)] were counted for each calculation:

$$D_n = \sum N_i D_i \Big/ \sum N_i \quad (1)$$

$$D_w = \sum N_i D_i^4 \Big/ \sum N_i D_i^3 \quad (2)$$

The polydispersity index (PI) of the particle size is expressed as D_w/D_n. With the Horiba LA-910, N_i and D_i correspond to the values of the frequency distribution and mean diameter, for the calculation of D_w/D_n values ranging from 1.0 to 1.1 were regarded as monodisperse distributions of particle size, and those ranging from 1.1 to 1.2 were regarded as nearly monodisperse distributions. The particle size and size distribution, obtained with the Horiba LA-910, were reproducible and similar to those measured via SEM.

The surface morphology of microspheres was investigated with a scanning electron microscope (SEM) (JSM 5800-LVV, JEOL, JAPAN) and an optical microscope. The DS of PVA/PVAc microspheres

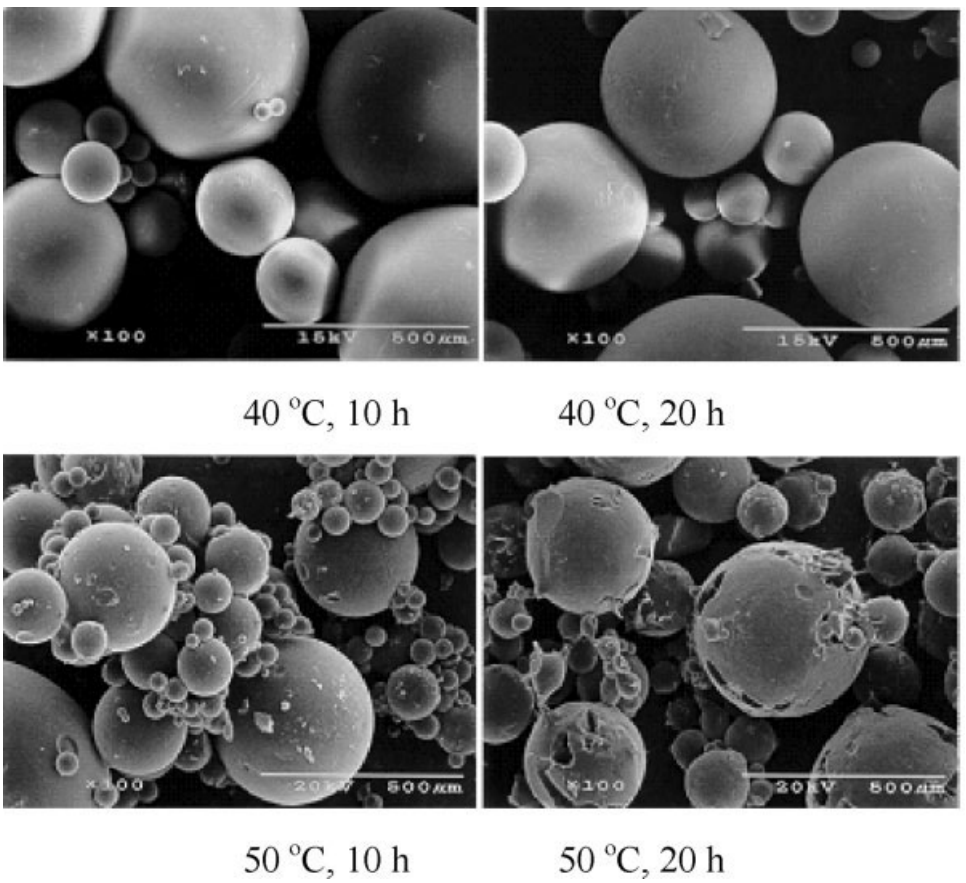

Figure 1 Scanning electron micrographs of saponified PVA microspheres in 30 wt % alkali aq. solution.

was determined by the ratio of areas of the methyl and methylene proton peaks in ^{1}H NMR spectrum (Varian, Sun Unity 300). T_m of PVA layer was measured using a differential scanning calorimeter (Perkin Elmer, DSC 7) with a sample of 10 mg and at a heating rate of 10°C/min. Radiopacity of complexed microspheres was analyzed by X-ray radiography (Spectro 70X, 70 Kvp, Toshiba).

RESULTS AND DISCUSSION

Heterogeneous surface saponification of the PVAc microspheres

PVAc was obtained through suspension-polymerized at 50°C with a suspending agent concentration of 1.5 g/dL of water, a monomer/water concentration of 0.5 L/L, and an agitation speed of 300 rpm with an AIBN concentration of 0.0001 mol/mol of VAc and its P_n was 20,800. It was expected that PVAc microspheres with higher molecular weight were more advantageous for maintaining spherical structures during the heterogeneous saponification.

The general method for preparing PVA is the saponification reaction of PVAc in a solution state; a concentrated aqueous solution of sodium hydroxide is dropped into a completely dissolved PVAc in methanol solution. Some problems arise in its application to the embolization because of its irregular surface and broad particle size distribution. To preserve the spherical shapes of PVAc particles with a uniform size distribution, we intended to restrict saponification to the surfaces by suspending monodisperse PVAc microspheres in an aqueous alkali solution.

To find out proper heterogeneous saponification temperature, polydisperse PVAc microspheres were saponified at 40 and 50°C. Surface morphologies of saponified PVAc microspheres were observed in Figure 1. The solubility of PVA to water is dependent of molecular parameters of PVA such as stereoregularity, degree of polymerization, and DS. In previous work, the syndiotacticity-rich PVA skin formed through the heterogeneous surface saponification of poly(vinly acetate-*co*-pivalate) microspheres was rarely dissolved during the reaction at 50°C due to increased syndiotacticity.[5] However, PVA/PVAc microspheres obtained by the heterogeneous saponification at 50°C had irregular surfaces and significantly pitted pores, which was caused by dissolution of saponified PVA skin to the saponification medium. Thus, the heterogeneous saponification tem-

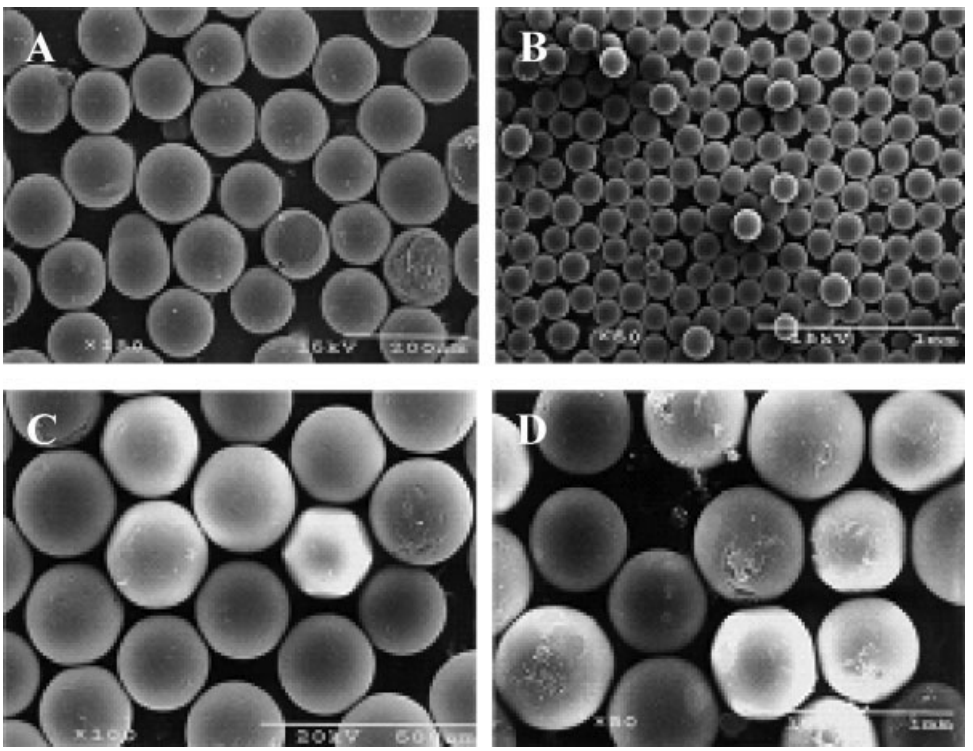

Figure 2 Electron scanning micrographs of monodisperse PVA microspheres with various diameters obtained by heterogeneous surface saponification. A: D_n 100 μm, DS, 28%; B: D_n, 138 μm, DS, 21%; C: D_n, 218 μm, DS, 20%; D: D_n, 540 μm, DS, 9%.

perature was fixed as 40°C to ensure saponified microspheres against being dissolved.

Monodisperse PVAc microspheres with various diameters were saponified in 30% alkali solution at 40°C during 4 h. Figure 2 shows monodisperse PVA/PVAc microspheres and there were not observed aggregates and irregular contours reflecting an unstable reaction. In reality, the dissolution of saponified PVA skin was minimized by using a precursor with high molecular weight and sodium sulfate making PVA skin contract in aqueous medium. It was possible to prepare PVA/PVAc microspheres with narrow particle size distribution and the diameters of saponified PVA microspheres were diverse from 50 to 1000 μm. It was interesting that the DSs were higher in the case of microspheres with a small diameter than those with a large diameter. Heterogeneous reactions were affected not only by chemical natures of reactants but also by physical properties such as surface area, density, degree of swelling.[48] In heterogeneous surface saponification of PVAc microspheres the amount of reacting acetate groups on the surface of small PVAc microspheres was greater than those of large ones assuming that these microspheres were monodisperse. Thus, saponification reactants could collide more frequently on the surface and rate of the saponification became faster, which could reasonably explain the increased DSs.

DSs of PVA microspheres obtained by heterogeneous surface saponification were calculated by the measuring peak area of ^{1}H NMR spectra. PVAc microspheres prepared by suspension polymerization and separated using standardized sieves had PI of 1.03 and D_n of 230 μm and were saponified for 2, 4, 8, 16, and 72 h, respectively. Figure 3 shows

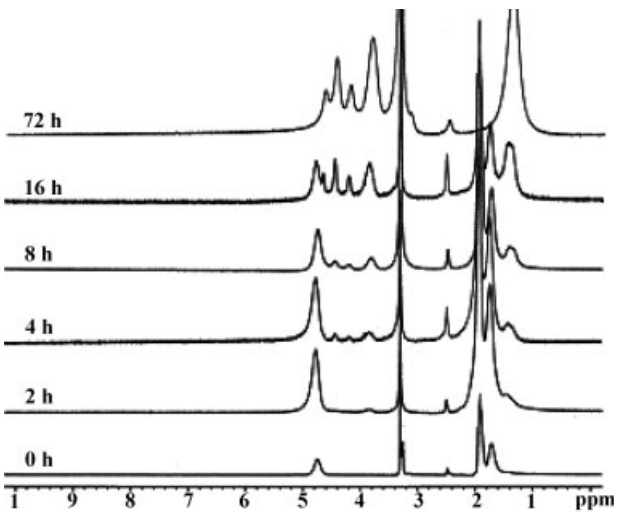

Figure 3 ^{1}H NMR spectra of PVAc obtained by suspension polymerization at standard polymerization condition and PVA microsphere obtained by heterogeneous surface saponification in 30 wt % aqueous alkali solution for 0, 2, 4, 8, 16, and 72 h.

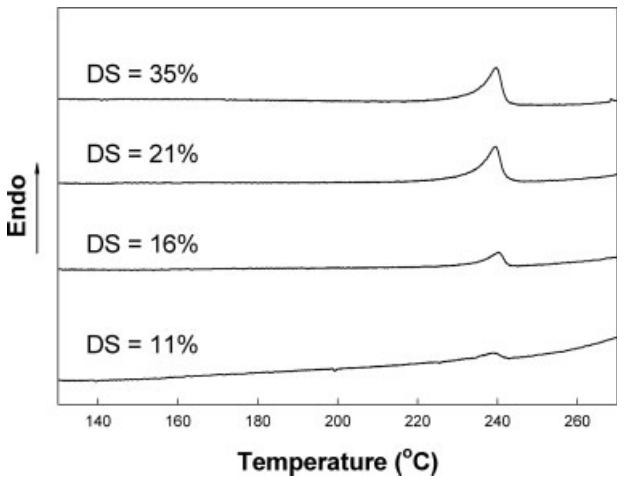

Figure 4 DSC thermograms of PVA microspheres obtained by heterogeneous surface saponification in 30 wt % aqueous alkali solution at 40°C for different DSs.

^{1}H NMR spectra of PVAc and saponified PVA microspheres. Peaks at 4.76, 1.74, and 1.92 ppm were those of methin (—CH—) and methylene (—CH_2—) in PVAc main chain and methyl (—CH_3) of acetate groups, respectively. With increasing heterogeneous saponification time, —CH— peak at 4.76 ppm shifted to 3.85 ppm, —CH_2— peak at 1.74 ppm shifted to 1.40 ppm, and peaks of isotactic-, atactic-, and syndiotactic-dyad appeared at 4.66, 4.46, and 4.22 ppm, respectively. After 72 h the peaks of PVAc disappeared and traditional spectra of atactic PVA were observed.

PVAc is amorphous polymer and has no crystal melting transition. For PVA, T_ms are observed at the range from 210 to 270°C according to the stereoregularity, DS, or thermal treatment. T_m of PVA obtained by a conventional saponification increases with increasing DS. Especially in the case of DS, when the

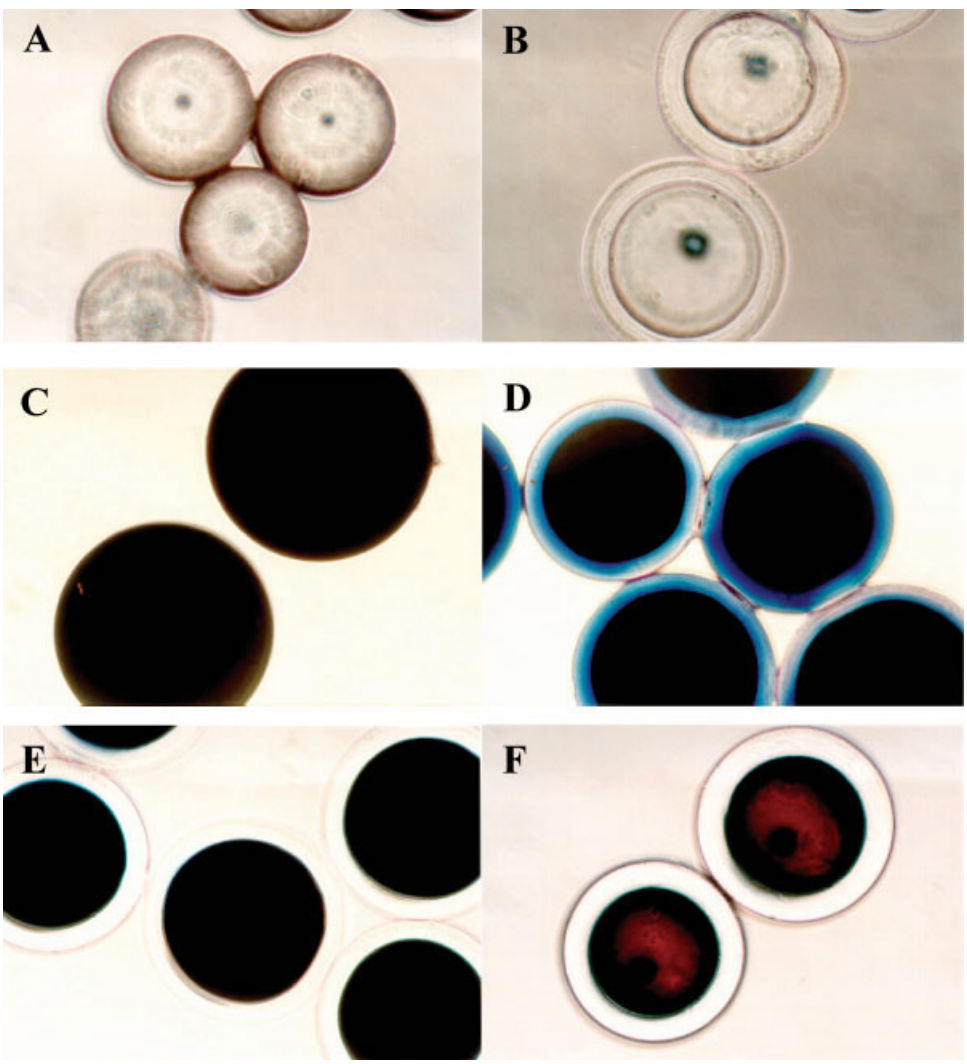

Figure 5 Optical micrographs of PVA microspheres with core/shell structure and DS of 41% obtained by heterogeneous surface saponification: A: dry state; B: swollen state with water; C: after iodine complex formation; D: decomposition of iodine complex with sodium sulfite solution; E: iodine complex in PVAc core; F: after storage of microspheres of E for 24 h in sodium sulfite solution. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

VAc content increased, T_m decreased significantly. Hirai et al.[43] prepared three different type of P(VA-*co*-VAc) through saponification, alcoholysis, and reacetylation with various VAc fraction ranging from 0.17 to 0.79 and confirmed the decrease of the T_ms from 230 to 170°C. In this study, microspheres with various DSs were prepared by stopping the reaction at different time. In spite of increasing DS, however, T_ms were constant as 238°C as shown in Figure 4. Heat of fusion of saponified PVA microspheres increased according to increasing DS owing to increased crystalline region of PVA formed by saponification. From these results, it was concluded that the skins of saponified microspheres were almost same PVA with very high DS independent of reaction time.

Iodine complex formation and decomposition

In general, when immerged in I_2/KI aqueous solution PVAc forms I_3^- complex[39–44] and PVA I_3^- and I_5^- complexes[27–38] and their absorption maxima were about 500 and 600 nm, respectively. For PVA with relatively lower DS and PVAc, I_5^- complex is rarely formed,[39–41,43,44] except using high ratio of I_2 concentration to KI ($[I_2]/[KI] = 2.2$).[42] In this study, to minimize the formation of I_5^- complex, molar concentration ratio of I_2 to KI was fixed to 0.5. The colors of I_3^- is brownish red and of I_5^- is deep blue, thus the color of iodine complex in PVAc will be brownish red and that in PVA will be dark gray owing to combined color of brownish red and deep blue.

To elucidate that the shell of the microspheres obtained by heterogeneous saponification was PVA with high DS, iodine complex was formed in PVA/PVAc skin/core microspheres and changes of the complex color were observed during formation and decomposition *in-situ* by streaming iodine/potassium iodide and sodium sulfite aqueous solution between slide and cover glasses. The decomposition of iodine complex could be expressed by following reaction.

$$I_3^- + Na_2SO_3 + H_2O \rightarrow I^- + 2HI + Na_2SO_4$$

$$I_5^- + 2Na_2SO_3 + 2H_2O \rightarrow I^- + 4HI + 2Na_2SO_4$$

Figure 5(A) is optical micrograph of microspheres obtained by heterogeneous surface saponification in 30 wt % aqueous alkali solution at 40°C for 5 h and captured in dry state. Thin layer of PVA shell was observed at the surface. When water was introduced to PVA, PVA skins absorbed water and was swollen. The spherical morphology still remained after swelling [Fig. 5(B)]. Deep brownish red color was observed in Figure 5(C) owing to iodine complex formation. By streaming sodium sulfite solution between slide and cover glasses, the iodine complexes were gradually decomposed. The color of

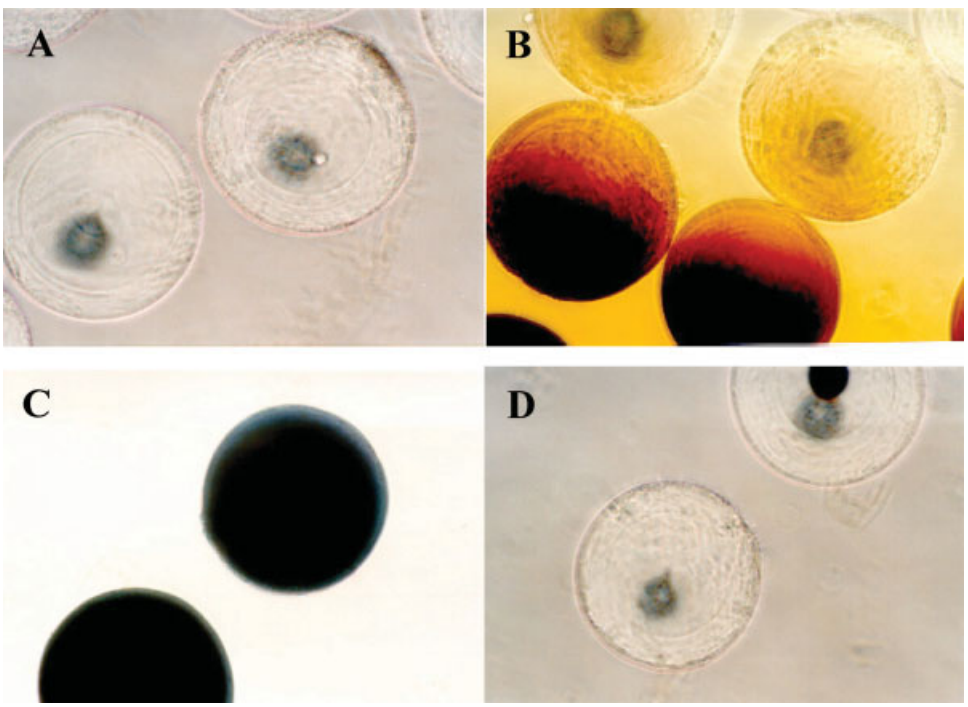

Figure 6 Optical micrographs of PVA microspheres with DS of 99.9% obtained by heterogeneous surface saponification: A: swollen state with water; B: during iodine complex formation; C: after iodine complex formation; D: decomposition of iodine complex with sodium sulfite solution. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

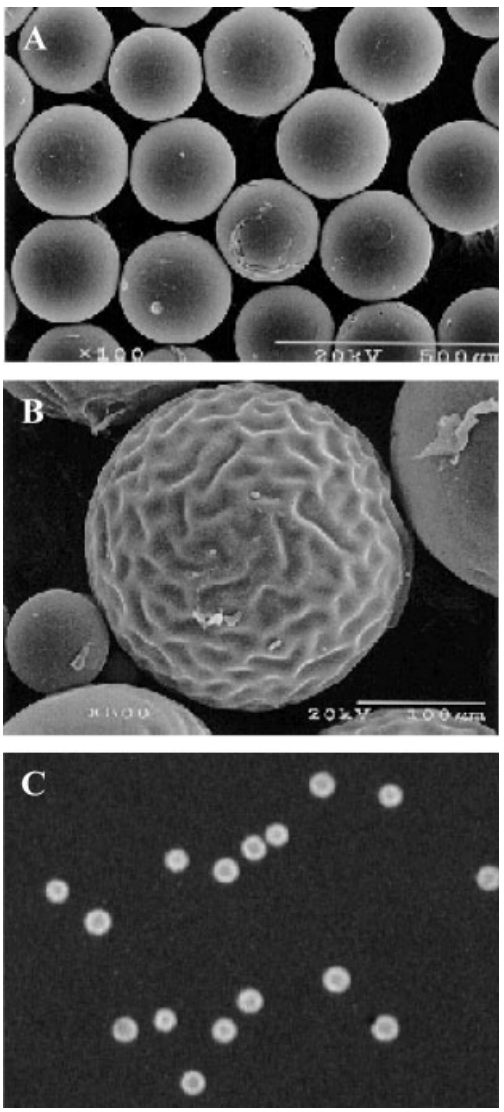

Figure 7 Iodine complex formation and radiopacity: A: monodisperse PVA microspheres with DS of 50%; B: SEM micrographs of iodinated PVA microspheres; C: image obtained after X-ray irradiation.

skins became blue, characteristic color of I_5^- complex, because I_3^- complex decomposed preferentially. If the skin of microspheres obtained by heterogeneous saponification was composed of poly(VA-*co*-VAc), the color of the skin in Figure 5(D) would be red. However, from the facts of blue color of the shell and constant T_m, it was obvious that the shell was composed of PVA with high DS, irrespective of different DSs, and the core was PVAc. It was shown in Figure 5(E,F) that the complexes in PVA shell was completely decomposed and red complex in the PVAc core still remained, which caused by considering the pour accessibility of SO_3^- to hydrophobic PVAc core. In all micrographs, the contours of shell and core were concentric circles, indicating that the saponification proceeded uniformly. PVA microspheres with DS 99.9% were obtained through the heterogeneous surface saponification for 72 h and spherical contour of PVA was still preserved in spite of long reaction time in aqueous medium [Fig. 6(A)]. It was observed in Figure 6(B) that the iodine complexation proceeded gradually to the direction of I_2/KI solution flow colored by free I_3^- and I_2. As in partially saponified microspheres, blue iodine complex formation were observed in Figure 6(C) and there was no core/shell structure and any red color was not appeared [Fig. 6(D)].

Generally a particular embolic material is not radiopaque, so it has been used in dispersed state in contrast medium. PVA forms complex with iodine which has high electron density showing excellent radiopacity. To prepare microspheres imparted a radiopacity, PVA/PVAc microspheres with DS of 50% and smooth surface as shown in Figure 7(A) were complexed with iodine. After complexation, the surfaces became significantly rugged. This is because iodine complex was formed by interactions between poly iodide ions and hydroxyl groups of adjacent four PVA chains, and acted as junction point in polymer matrix,[51] resulting in slightly collapsed morphology on the surface of iodinated PVA microspheres as shown in Figure 7(B). White spherical images were shown in Figure 7(C) reflecting the radiopacity of iodinated microspheres exposed to X-ray, which property is vital in guiding the surgeon to decide whether or not the position of microspheres in vein is correct.[46]

CONCLUSIONS

To prepare PVA/PVAc or PVA microspheres hardly obtained by a general saponification method, high molecular weight PVAc microspheres prepared by suspension polymerization of VAc at 50°C using AIBN as initiator were saponified in 30 wt % aqueous alkali solution. Surfaces of microspheres saponified 50°C were irregular and significantly pitted owing to dissolution of formed PVA skins. At 40°C the heterogeneous surface saponification made the surface of PVAc microspheres converted to PVA stably. It was possible to prepare monodisperse PVA/PVAc microspheres and the diameters of saponified microspheres were diverse from 50 to 1000 μm, which will be feasible for the selective embolization. The heterogeneous surface saponification proceeded from the surface to the core centrically and after 72 h PVA microspheres with no acetate groups were confirmed by ^{1}H NMR and optical microscope. T_ms of PVA microspheres were measured as 238°C for every specimen with different DSs. Iodine develops red or blue complexes with PVA and PVAc. Especially, blue complex owing to I_5^- is developed in

PVA with high DS. In this study, the observation of blue color development during complex formation and decomposition by streaming iodine/potassium iodide and sodium sulfite elucidated that the PVA skins formed by heterogeneous surface saponification had high DSs. Such complexes endowed polymeric microspheres excellent radiopacity and examined by X-ray irradiation image. It was expected that hydrogel type PVA or PVA/PVAc skin/core type microspheres obtained by the heterogeneous surface saponification would be one of the promising embolic materials. In the near future, we will report on the preparation of monodisperse stereoregular PVA/I_2 complex microspheres.

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