Preparation, structure, and *in vitro* chemical durability of yttrium phosphate microspheres for intra-arterial radiotherapy

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Running head: Yttrium phosphate microspheres for intra-arterial radiotherapy

Abstract: Chemically durable microspheres containing yttrium and/or phosphorus are useful for intra-arterial radiotherapy. In the present study, we attempted to prepare yttrium phosphate (YPO_4) microspheres with high chemical durability. YPO_4 microspheres with smooth surfaces and diameters of around 25 μm were successfully obtained when gelatin droplets containing yttrium and phosphate ions were cooled and solidified in a water-in-oil emulsion and then heat-treated at 1100ºC. The chemical durability of the heat-treated microspheres in a simulated body fluid at pH = 6 and 7 was high enough for clinical application of intra-arterial radiotherapy.

Keywords: yttrium phosphate; chemical durability; microspheres; intra-arterial radiotherapy

INTRODUCTION

Intra-arterial radiotherapy of malignant liver tumors has been performed using radioactive yttrium-containing microspheres.[1,2] Yttrium-89 (^{89}Y) is a nonradioactive isotope with a natural abundance of 100%; neutron bombardment activates ^{89}Y to form the β-emitter ^{90}Y, which has a half-life of 64.1 h. When radioactive microspheres 20–35 μm in diameter are injected into a target organ, they are trapped inside small blood vessels in the tumor, blocking the nutritional supply to the tumor and delivering a large, localized dose of short-range, highly ionizing β-rays. The β-rays penetrate only about 2.5 mm in living tissue, thus causing little radiation damage to neighboring healthy tissues. These microspheres show high chemical durability, and the radioactive ^{90}Y remains essentially within the microspheres and does not affect neighboring healthy tissues. The radioactivity of ^{90}Y decays to a negligible level within 21 days after neutron bombardment. The microspheres therefore become inactive soon after the cancer treatment.

So far, Y_2O_3–Al_2O_3–SiO_2 (YAS) glass microspheres (TheraSphere®)[3-5] and yttrium-containing resin microspheres (SIR-Spheres®)[6-8] have yielded good results in clinical trials.[9–12] They have been used clinically to treat unresectable hepatocellular carcinoma in various countries including the USA, Canada, China, Australia, New Zealand and

Singapore.[13–28] The Y_2O_3 content in TheraSpheres® is 17 mol%, and the yttrium content in SIR-Spheres® is around 2 mol%. The radioactivity of these microspheres decays significantly even before cancer treatment is started because of the short half-life. Therefore, the development of chemically durable microspheres having a higher yttrium content is desirable. We have developed dense Y_2O_3 microspheres,[29] hollow Y_2O_3 microspheres,[30] and porous Y_2O_3 microparticles[31] with high chemical durability *in vitro*.

On the other hand, phosphorus-31 (^{31}P), found at a natural abundance of 100%, can also be activated by neutron bombardment to form the β-emitter ^{32}P, which has a half-life of 14.3 days. Microspheres containing a high phosphorus content are therefore expected to be effective for cancer treatment, similar to yttrium-containing microspheres.[32,33] Previously, we attempted to prepare yttrium phosphate (YPO_4) microspheres by a high-frequency induction thermal plasma melting method and found that they showed high chemical durability *in vitro*.[29] However, they lost a certain amount of phosphorus to form Y_2O_3, and their surfaces were rather rough owing to the loss of phosphorus from volatilization at the higher synthesis temperatures (above 10,000ºC). It is feared that the rough surfaces of the microspheres would damage blood vessels. In this study, we attempted to prepare YPO_4 microparticles with a smooth surface and investigated their structure and *in vitro* chemical durability in order to evaluate their potential as a radioactive source in intra-arterial radiotherapy.

MATERIALS AND METHODS

Sample preparation

A precursor precipitate containing yttrium and phosphate ions was obtained by the following solution precipitation process.[34] Equimolar (8.4 mM) amounts of yttrium nitrate ($Y[NO_3]_3$: Wako Pure Chemical Industries Ltd., Osaka, Japan) and phosphoric acid (H_3PO_4: Wako Pure Chemical Industries Ltd., Osaka, Japan) were dissolved in 300 mL of pure water. Aqueous NaOH solution (56 mM, 150 mL) was added to the $Y(NO_3)_3$–H_3PO_4 solution under stirring for 20 min, resulting in an opaque solution. This opaque solution was centrifuged at 4000 rpm for 5 min and decanted to obtain white precipitates. The precipitates were washed several times with pure water. Then, 2.5 mL of 0.1M nitric acid aqueous solution was added to 10 g

of the white precipitates to obtain a stable sol solution.[35] Gelatin (0.5 g; APH-250, Nitta Gelatin Inc., Osaka, Japan) was dissolved in 5 mL of the sol solution. The resultant solution was dropped into 50 mL of corn oil (Wako Pure Chemical Industries Ltd., Osaka, Japan) at 30ºC and stirred at 1000 rpm for 10 min to obtain a water-in-oil emulsion. The emulsion was cooled in an ice bath to solidify the gelatin-containing water droplets. The solidified droplets were filtered and washed with cold ethanol and then freeze-dried for 6 h in a freeze dryer (FD-1000; Tokyo Rikakikai Co. Ltd., Tokyo, Japan). Finally, the freeze-dried samples were placed in an alumina boat, heated to various temperatures (700–1500°C) at a rate of $5°C \cdot min^{-1}$ in a SiC or $MoSi_2$ electric furnace, and kept at the given temperature for 1 h.

Structural analysis

The shapes of the microspheres were observed using a scanning electron microscope (SEM; VE-8800, Keyence, Tokyo, Japan). The precipitated phase was examined with a powder X-ray diffractometer (XRD; RINT-2200VL, Rigaku Co. Ltd., Tokyo, Japan) using the following settings: X-ray source, Ni-filtered CuKα radiation; X-ray power, 40 kV, 40 mA; scanning rate, $2\theta = 2° \cdot min^{-1}$; and sampling angle, 0.02°. The structure of the heat-treated microspheres before and after an *in vitro* chemical durability test was investigated by Fourier-transform infrared spectroscopy (FT-IR; FT/IR-6200, JASCO, Tokyo, Japan) with a diffusive reflection attachment (DR-PRO410M, JASCO, Tokyo, Japan). For the FT-IR diffusive reflection spectroscopic measurement, potassium bromide (KBr) powder was mixed with the samples. The sample content in KBr pellets was around 0.5 wt%.

***In vitro* chemical durability test**

A simulated body fluid (SBF) with ion concentrations of Na^+ 142.0, K^+ 5.0, Mg^{2+} 1.5, Ca^{2+} 2.5, Cl^- 147.8, HCO_3^- 4.2, HPO_4^{2-} 1.0, and SO_4^{2-} 0.5 mM was prepared by dissolving reagent-grade NaCl, $NaHCO_3$, KCl, $K_2HPO_4 \cdot 3H_2O$, $MgCl_2 \cdot 6H_2O$, $CaCl_2$, and Na_2SO_4 (Nacali Tesque Inc., Kyoto, Japan) in ultrapure water and buffering to pH 7.40 with tris(hydroxymethyl) aminomethane ($[CH_2OH]_3CNH_2$) and 1M HCl (Nacali Tesque Inc., Kyoto, Japan) at 36.5ºC.[36] Then, the pH value of the SBF was adjusted to 6 (SBF-6) or 7

(SBF-7) by further addition of 1M HCl.

The microspheres (0.025 g) heat-treated at 1100ºC were soaked in 10 mL of SBF-6 or SBF-7 in a polypropylene bottle at 36.5ºC for various periods up to 21 days. The pH value of a normal body fluid is maintained at around pH 7, but this value is liable to fall to around pH 6 near a cancer owing to the production of lactic acid.[37] The SBF was shaken at a rate of 120 strokes·min^{-1} using a stroke length of 3 cm. The samples were soaked for up to 21 days, since the radioactivity of ^{90}Y decays to a negligible level after 21 days. An inductively coupled plasma (ICP) atomic emission spectrometer (Optima 2000DV, PerkinElmer Co., Ltd., Germany) was used to determine the concentrations of yttrium and phosphorus released from the microspheres into SBF-6 or SBF-7. The fraction of yttrium released from the microspheres was calculated using the following formula.

$$\text{Released fraction} = \frac{\text{Molar quantity of yttrium released from the microsphere into the SBF (mol)}}{\text{Total molar quantity of yttrium contained in the microsphere (mol)}}$$

RESULTS

Figure 1 shows XRD patterns of samples before and after heat treatment at different temperatures. The untreated sample exhibited a halo, indicating that its structure was amorphous. Several peaks of tetragonal YPO_4 with the xenotime structure (PDF File No. 11-0254) were clearly observed after heat treatment at temperatures above 700ºC. With a further increase in heat treatment temperature to 1500ºC, the structure of the sample remained dehydrated YPO_4 with tetragonal xenotime-type structure,[34] but the diffraction peaks became more intense and narrower, indicating crystal growth of YPO_4 with increasing heat treatment temperature.

Figure 2 shows SEM photographs of samples before and after heat treatment at different temperatures. Microspheres around 25 μm in diameter with smooth surfaces were successfully obtained by the present method, although their diameters ranged from 10 to 80 μm. The surface smoothness of the microspheres was improved slightly by heat treatment at 700ºC or 1100ºC. This might be attributed to partial sintering of YPO_4 by the heat treatment. With heat treatment at 1500ºC, the surface of the microspheres became rather rough, and

remarkable aggregation of the microspheres occurred. It seems plausible that the microspheres heat-treated at higher temperatures will show higher chemical durability in the human body, since sintering of YPO_4 will proceed at higher temperatures. However, the rough surface and aggregation of the microspheres are unfavorable for clinical application of intra-arterial therapy. Therefore, we considered that the maximum useful heat treatment temperature is 1100ºC, and an *in vitro* chemical durability test was conducted for the microspheres heat-treated at 1100ºC in this study. Figure 3 shows SEM photographs of cross-sections of these microspheres. Figures 2 and 3 show that both the inside and the outer surface of the microspheres heat-treated at 1100ºC were dense.

Figure 4 shows the concentrations of yttrium and phosphorus released from the microspheres heat-treated at 1100ºC into SBF-6 or SBF-7 after immersion for 21 days, in comparison with those of the original SBF without soaking of the microspheres. The concentrations of yttrium released from the microspheres into SBF-6 and SBF-7 were as low as 0.3 mg/g, which is almost the same as the yttrium concentration of the original SBF without microsphere soaking (Fig. 4[a]). It is interesting to note that the concentrations of phosphorus in SBF-6 and SBF-7 in which the microspheres were soaked for 21 days were slightly lower than those of the original SBF (Fig. 4[b]). This suggests that the microspheres heat-treated at 1100ºC released hardly any yttrium into either SBF-6 and SBF-7 after 21 days, and a small amount of phosphorus might adsorb onto the surfaces of the microspheres.

Figure 5 shows the XRD patterns (a) and SEM photographs (b) of the microspheres heat-treated at 1100ºC before and after soaking in SBF-6 and SBF-7 for 21 days. No appreciable change was observed in the XRD patterns and the SEM photographs of the microspheres after soaking in either of the SBF solutions. Figure 6 shows the FT-IR diffusive spectra of the microspheres heat-treated at 1100ºC before and after soaking in SBF-6 and SBF-7 for 21 days. The microspheres before soaking showed several bands assigned to PO_4.[38,39] The bands at around 3500 cm^{-1} and 1630 cm^{-1}, which are assigned to H_2O,[38,39] appeared after the microspheres were soaked in SBF-6 or SBF-7. This might be attributed to partial hydration of the microspheres' surfaces due to the chemical durability test. The intensity of the bands at around 1300 and 3000 cm^{-1} increased after the chemical durability

test. These two bands are assigned to PO_4 and CH_3, respectively.[38-40] This result suggests adsorption of a small amount of phosphorus-containing organic compounds onto the surfaces of the microspheres, although the detailed structure of the compounds is unclear. Also, it is consistent with the results of the *in vitro* chemical durability test, indicating that the concentrations of phosphorus in SBF-6 and SBF-7 in which the microspheres were soaked for 21 days were slightly lower than those of the original SBF (see Fig. 4). According to these results, we can conclude that the present microspheres heat-treated at 1100ºC are quite chemically stable under acidic and neutral SBF solutions.

DISCUSSION

We examined the durability of the heat-treated microspheres by immersion for 21 days in SBF (Fig. 4). Note, however, that the radioactivity of ^{32}P decays to a negligible level only after 112 days, and hence it might be advisable to evaluate the chemical durability of the microspheres for a longer period of 112 days. However, we can expect that the present YPO_4 microspheres would show high chemical durability for long periods such as 112 days because we confirmed that microspheres consisting of YPO_4 and Y_2O_3 (YPO_4–Y_2O_3 microspheres) showed excellent chemical durability for 112 days in saline with both pH = 6 and pH = 7 in our previous study.[29] Moreover, the activity product of YPO_4 is reportedly as low as $10^{-24.76}$ at 25±1ºC.[41]

In Table 1, the fraction of yttrium released from the present YPO_4 microparticles is compared with that of previously reported samples. The present YPO_4 microspheres showed smaller released yttrium fractions than the previously reported samples, although the chemical durability of some samples (dense Y_2O_3 microspheres, YPO_4–Y_2O_3 microspheres, and Y_2O_3–Al_2O_3–SiO_2 [TheraSphere®-type] glass) was evaluated in saline solutions buffered at pH = 6 or 7. In particular, we noted that the fraction of yttrium released from the present YPO_4 microspheres was much smaller than that from TheraSphere®-type glass and dense Y_2O_3 microspheres, which showed no acute toxicity in animal tests,[42] indicating that the chemical durability of the present YPO_4 microspheres is high enough for clinical application in intra-arterial radiotherapy.

CONCLUSIONS

YPO_4 microspheres around 25 μm in diameter with smooth surfaces were successfully obtained by cooling and solidifying gelatin droplets containing yttrium phosphate precursor precipitates in a water-in-oil emulsion and then heat-treating them at 1100ºC. The *in vitro* chemical durability of the heat-treated microspheres in a simulated body fluid at pH = 6 and 7 was high enough for clinical application of intra-arterial radiotherapy. We believe that the present YPO_4 microspheres are useful for intra-arterial radiotherapy of cancer, since they have smooth surfaces and can be activated to β-emitters by neutron bombardment.

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Table legends and figure captions

Table 1 Fraction of yttrium released from the samples into SBF-6, SBF-7, and saline solutions buffered at pH = 6 or 7 at 36.5ºC for 21 days.

Figure 1 XRD patterns of samples before and after heat treatment at different temperatures.

Figure 2 SEM photographs of samples before and after heat treatment at different temperatures.

Figure 3 SEM photographs of cross-sections of samples after heat treatment at 1100ºC.

Figure 4 Concentrations of yttrium and phosphorus released from the microspheres heat-treated at 1100ºC into SBF-6 or SBF-7 after 21 days, in comparison with those of the original SBF without soaking of the microspheres.

Figure 5 XRD patterns (a) and SEM photographs (b) of the microspheres heat-treated at 1100ºC before and after soaking in SBF-6 or SBF-7 for 21 days.

Figure 6 FT-IR diffusive spectra of samples before and after soaking in SBF-6 or SBF-7 for 21 days.

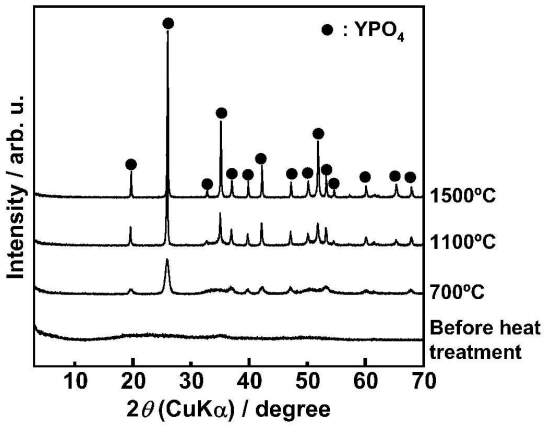

Figure 1 M. Kawashita *et al.*

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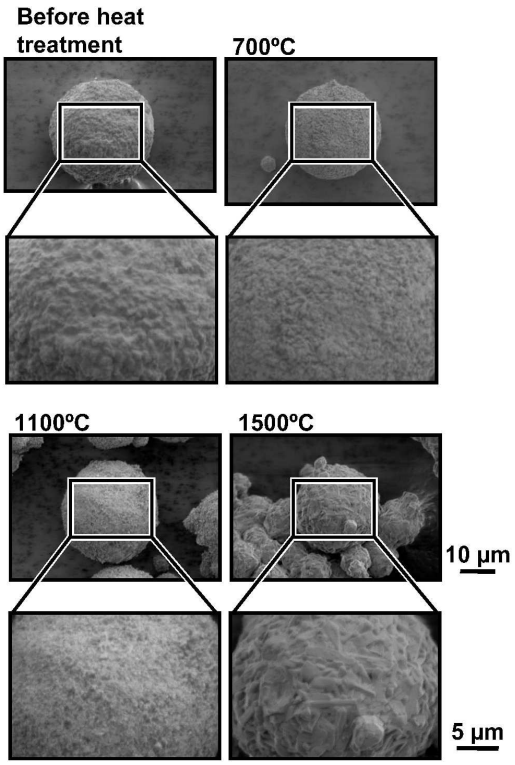

Figure 2 M. Kawashita *et al.*

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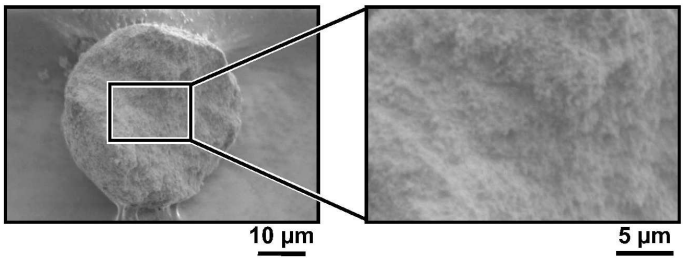

Figure 3 M. Kawashita *et al.*

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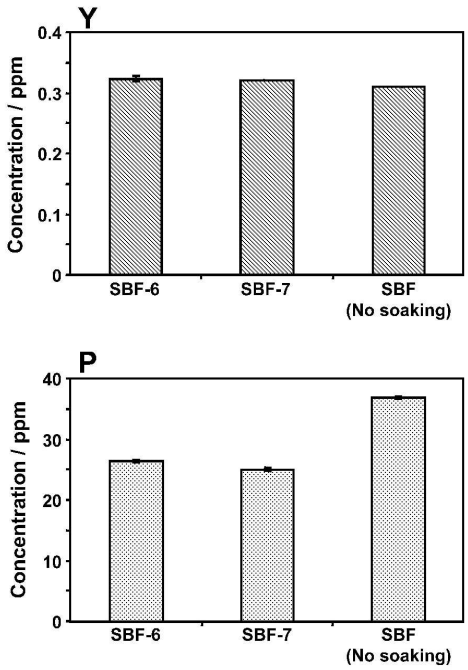

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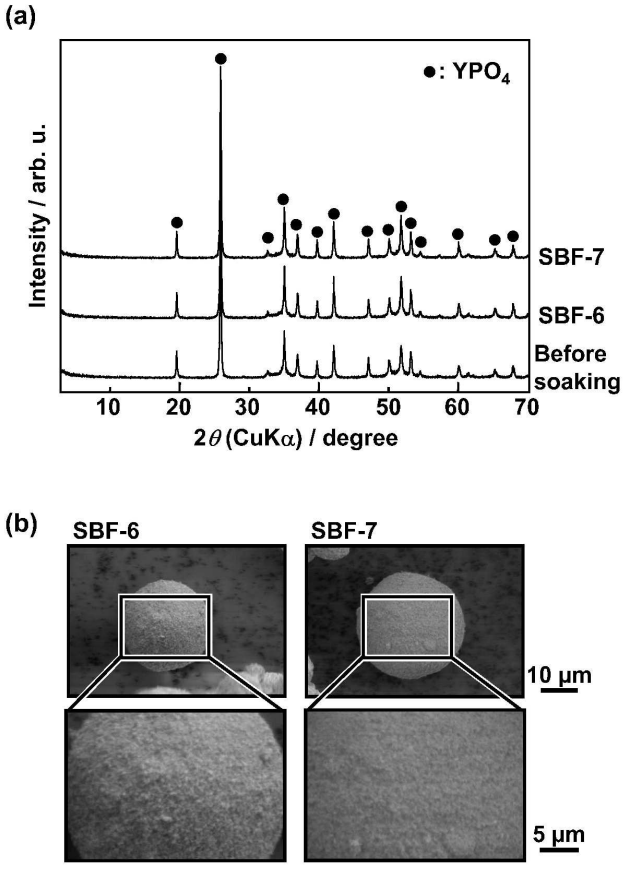

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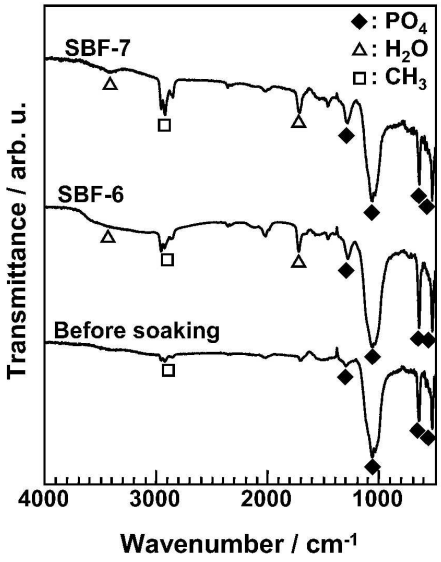

Figure 6 M. Kawashita *et al.*

205x292mm (600 x 600 DPI)

Table 1 Fraction of yttrium released from the samples into SBF-6, SBF-7, and saline solutions buffered at pH = 6 or 7 at 36.5ºC for 21 days.

Sample	Immersion fluid	
	SBF-6	SBF-7
Present YPO_4 microspheres	2.5×10^{-5}	2.5×10^{-5}
Hollow Y_2O_3 microspheres[30)]	1.8×10^{-3}	1.3×10^{-3}
Porous Y_2O_3 microparticles[31)]	5.6×10^{-3}	5.2×10^{-3}
	Saline solutions buffered at pH = 6	Saline solutions buffered at pH = 7
Dense Y_2O_3 microspheres[29)]	4×10^{-3}	2×10^{-3}
YPO_4-Y_2O_3 microspheres[29)]	2.5×10^{-3}	undetectable level
Y_2O_3-Al_2O_3-SiO_2 (TheraSphere®-type) glass[29)]	9×10^{-3}	3×10^{-3}