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Preparation of porous yttrium oxide microparticles by gelation of ammonium alginate in aqueous solution containing yttrium ions

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Abstract Porous Y_2O_3 microparticles 500 μm in size were obtained, when 1 wt%-ammonium alginate aqueous solution was dropped into 0.5 M-YCl_3 aqueous solution by a Pasteur pipette and the resultant gel microparticles were heat-treated at 1100°C. Small pores less than 1 μm were formed in the microparticles by the heat treatment. The bulk density of the heat-treated microparticle was as low as 0.66 g cm^{-3}. The chemical durability of the heat-treated microparticles in simulated body fluid at pH = 6 and 7 was high enough for clinical application of in situ radiotherapy. Although the size of the microparticles should be decreased to around 25 μm using atomizing device such as spray gun for clinical application, we found that the porous Y_2O_3 microparticles with high chemical durability and low density can be obtained by utilizing gelation of ammonium alginate in YCl_3 aqueous solution in this study.

1 Introduction

Generally, an organ diseased with cancer is surgically resected; however, the functions of the resected organ are often not recovered. It is therefore desirable to develop a treatment for cancer that can destroy only cancerous cells, so that normal tissue can regenerate after treatment. Radiotherapy is a treatment that shows such potential. However, irradiation is performed from an external source in most cases. Consequently, the cancer often receives an insufficient dose of radiation, especially if it is deep-seated, and irradiation can cause severe damage to healthy tissues.

A new type of in situ radiation method has been tried using $17Y_2O_3$–$19Al_2O_3$–$64SiO_2$ (mol%) (YAS) glass microspheres that are prepared by a conventional melt-quench method [1–3] The yttrium-89 (^{89}Y) in this glass is a non-radioactive isotope, with a natural abundance of 100%, but neutron bombardment activates ^{89}Y to form the β-emitter ^{90}Y, which has a half-life of 64.1 h. When radioactive glass microspheres 20–30 μm in diameter are injected into a target organ (e.g., a liver tumor), 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 have a short penetration range of only about 2.5 mm in living tissue, thus presenting little radiation damage to neighboring healthy tissues. These microspheres show high chemical durability, and the radioactive ^{90}Y remains essentially within the microspheres inside a patient, 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. They are already used clinically for the treatment of inoperable liver cancer in Canada, the USA, and China, etc. [4–15].

The Y_2O_3 content in the microspheres is limited to 17 mol%, in so far as they are prepared in the glassy state using a conventional melt-quench method. The small content of yttrium results in the long time for radio-activation of microspheres by neutron bombardment. The development of chemically durable microspheres containing a higher Y_2O_3 content is therefore desirable. Radioactive yttrium-containing resin microspheres 30–35 μm in

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diameter have been also used clinically for treatment of liver cancer in Australia, China, New Zealand, and Singapore, etc. [16–26]. However, the yttrium content is limited to only 2 mol%. In 2003, we reported that dense Y_2O_3 microspheres 20–30 μm in diameter with high chemical durability can be prepared using a high-frequency induction thermal plasma melting method [27], and the radioactive Y_2O_3 microspheres suppress the growth of tumor effectively [28]. It is, however, feared that, because of their high density, microspheres implanted into a tumor may accumulate in the dorsal blood vessels of patients.

We recently found that hollow Y_2O_3 microspheres 20–30 μm in diameter were obtained when an aqueous carboxymethylcellulose sodium salt (CMC-Na) solution containing urease was atomized into an aqueous yttrium nitrate solution containing urea using a spray gun, and the resultant solid materials were heat-treated at 1300°C [29]. However, it was not easy to obtain microspheres owing to the high viscosity of CMC-Na solution as a template, and several days were needed to complete the enzymatic reaction. Alginate salts are well known to form gels easily in solution containing multivalent cations [30]. Therefore, we can expect that porous Y_2O_3 microparticles are easily obtained, when microdroplets of polysaccharide solution are added into solutions containing yttrium ions and resultant gel particles are heat-treated at elevated temperature to remove an organic phase of polysaccharide. Such porous structure will decrease the density of the microparticles and give the capability as drug carries in drug delivery system.

In this study, we considered the possibility to obtain porous Y_2O_3 microparticles by utilizing gelation of ammonium alginate in aqueous solution containing yttrium, and the structure and chemical durability of the resultant products were investigated fundamentally.

2 Materials and methods

2.1 Preparation of samples

Different amounts (0.05–0.2 g) of ammonium alginate (Wako Pure Chemical Industries Ltd., Osaka, Japan, average molecular weight 860,000) [31] were dissolved into ultra pure water of 10 ml in a glass beaker with a magnetic stirrer for 1 h at room temperature. On the other hand, different amounts of yttrium chloride (YCl_3, Wako Pure Chemical Industries Ltd., Osaka, Japan) were dissolved into 50 ml ultra pure in a glass beaker with a magnetic stirrer for 10 min at room temperature in order to prepare 0.01–2 M YCl_3 aqueous solutions. The former solution was dropped gently into the latter solution under stirring by a Pasteur pipette at room temperature. Thus obtained solution was further stirred for 1 h to complete the gelation of ammonium alginate. The resulting gel materials were filtered and washed with distilled water and dried at 60°C for 1 day. The dried materials were placed in an alumina boat, heated to various temperatures (500–1300°C) at a rate of 5°C min^{-1} in SiC or $MoSi_2$ electric furnace, and kept at the given temperature for 1 h. Some gel materials were freeze-dried in a freeze dryer (FD-1000; Tokyo Rikakikai Co. Ltd., Tokyo, Japan) and heat-treated at 1100°C for 1 h. The materials were then allowed to cool to room temperature in the furnace.

2.2 Structural analysis of samples

The shape of the microparticle was 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, $2\theta = 2°$ min^{-1}; and sampling angle, 0.02°. The porosity and bulk density of the microparticles were measured by mercury porosimeter (PoreMaster 60GT, Quantachrome, FL, USA).

2.3 Chemical durability test of samples

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 were 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 ultra pure water, and buffering to pH 7.40 with tris(hydroxymethyl) aminomethane ($(CH_2OH)_3CNH_2$) and 1.00 M aqueous HCl (Nacali Tesque Inc., Kyoto, Japan) at 36.5°C [32].

The microparticles (0.025 g), which were prepared by 0.5 M-YCl_3 and 1.0 wt%-ammonium alginate aqueous solutions and then heat-treated at 1100°C, were soaked in 10 ml of SBF with pH 6 (SBF-6) or 7 (SBF-7) in a polypropylene bottle at 36.5°C for various periods up to 21 days. The pH value of normal body fluid is maintained at around pH 7, but this value is liable to fall to around pH 6 in the vicinity of a cancer, owing to the production of lactic acid [33]. The SBF was shaken at a rate of 120 strokes min^{-1} using a stroke length of 3 cm. The solid materials were soaked for up to 21 days. The radioactivity of ^{90}Y decays to a negligible level after 21 days. An inductively coupled plasma atomic emission spectrometer (ICP; Optima 2000DV, PerkinElmer Co., Ltd., Germany) was used to determine the concentrations of yttrium released from the microparticles into the SBF-6 or SBF-7, and the fraction of yttrium released from the microparticles was calculated using the following formula:

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

3 Results and discussion

Figure 1 shows the SEM photographs of the gel microparticles prepared under different concentrations of YCl_3 and ammonium alginate after drying at 60°C. It is assumed that gel particles were formed by a rapid gelation reaction between ammonium alginate and trivalent yttrium (Y^{3+}) ions, according to the reaction formula in Fig. 1.

The YCl_3 concentration of 0.5 M gave stable particles around 850 μm in size, when the content of ammonium alginate was 1 or 2 wt%. If the YCl_3 concentration was decreased from 0.5 to 0.01 M, the particles were not able to retain their shapes during the subsequent drying process at 60°C. This might because the amount of Y^{3+} ions in the YCl_3 aqueous solution, contributing the gelation reaction of ammonium alginate, was not sufficient to give stable gel particles. If the gelation of ammonium alginate is caused by the reaction in Fig. 1, only 7.7×10^{-8} mol of YCl_3 is needed to perform the gelation reaction for 0.2 g of ammonium alginate. However, a concentration around 0.5 M of YCl_3 was required to form stable gel particles in this study. This remarkable difference between the theoretical and experimental concentrations of YCl_3 for gelation is unknown, but the similar phenomena were observed in the gelation of ammonium alginate in hydrochloric acid solution [31]. In addition, the surface of particles became rough and wrinkled, when the YCl_3 concentration increased from 0.5 to 2 M at a constant content (1 or 2 wt%) of ammonium alginate.

At the constant YCl_3 concentration of 0.5 M, the particle prepared at the ammonium alginate of 1 and 2 wt% retained its shape and had a relatively smooth surface. When the ammonium alginate was decreased from 1 to 0.5 wt%, the shape of particles was not retained during the subsequent drying process. It is well known that the viscosity of the solution containing polysaccharides such as ammonium alginate rapidly increases with increasing content of polysaccharide [30]. Also, in this study, the viscosity of 2 wt% ammonium alginate solution was too high to give stable droplets from a Pasteur pipette. Therefore, the samples prepared using 1 wt% ammonium alginate aqueous solution and 0.5 M YCl_3 aqueous solution were used in the following experiments.

Figure 2 shows the XRD patterns of the microparcticles prepared by 0.5 M-YCl_3 and 1.0 wt%-ammonium alginate aqueous solutions and then heat-treated at various temperatures. Before heat treatment and after heat treatment at 500°C, no peaks were observed, which suggested that the sample took an amorphous structure. When the sample was heat-treated at 700°C, cubic Y_2O_3 started to precipitate. The amount of cubic Y_2O_3 increased with increasing heat treatment temperature up to 1300°C.

Figure 3 shows the SEM photographs of the microparcticles prepared by 0.5 M-YCl_3 and 1.0 wt%-ammonium alginate aqueous solutions and then heat-treated at various temperatures. The sample before heat treatment gave a homogeneous and dense structure from its surface to interior. After the heat treatments at 500°C and above, the

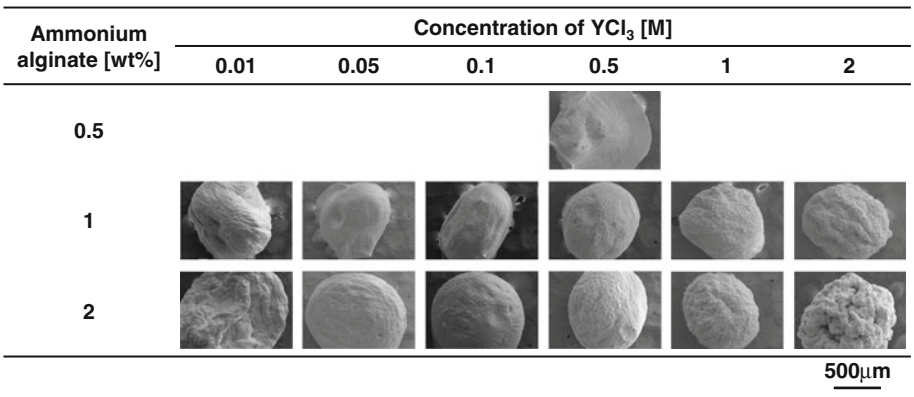

Fig. 1 SEM photographs of the microparticle prepared under different concentrations of YCl_3 and ammonium alginate after drying at 60°C

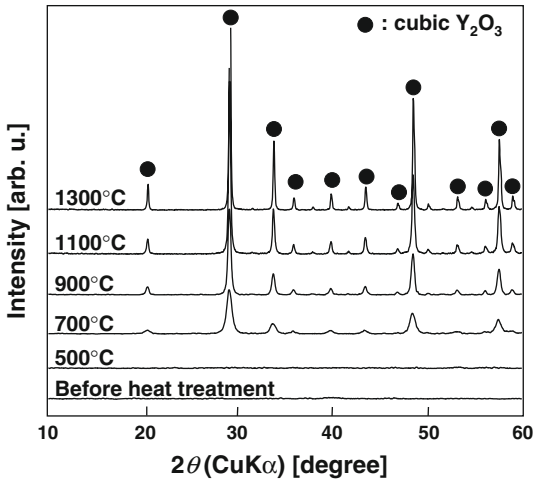

Fig. 2 XRD patterns of the microparticles prepared by 0.5 M-YCl_3 and 1.0 wt%-ammonium alginate aqueous solutions, dried at 60°C and then heat-treated at various temperatures

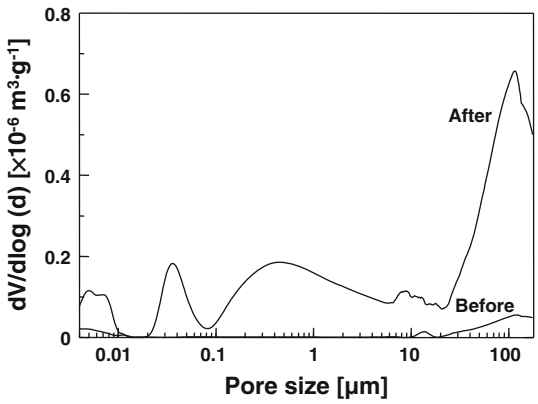

Fig. 4 Pore size distributions of the microparticles prepared by 0.5 M-YCl_3 and 1.0 wt%-ammonium alginate aqueous solutions and dried at 60°C before and after heat treatment at 1100°C

size of sample decreased from 1 mm to around 500 μm. The surface and interior of particles produced some cracks after the heat treatments, irrespective of the heat treatment temperature. The samples heat-treated at 900 or 1000°C had relatively small cracks at their surfaces and porous inner structure, but, after the heat treatment at 1300°C, the surface cracks were grown. We can easily speculate that the microparticles heat-treated at higher temperature will show higher chemical durability in body environment, since a sintering of Y_2O_3 will proceed at higher temperature. However, the large cracks at the particle surface might cause easy fracture of the particles in blood vessels in clinical application [29]. Therefore, we considered that maximum heat treatment temperature should be limited to 1100°C, and the chemical durability test was conducted for the particles heat-treated at 1100°C in this study.

Figure 4 shows the Pore size distributions of the microparticles prepared by 0.5 M-YCl_3 and 1.0 wt%-ammonium alginate aqueous solutions and dried at 60°C before and after heat treatment at 1100°C. The unheated microparticle hardly has meso- and micro-pores, but the heat-treated one had pores with different sizes. The small pores less than 1 μm might be formed by the removal of ammonium alginate during the heat treatment, whereas the large pores around 100 μm might be attributed to the cracks in the heat-treated samples according to the SEM photograph in Fig. 3. The mesoporous structure of the present heat-treated microparticle would be useful for drug support [34, 35]. Table 1 summarizes pore volume, surface area, and porosity of the microparticles before and after heat treatment at 1100°C. The microparticle after heat treatment has larger pore volume, larger surface area, and higher porosity. The bulk densities estimated from these results were 2.78 and 0.66 g cm^{-3} for unheated and heat-treated microparticles, respectively. The low density of heat-treated microparticles would be favorable for obtaining a stable suspension in clinical application of in situ radiotherapy.

Table 2 shows the fraction of yttrium released from the microparticles prepared by 0.5 M-YCl_3 and 1.0 wt%-ammonium alginate aqueous solutions and then heat-treated at 1100°C into SBF-6 or SBF-7 at 36.5°C for 21 days. The released fraction of yttrium form the microparticles were 1.4×10^{-5} and 1.3×10^{-5} in SBF-6 and SBF-7, respectively. We previously reported that the released fractions of yttrium from hollow Y_2O_3 particles around

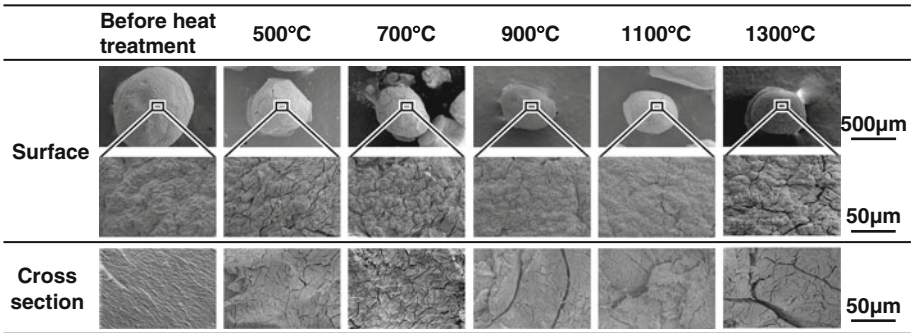

Fig. 3 SEM photographs of the microparticle prepared by 0.5 M-YCl_3 and 1.0 wt%-ammonium alginate aqueous solutions, dried at 60°C and then heat-treated at various temperatures

Table 1 Pore volume, surface area, and porosity of the microparticles prepared by 0.5 M-YCl_3 and 1.0 wt%-ammonium alginate aqueous solutions before and after heat treatment at 1100°C

Sample	Pore volume [$\times 10^{-6}$ m^3 g^{-1}]	Surface area [m^2 g^{-1}]	Porosity [%]
Before	0.043	5.68	12.07
After	0.759	36.31	50.11

Table 2 Fraction of yttrium released from the microparticles prepared by 0.5 M-YCl_3 and 1.0 wt%-ammonium alginate aqueous solutions and then heat-treated at 1100°C into SBF-6 or SBF-7 at 36.5°C for 21 days

Immersion fluid	Released fraction of yttrium
SBF-6	1.4×10^{-5}
SBF-7	1.3×10^{-5}

25 μm in size were around 1.8×10^{-3} and 1.3×10^{-3} in SBF-6 and SBF-7, respectively [29], which were smaller than those ($\approx 9 \times 10^{-3}$) of YAS glass in saline solutions buffered at pH = 6 or 7 for 21 days [27]. The measured fraction of yttrium released from the present Y_2O_3 microparticles was smaller than that from hollow Y_2O_3 particles, but we should consider here the difference in surface area between these particles with different sizes. The surface area of the present Y_2O_3 particles is calculated to be four hundredth part of that of hollow Y_2O_3 particles, because the size of the present Y_2O_3 particles was around 500 μm according to SEM photograph in Fig. 3. Therefore, if the size of present Y_2O_3 microparticles is decreased to around 25 μm, which is appropriate for clinical application, the fractions of yttrium released form the present Y_2O_3 microparticles are estimated to be around 5.6×10^{-3} (=$1.4 \times 10^{-5} \times 400$) and 5.2×10^{-3} (=$1.3 \times 10^{-5} \times 400$) in SBF-6 and SBF-7, respectively. These values are slightly larger than the released fractions of yttrium from hollow Y_2O_3 particles but smaller than those of YAS glass which is clinically used. Therefore, we can conclude that the chemical durability of the present Y_2O_3 microparticles is high enough for clinical application.

Figure 5 shows the SEM photographs of the microparticle prepared by 0.5 M-YCl_3 and 1.0 wt%-ammonium alginate aqueous solutions, freeze-dried and then heat-treated at 1100°C. We confirmed by XRD measurement that the precipitated crystalline phase was cubic Y_2O_3 (data were not shown). The microparticle 500 μm in size was obtained. Their outer surfaces were dense but wrinkled (see Fig. 5a), and inside they had a porous structure (see Fig. 5b). This structure might be constructed during the freeze-dry process. This result suggests that the structure of the microparticle can be controlled by modifying the dry process for the gel particles.

We will investigate the possibility for decreasing the particle size to around 25 μm and improving the surface smoothness in future study. In fact, we attempted to produce small droplets of 1.0 wt%-ammonium alginate aqueous solution by utilizing a commercially available atomizer and investigated the particle size distribution of the droplets in order to explore the possibility for obtaining microspheres around 25 μm. As a result, we obtained the particle size distribution of the droplets with its peak around 40 μm (data were not shown). We should further investigate the structure of the resultant droplets in detail, but we believe that small particles around 25 μm in size can be obtained by optimizing the atomizing condition.

4 Conclusions

Porous Y_2O_3 microparticles 500 μm in size were obtained, when ammonium alginate solution was dropped into YCl_3 aqueous solution and the resultant gel particles were heat-

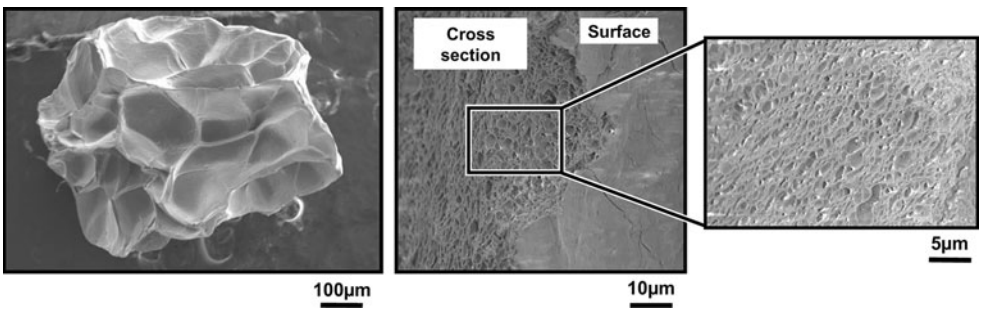

Fig. 5 SEM photographs of the microparticle prepared by 0.5 M-YCl_3 and 1.0 wt%-ammonium alginate aqueous solutions, freeze-dried and then heat-treated at 1100°C

treated at 1100°C. The chemical durability of the porous Y_2O_3 microparticles was estimated to be high enough for clinical application of in situ radiotherapy of cancer. Although the size of particles should be decreased to around 25 μm for clinical application, we believe that a fundamental condition for obtaining porous Y_2O_3 micoparticles by utilizing gelation of polysaccharide in aqueous solution containing yttrium are revealed in this study.

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