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Yttrium phosphate microspheres with enriched phosphorus content prepared for radiotherapy of deep-seated cancer

Toshiki Miyazaki[a,*], Toru Tanaka[a], Yuki Shirosaki[b], Masakazu Kawashita[c]

[a]*Graduate School of Life Science and Systems Engineering, Kyushu Institute of Technology, 2-4 Hibikino, Wakamatsu-ku, Kitakyushu 808-0196, Japan*
[b]*Frontier Research Academy for Young Researchers, Kyushu Institute of Technology, Kitakyushu, Japan*
[c]*Graduate School of Biomedical Engineering, Tohoku University, Sendai, Japan*

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Abstract

Ceramic microspheres composed of β-emitters are useful for *in situ* radiotherapy of deep-seated cancer by implantation around the tumor. In addition, microspheres 20–30 μm in diameter can combine β-emission with the embolization effect. Yttrium phosphate is an attractive candidate material for such microspheres, because both Y and P play roles as β-emitters. The half-life of ^{31}P is known to be much larger than that of ^{90}Y. Therefore, it is expected that yttrium phosphate microspheres with high P content can maintain a longer radiotherapy effect. In the present study, preparation of microspheres with enriched P content has been attempted by water-in-oil emulsions using polyphosphate as a starting material. Yttrium phosphate microspheres with a higher P/Y molar ratio (2.5) than in previously reported YPO_4 microspheres were obtained. It was found that emulsification for sufficient time (more than 10 min) is necessary to obtain microspheres that are 20–30 μm in size. Although the microspheres released Y sparingly, they released larger amounts of P than previously reported YPO_4 microspheres in a simulated body environment. Heat treatment at moderate temperature can suppress P release to some extent. Further improvement in chemical durability through surface modification is essential for long-term clinical use.

Keywords: A. Powders: chemical preparation; C. Chemical properties; E. Biomedical applications; Yttrium phosphate

1. Introduction

Recently, the development of less invasive deep-seated cancer treatments has become an urgent issue in improving the quality of life for cancer patients. In choosing radiation for this type of cancer treatment, β-rays are the most suitable because of their moderate range. Ceramic microspheres composed of β-emitters are useful for *in situ* radiotherapy of deep-seated cancer by implantation around the tumor through blood vessels. It is known that several elements, such as P, Y, and Re can be converted to β-emitting radioisotopes by neutron bombardment [1]. Additionally, when their particle size is controlled to the range 20–30 μm, they are promising as multifunctional biomaterials that exhibit not only radiotherapy but also embolization effects in tumors. They are especially useful for liver and kidney cancer treatment.

For these reasons, microspheres comprising Y_2O_3-based glasses, ceramics and composites have been proposed [2–7]. ^{31}P is a β-emitter that has a larger half-life (14.3 days) than that of ^{90}Y (64.1 h). Therefore, it is expected that yttrium phosphate will maintain a prolonged radiotherapy effect. Previously, yttrium phosphate microspheres containing the above elements were prepared by various techniques such as high frequency induction thermal plasma melting and gel formation in water-in-oil (W/O) emulsions [4,8,9]. The major composition of such microspheres is xenotime-type YPO_4. Improvement in the radiotherapy effect may be expected if the P content in yttrium phosphate can be increased.

In the present study, preparation of microspheres with enriched P has been attempted in W/O emulsions using polyphosphate as a starting material. Optimum conditions for

*Corresponding author. Tel./fax: +81 93 695 6025.
E-mail address: tmiya@life.kyutech.ac.jp (T. Miyazaki).

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preparation of particles 20–30 μm in size, suitable for radiotherapy combined with embolization, were determined. Chemical durability of the microspheres was also assessed in a simulated body environment.

2. Materials and methods

Chemical reagents for preparation of microspheres and SBF were purchased from Wako Pure Chemical Industries, Ltd., Osaka, Japan, and Nacalai Tesque, Inc., Kyoto, Japan, respectively.

Initially, precipitate was obtained by mixing 50 mL of 0.3 M yttrium acetate tetrahydrate ($(CH_3COO)_3Y \cdot 4H_2O$) and an equal volume of 0.15 M sodium hexametaphosphate ($(NaPO_3)_n$). The precipitate was washed with ultrapure water twice, dispersed in 15 mL of 0.1 M HNO_3 solution and stirred for 24 h to form a sol. The W/O emulsion was prepared by vigorous mixing of 5 mL of the sol, 25 mL of toluene, 25 mL of 1,1,1-trichloroethane and 0.55 g of sorbitan monooleate (Span80) as a surfactant at 3000 rpm using a rotary homogenizer (Homo Mixer Mark II, Tokushu Kika Co., Osaka, Japan) for various periods ranging from 5 to 20 min. The prepared emulsion was immediately added into 300 mL of 1-butanol and stirred for 10 min. In this process, the separated water phase that remained without homogeneous emulsification was not added to the 1-butanol. The obtained precipitates were filtered, washed with acetone and dried at 60 °C for 24 h. They were then heated at the rate of 5 °C/min in an electric furnace (KDF-S70, Denken Co. Ltd., Kyoto, Japan), kept at various temperatures for 1 h and cooled to room temperature in the furnace.

The microstructure of the powder product was characterized by X-ray diffraction (XRD; MXP3V, Mac Science Ltd., Yokohama, Japan) and scanning electron microscopy (SEM; S-3500N, Hitachi Co., Tokyo, Japan) equipped with energy dispersive X-ray spectroscopy (EDX; EMAX Energy, Horiba Co., Kyoto, Japan). Particle size distribution was measured by a laser diffraction particle size analyzer (LA-950, Horiba Co., Kyoto, Japan).

Chemical durability of the microspheres was examined as follows. Fifty milligrams microspheres material was soaked in 20 mL of simulated body fluid (SBF; Na^+ 142.0, K^+ 5.0, Mg^{2+} 2.5, Cl^- 147.8, HCO_3^- 4.2, HPO_4^{2-} 1.0 and SO_4^{2-} 0.5 mM) with ion concentrations similar to those of human extracellular fluid, and kept at 36.5 °C under static conditions for various periods. SBF was prepared following methods described in the literature [10]. The pH of the solution was adjusted to 6 by addition of 1 M HCl because the pH around tumors is reported to be often weakly acidic through secretion of lactic acid. Y and P concentrations released from the microspheres into the solution were measured by inductively coupled plasma atomic emission spectroscopy (ICP; Optima 4300DV Cyclon, Perkin-Elmer Co., Cambridge, England).

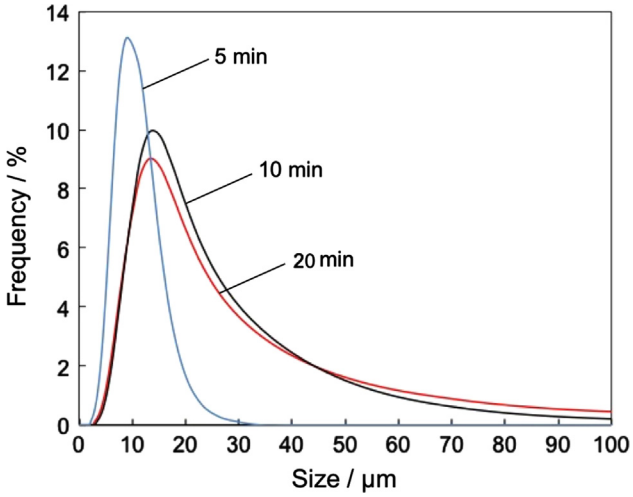

Fig. 2. Particle size distribution of microspheres before heat treatment, as a function of emulsification time.

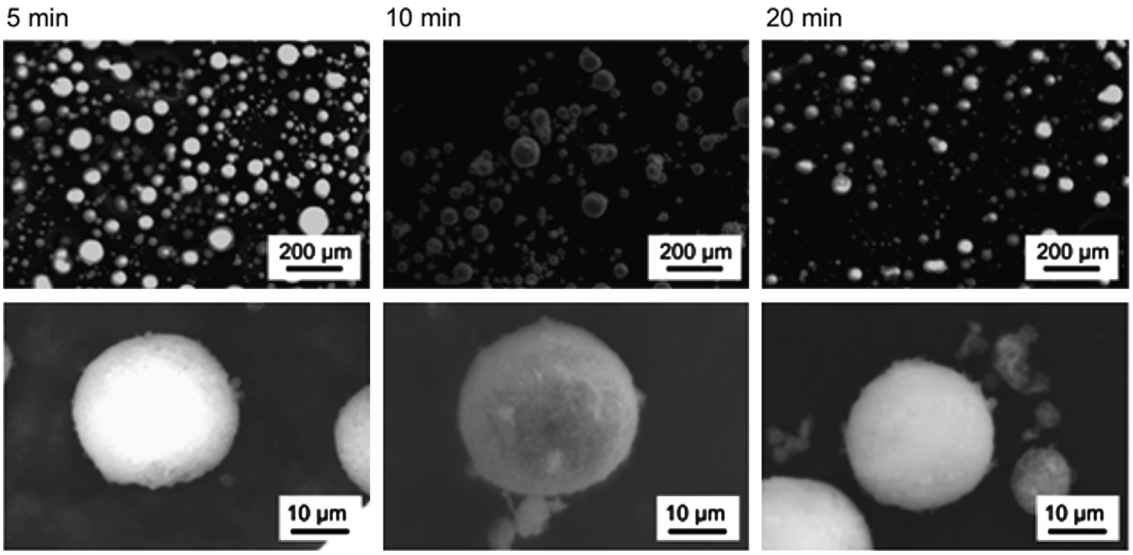

Fig. 1. SEM photographs of particles before heat treatment, as a function of emulsification time.