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

Toshiki Miyazaki[1], Toru Tanaka[1], Yuki Shirosaki[2], Masakazu Kawashita[3]

[1]Graduate School of Life Science and Systems Engineering, Kyushu Institute of Technology, Kitakyushu, Japan

[2]Frontier Research Academy for Young Researchers, Kyushu Institute of Technology, Kitakyushu, Japan

[3]Graduate School of Biomedical Engineering, Tohoku University, Sendai, Japan

Corresponding Author:

Toshiki Miyazaki

Associate Professor, Graduate School of Life Science and Systems Engineering, Kyushu Institute of Technology

2-4 Hibikino, Wakamatsu-ku, Kitakyushu 808-0196, Japan

Tel & Fax: +81-93-695-6025

E-mail: tmiya@life.kyutech.ac.jp

Abstract

Ceramic microspheres composed of β-emitter 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 the β-emitter. The half-life of ^{31}P is known to be much longer 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 previously reported YPO_4 microspheres were obtained. It was found that emulsification for sufficient time (more than 10 minutes) 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, D. Yttrium phosphate, E. Biomedical applications

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 longer half-life (14.3 days) than that of ^{90}Y (64.1 hours). 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 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.

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.

At first, 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 and dispersed in 15 mL of 0.1 M HNO_3 solution and stirred for 24 hours to form a sol. The

W/O emulsion was prepared by vigorous mixing 5 mL of the sol, 25 mL of toluene, 25 mL of 1,1,1-trichloriethane 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 minutes. The prepared emulsion was immediately added into 300 mL of 1-butanol and stirred for 10 minutes. At this time, 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 hours. They were then heated at rate of 5°C/min in an electric furnace (KDF-S70, Denken Co. Ltd., Kyoto, Japan), kept at various temperatures for 1 hour 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), 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

of microspheres were 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 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 Perkin-Elmer Co., Cambridge, England).

Results and Discussion

The P/Y atomic ratio of the obtained microspheres before heat treatment was determined as 2.5 by EDX, confirming that the P content in microspheres can be increased by using polyphosphate instead of orthophosphate as a starting material.

Figure 1 shows SEM photographs of the obtained particles before heat treatment, as a function of emulsification time. We can see that spherical microspheres with smooth surfaces 10–100 μm in size were obtained, irrespective of emulsification time.

Figure 2 shows the particle size distribution of the microspheres. The size distribution shifted to the larger region with increasing emulsification time, while no significant difference was observed between samples at 10 and 15 min. Few particles 20–30 μm in size were observed at 5 min. In this case, a portion of the water phase was not sufficiently homogenized with the oil phase and was therefore not available for microsphere formation. Therefore, the content of the water phase within the emulsion was low and consequently smaller particles were formed. This assumption is supported by the fact that the size of the microspheres tends to increase with increasing water content in the emulsion [11]. The present results indicate that emulsification for sufficient time is essential for preparing large quantities of microspheres 20–30 μm in size.

Figure 3 shows XRD patterns of microspheres made with an emulsification time of 10 min, after heat treatment at various temperatures. A diffraction peak assigned to $Y(PO_3)_3$ (JCPDS #42-0501) was observed after heat treatment at 600°C, but not at other temperatures, meaning that crystallization of the yttrium phosphate occurs at 600°C. SEM photographs of the heated microspheres are shown in Fig. 4. A spherical shape was maintained even after heat treatment. Although some particles aggregated, surfaces

of the microspheres were smooth at 400 and 500°C. Conversely, many micropores of sizes 1–3 μm were observed on the surfaces and almost all particles aggregated at 600°C.

Figure 5 shows the particle size distribution of the microspheres before and after heat treatments at different temperatures. The distribution of the sample heated at 600°C could not be measured because particles were significantly aggregated. A new peak maximum at 40–50 μm was observed in the distribution after the heat treatment, which could be attributed to aggregation of the microspheres. Previously reported YPO_4 microspheres did not show such aggregation even after sintering at 1000°C [9]. The melting point of the glass is generally reduced at increased phosphate content. Therefore, the high P content in the present microspheres would cause the aggregation.

Figure 6 shows Y and P concentrations of SBF after soaking of the microspheres with and without heat treatments at different temperatures. Y was only sparingly released, irrespective of heating temperature, while P was released from all specimens. The content of the released P showed a tendency to decrease with an increase in heating temperature. This means that P was released more preferably than Y. $AlPO_4 \cdot 1.5H_2O$ was reported to release a larger amount of P than Al in weakly acidic conditions around pH 6,

because the released Al^{3+} is hydrated and re-precipitated in this pH region [12]. A similar phenomenon may have occurred in the case of the present microspheres.

The samples heat-treated at 600°C released about 4.7% of the P content from the microspheres, 70 times more than from the YPO_4 microspheres in our previous study [8]. Sintering would be less extensive, because the heat treatment temperature in the present study (600°C or less) was lower than that used previously (1000°C). In addition, dissolution of phosphate glass was reported to be enhanced under acidic conditions [13]. These factors would cause a high P release from the present microspheres. It is concluded that heat treatment at 500°C or less is desirable in terms of aggregation and chemical durability. However, further suppression of P release should be attempted in future studies. Prior acid treatment to remove water-soluble portions or coating with a protective layer are two potential approaches to solve this problem.

Conclusions

Yttrium phosphate microspheres with enriched P were prepared by using a W/O emulsion as a reaction environment. The size of the microspheres depends on emulsification time. If P release can be suppressed, for example by further surface

modification, the resultant microspheres may show promise as a β-emitter for *in situ* cancer radiotherapy.

Acknowledgments

This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas for "Fusion Materials: Creative Development of Materials and Exploration of Their Function through Molecular Control" (No. 2206) from the Ministry of Education, Culture, Sports, Science and Technology, Japan (MEXT).

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Figure captions

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

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

Figure 3 XRD patterns of microspheres produced with an emulsification time of 10 min, after heat treatments at various temperatures.

Figure 4 SEM photographs of microspheres produced with an emulsification time of 10 min, after heat treatments at various temperatures.

Figure 5 Particle size distribution of microspheres produced with an emulsification time of 10 min, after heat treatments at various temperatures.

Figure 6 Y and P concentrations of SBF after incubation with microspheres produced with an emulsification time of 10 min, before and after heat treatments at different temperatures.

Figure1
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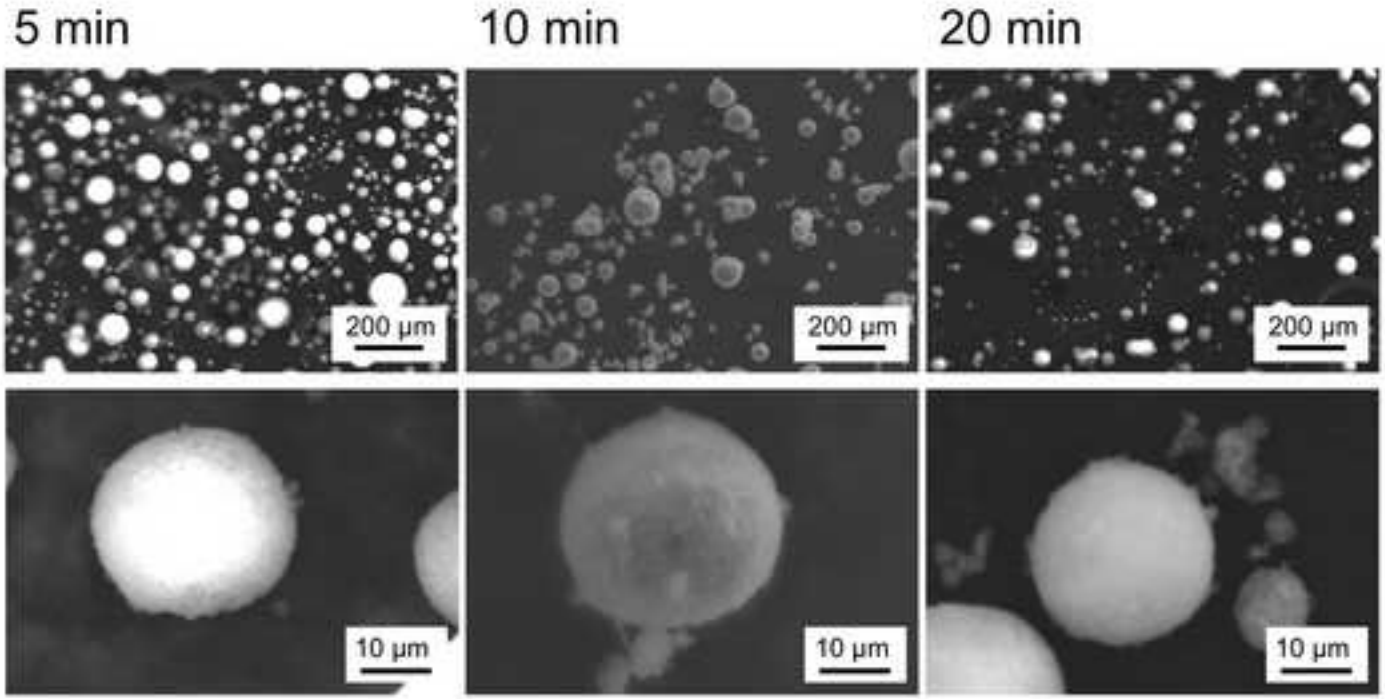

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Fig. 1

Figure2
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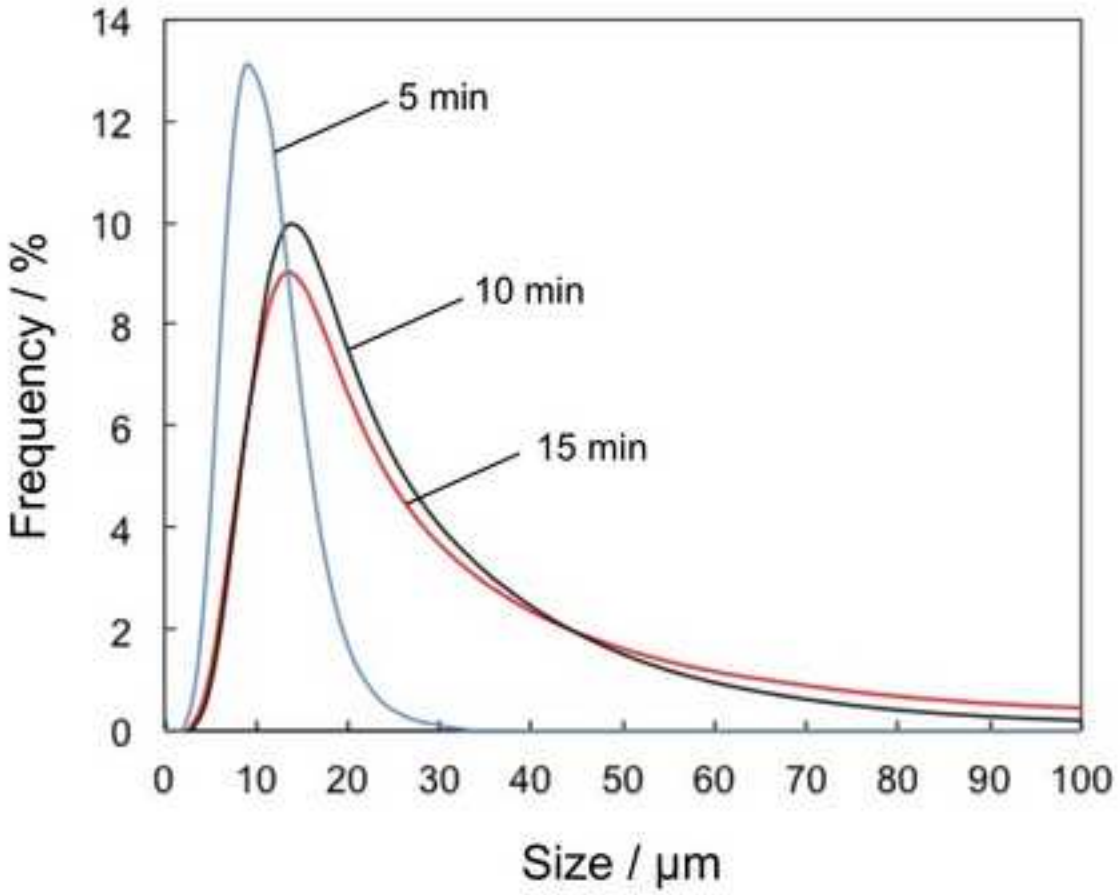

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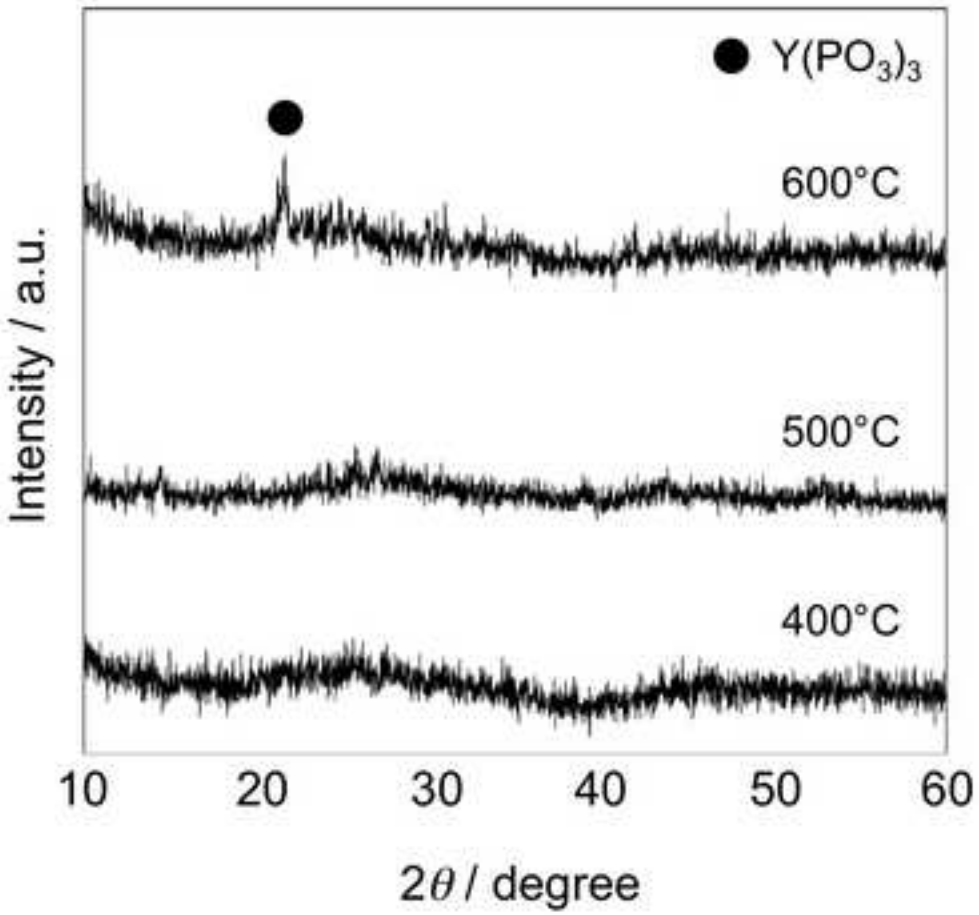

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Fig. 3

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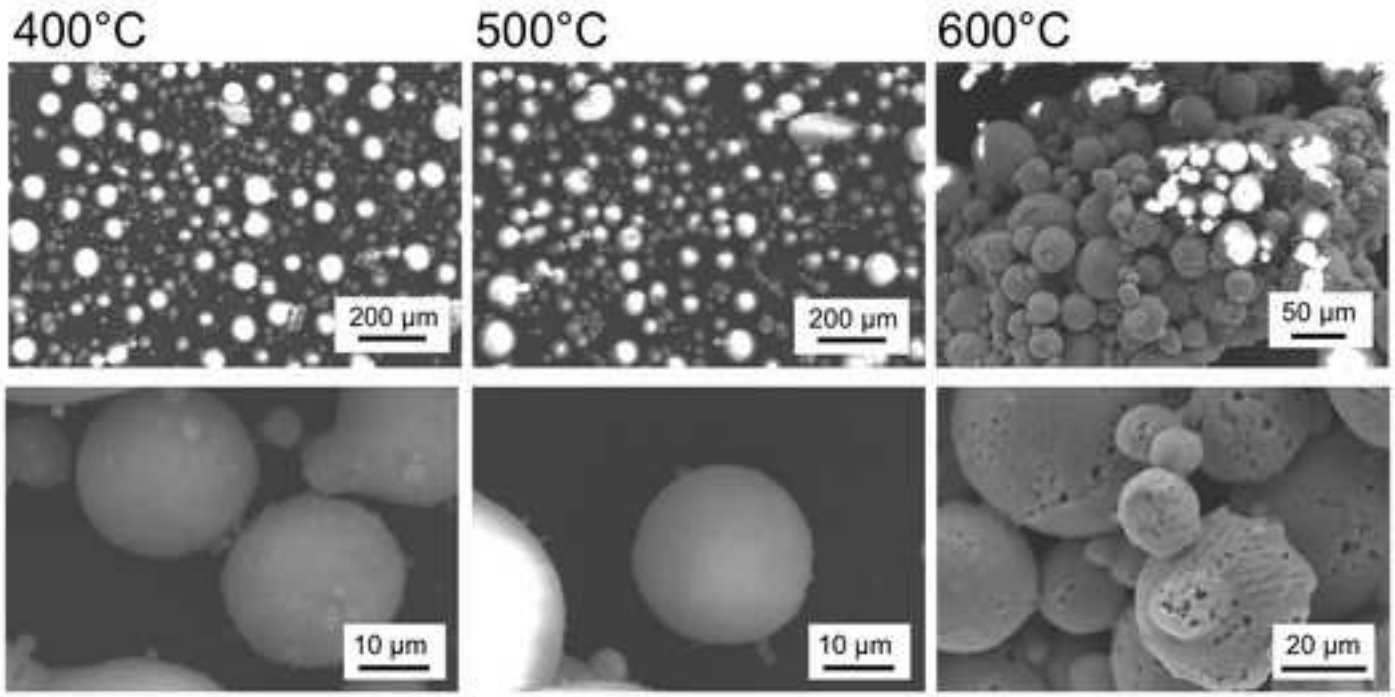

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Fig. 4

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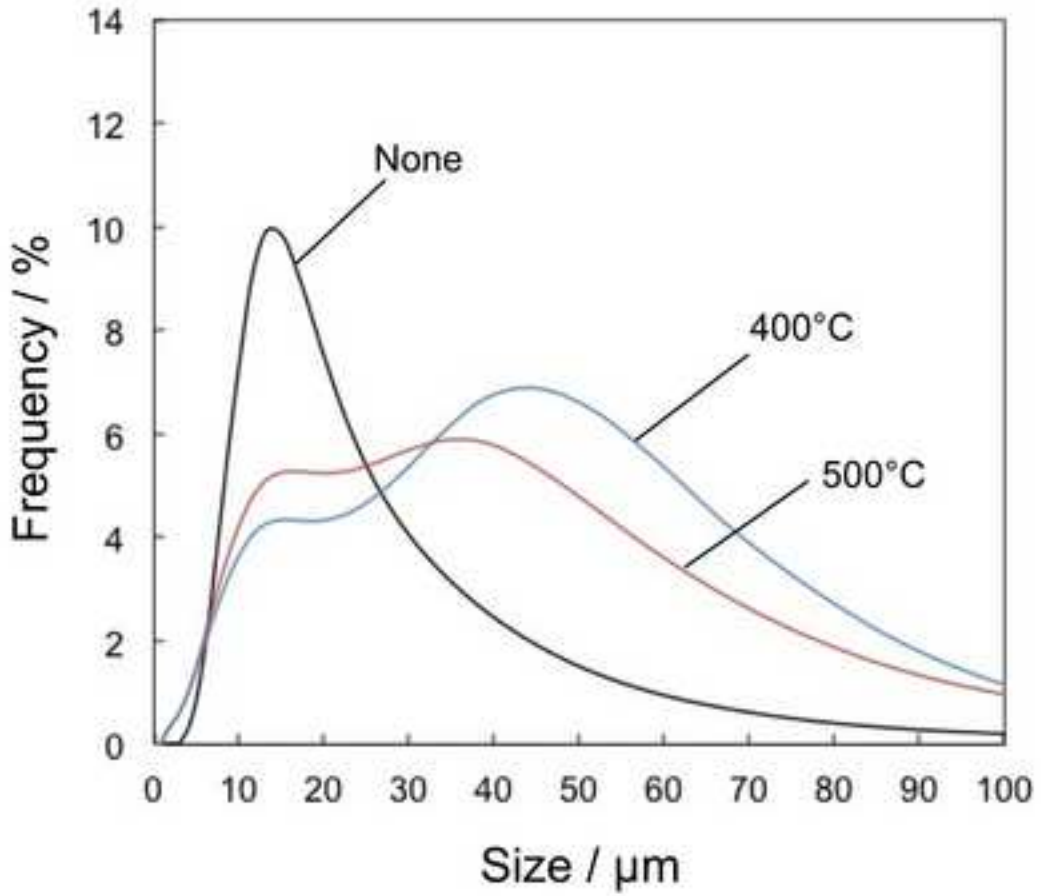

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Fig. 5

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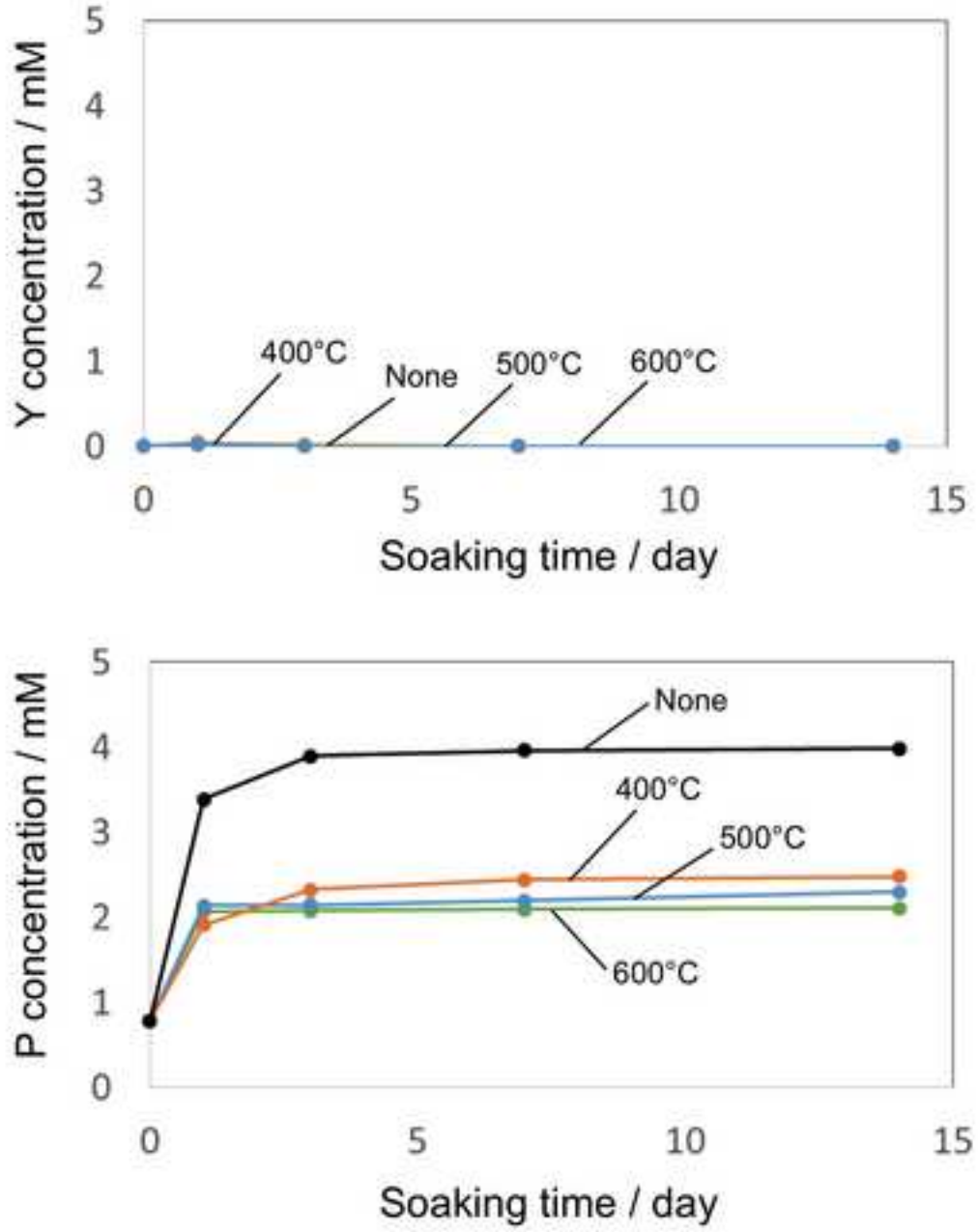

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Fig. 6