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Preparation of phosphorus-containing silica glass microspheres for radiotherapy of cancer by ion implantation

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A chemically durable glass microsphere containing a large amount of phosphorus is useful for *in situ* irradiation of cancers, since they can be activated to be a β-emitter with a half-life of 14.3 d by neutron bombardment. When the activated microspheres are injected to the tumors, they can irradiate the tumors directly with β-rays without irradiating neighboring normal tissues. In the present study, P^+ ion was implanted into silica glass microspheres of 25 μm in average diameter at 50 keV with nominal doses of 2.5×10^{16} and $3.35 \times 10^{16}\,cm^{-2}$. The glass microspheres were put into a stainless container and the container was continuously shaken during the ion implantation so that P^+ ion was implanted into them uniformly. The implanted phosphorus was localized in deep regions of the glass microsphere with the maximum concentration at about 50 nm depth without distributing up to the surface even for a nominal dose of $3.35 \times 10^{16}\,cm^{-2}$. Both samples released phosphorus and silicon into water at 95 °C for 7 d. On the basis of the previous study on P^+-implanted silica glass plates, the silica glass microspheres containing more phosphorus which is desired for actual treatment could be obtained, without losing high chemical durability, if P^+ ion would be implanted at higher energy than 50 keV to be localized in deeper region.

1. Introduction

Radiotherapy is one of the most effective treatments of cancers. External irradiation, however, often causes damage to healthy tissues. It has been reported that glass microspheres 20–30 μm in diameter of $17Y_2O_3-19Al_2O_3-64SiO_2$ (mol %) composition are useful for *in situ* irradiation of cancers [1–3]. Yttrium-89 in the glass can be activated to β-emitter, ^{90}Y, with a half-life of 64.1 h by neutron bombardment. Other elements constituting the glass are not activated by the neutron bombardment. The glass is insoluble in body fluids and non-toxic. When microspheres of the activated glass are injected into liver tumors through the hepatic artery, they can give large local irradiation of short-ranged highly ionizing β-ray to the tumors with only a small radiation dose to the neighboring healthy organs. These glass microspheres have been subjected to clinical trials on the irradiation of diseased kidneys and malignant tumors in the liver, radiation synovectomy of arthritic joints and so on [4–12]. They have been in commercial use in Canada since 1991 [11].

The ^{90}Y, however, may result in substantial decay even before cancer treatment, owing to the short half-life of 64.1 h [13]. Phosphorus-31, with 100% natural abundance, similar to ^{89}Y, can be activated to β-emitter, ^{32}P, by neutron bombardment [13] and the half-life of ^{32}P (14.3 days) is about five times as long as that of ^{90}Y (64.1 h). Phosphorus-rich glasses prepared by the conventional melting method are, however, usually less chemically durable.

The authors have attempted to prepare a chemically durable glass containing phosphorus in high concentration by P^+ ion implantation into a silica (SiO_2) glass. Previous studies, where a plate of silica glass was used, showed that such glass can be obtained if the P^+ ions are implanted into the silica glass at higher energy localized in a deep region [14–18]. The elements constituting the glass (Si and O) are not activated by neutron bombardment. Microspheres in various sizes of silica glass with a high purity are easily available commercially. A technique of P^+ ion implantation into microspheres of silica glass, however, has not been established yet. In the present study, P^+ ions were implanted into silica glass microspheres 25 μm in average diameter at 50 keV with nominal doses of 2.5×10^{16} and $3.35 \times 10^{16}\,cm^{-2}$. The distribution and

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state of the implanted phosphorus, and surface structural change of the glass microsphere due to ion implantation were examined. The chemical durability of the glass microspheres implanted with P^+ ions was also investigated in terms of their surface structures.

2. Materials and methods

2.1. Ion implantation into silica glass microspheres

Highly pure silica glass microspheres 25 μm in average diameter (metallic impurities < 300 p.p.m.) were prepared by flame spherodization (Harimic SW-CO5, Maikuron Corp., Himeji, Japan). Phosphorus ion (P^+) was produced by thermoelectron bombardment to red phosphorus vapor, and implanted into the glass microspheres at 50 keV with nominal doses of 2.5×10^{16} and $3.35 \times 10^{16}\,\mathrm{cm}^{-2}$ by an ion implanter (NH-20SR, Nissin Electrical Co. Ltd, Tokyo, Japan). As shown in Fig. 1, the glass microspheres of 5.0 g were put into a stainless steel container $30 \times 40 \times 20\,\mathrm{mm}^3$ in size on a vibrator, and this container was continuously vibrated with a frequency of 200 Hz during the ion implantation so that the P^+ ions were implanted into the microspheres uniformly. A secondary-electron shower was irradiated to the microspheres to reduce charge-up at their surfaces. A low mean current density ($100–400\,\mu\mathrm{A\,cm}^{-2}$) was used to prevent a remarkable temperature increase of the glass microspheres during ion implantation.

2.2. Structural analysis of silica glass microspheres

The depth profile of the phosphorus was measured with a three-dimensional secondary ion mass spectroscope (3D-SIMS; SIMS4000, Atomica Analysetechnik GMBH, München, Germany). The ^{31}P (100% natural abundance) and ^{18}O (20.4% natural abundance) signals were detected by a Cs^+ primary beam with 0.5 μm ϕ at 10 keV and 100 nA. For each measurement point up to 0.3 μm depth, a $300 \times 300\,\mu\mathrm{m}^2$ area was resolved into 256×256 mesh points. The intensity of the ^{31}P signal was normalized by being divided by that of the ^{18}O signal in the silica glass matrix.

The chemical state of elements in the glass microspheres was investigated by measuring survey spectrum with X-ray photoelectron spectroscopy (XPS, MT-5500, ULVAC-PHI Co. Ltd, Chigasaki, Japan). MgK_α (1253.6 eV) X-rays were used as an excitation source at a residual pressure of 10^{-9} Pa. The photoelectron take-off angle (the angle between the surface of the sample and the detector axis) was set at 45°. The measured binding energies were corrected with reference to the binding energy of $\mathrm{C}_{1\mathrm{s}}$ (284.6 eV) of the hydrocarbon adsorbed on the surface of the sample.

Surface structures of the glass microspheres were analyzed with Fourier transform infrared diffusive reflection spectroscopy (FTIR 5M, JASCO, Tokyo, Japan) with a 45° incident angle. For the FTIR diffusive reflection spectroscopic measurement, the glass microspheres were pulverized, and mixed homogeneously with powdered KBr at a sample : KBr ratio of 1 : 100.

2.3. Chemical durability test

The P^+-implanted glass microspheres of 0.20 g were immersed in 20 ml of distilled water at 95 °C in a polypropylene bottle, shaken at a rate of 120 strokes min^{-1} with a stroke length of 3 cm. After seven days, the concentration of the phosphorus and silicon, released from the glass microspheres into the hot water, was measured with inductively coupled plasma (ICP) atomic

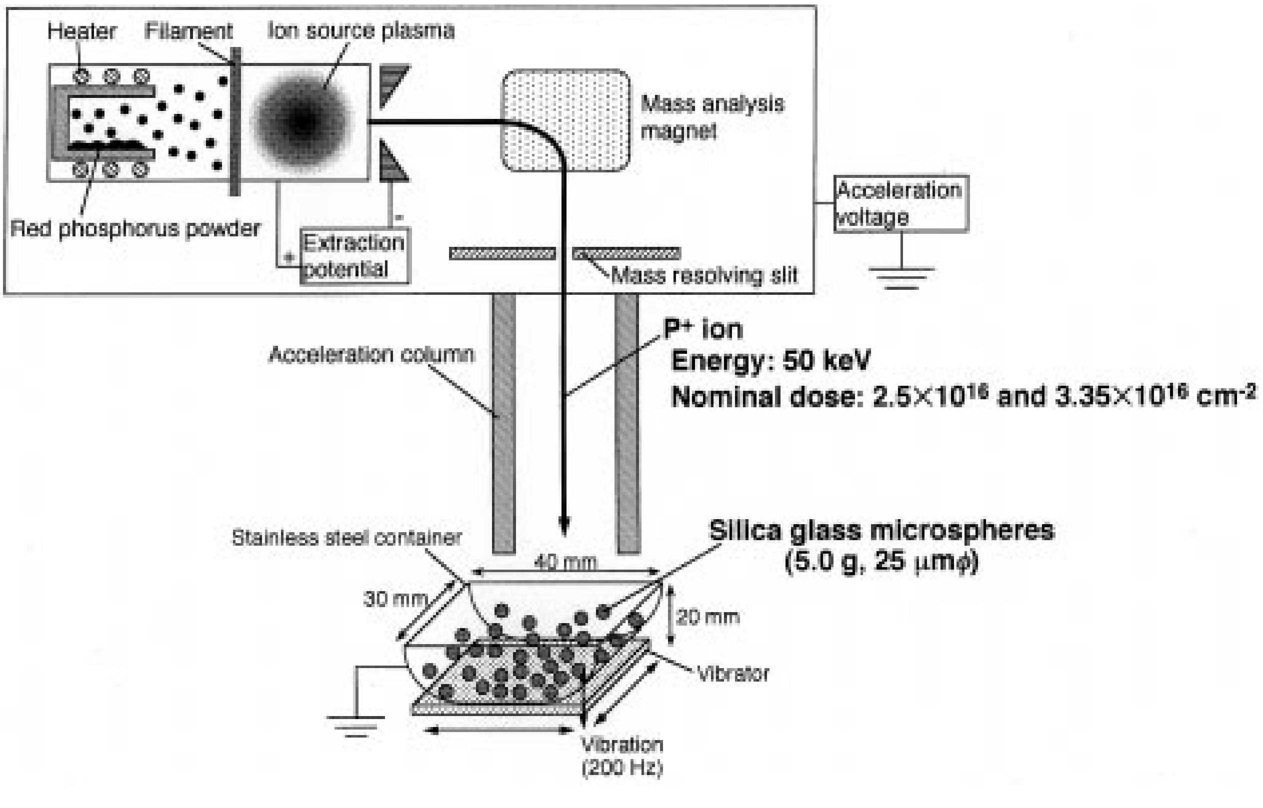

Figure 1 Schematic representation of P^+ ion implantation into silica glass microspheres.

emission spectroscopy (SPS-1500VR, Seiko Instruments Inc., Tokyo, Japan).

3. Results

The P^+ ion-implanted silica glass microspheres were brown in color.

Fig. 2 shows the 3D-SIMS image of silica glass microspheres, which were implanted with P^+ ions at 50 keV with a nominal dose of $3.35 \times 10^{16}\,\mathrm{cm}^{-2}$, at 25 nm depth. It can be seen from this figure that P^+ ions were successfully implanted into silica glass microspheres by the present method. The intensity of the phosphorus SIMS signal was relatively larger in the center than in the periphery of the microsphere, since the sputtering yield in the SIMS measurement was higher in the center than in the periphery of the microsphere.

Fig. 3 shows the depth profile of phosphorus concentration in a silica glass microsphere implanted with P^+ ions at 50 keV with a nominal dose of $3.35 \times 10^{16}\,\mathrm{cm}^{-2}$. The implanted phosphorus is widely distributed in deep regions centered at about 50 nm depth. The maximum concentration of phosphorus was estimated at about $2.0 \times 10^{22}\,\mathrm{cm}^{-3}$ at about 50 nm depth. The real dose of phosphorus was calculated at $1.5 \times 10^{17}\,\mathrm{cm}^{-2}$ from the area of phosphorus concentration.

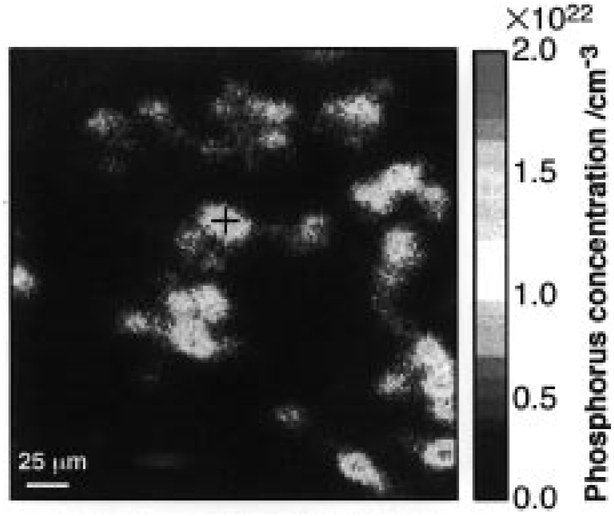

Figure 2 3D-SIMS image of silica glass microspheres implanted with P^+ ions at 50 keV with a nominal dose of $3.35 \times 10^{16}\,\mathrm{cm}^{-2}$ at 25 nm depth. (+) Measuring point for depth profile of phosphorus concentration in Fig. 3.

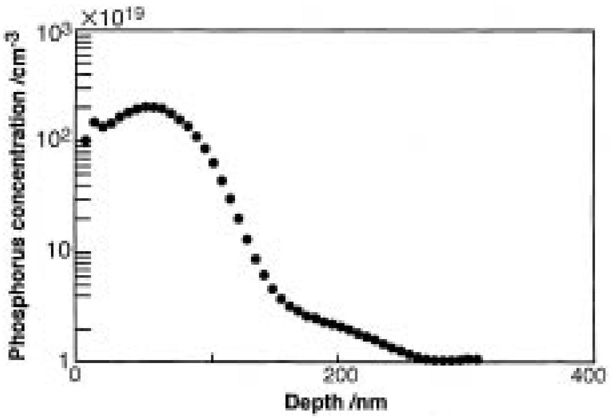

Figure 3 Phosphorus concentration depth profile of silica glass microspheres implanted with P^+ ions at 50 keV with a nominal dose of $3.35 \times 10^{16}\,\mathrm{cm}^{-2}$.

Fig. 4 shows the survey XPS spectrum of the surface of silica glass microspheres implanted with P^+ ions at 50 keV with a nominal does of $3.35 \times 10^{16}\,\mathrm{cm}^{-2}$. Peaks ascribed to oxygen, silicon and carbon were observed, whereas no peak ascribed to phosphorus was observed.

Fig. 5 shows the FTIR diffusive reflection spectra of the glass microspheres implanted with P^+ ions at 50 keV

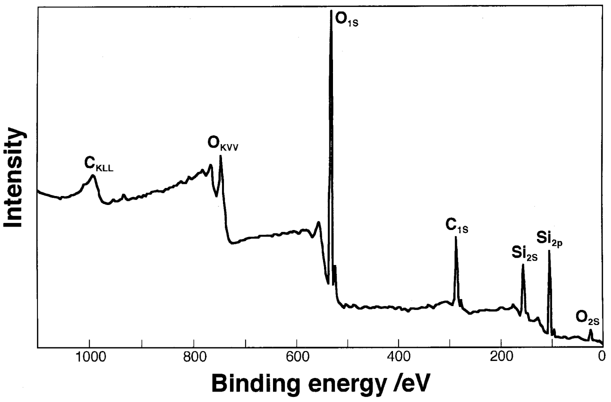

Figure 4 Survey XPS spectra of silica glass microspheres implanted with P^+ ions at 50 keV with a nominal dose of $3.35 \times 10^{16}\,\mathrm{cm}^{-2}$.

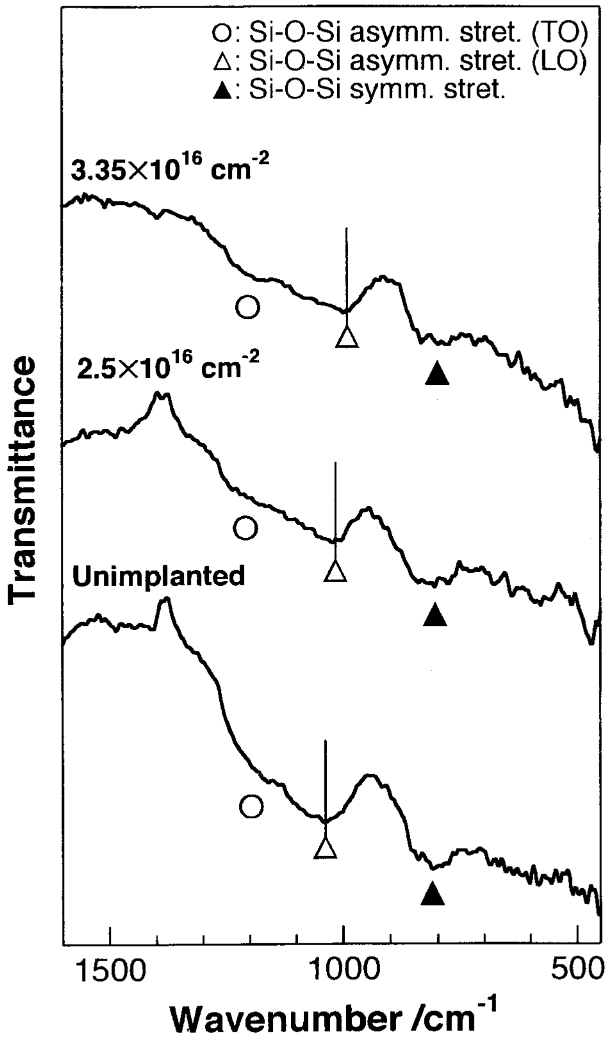

Figure 5 FTIR diffusive reflection spectra of silica glass microspheres implanted with P^+ ions at 50 keV with nominal doses of 2.5×10^{16} and $3.35 \times 10^{16}\,\mathrm{cm}^{-2}$.

with nominal doses of 2.5×10^{16} and $3.35 \times 10^{16}\,cm^{-2}$, in comparison with that of unimplanted original glass microspheres. Three broad peaks were observed at about 800 (▲), 1050 (△) and 1200 (○), for all the samples. These peaks are assigned to the Si–O–Si symmetric stretching vibration, the Si–O–Si asymmetric stretching vibration (transverse optical mode) and the Si–O–Si asymmetric stretching vibration (longitudinal optical mode), respectively [19–21]. For both doses, the $1050\,cm^{-1}$ band was shifted to a lower wave number by ion implantation.

Fig. 6 shows the concentration of phosphorus and silicon released from the glass microspheres implanted with P^+ ions at 50 keV with nominal doses of 2.5×10^{16} and $3.35 \times 10^{16}\,cm^{-2}$ into water at 95 °C for seven days. Both glass microspheres released little phosphorus and silicon into hot water.

4. Discussion

It can be seen from Figs 2 and 3 that P^+ ions were successfully implanted into silica glass microspheres by the present method and that the implanted phosphorus was mainly distributed in deep regions centered at about 50 nm depth from the surface of the glass microsphere. It is estimated theoretically that the phosphorus implanted into the silica glass plate at 50 keV shows Gaussian distribution giving a maximum concentration at 48.6 nm in depth from the glass surface [22]. The measured maximum concentration depth (50 nm) coincides well with the calculated one (48.6 nm) in a silica glass plate. It is assumed that the penetration depth of phosphorus implanted into a silica glass microsphere is almost the same as that into a silica glass plate.

The real dose of phosphorus calculated from the phosphorus concentration profile in Fig. 3 ($1.5 \times 10^{17}\,cm^{-2}$) was about four times as large as the nominal one ($3.35 \times 10^{16}\,cm^{-2}$). This phenomenon can be explained as follows. The nominal dose is calculated by assuming that P^+ ions are implanted into the microspheres only at an angle normal to the microsphere surfaces. In actual ion implantation, however, it is clear that P^+ ions are also implanted at off-normal angles simultaneously. As a result, a larger amount of phosphorus was implanted into the microsphere.

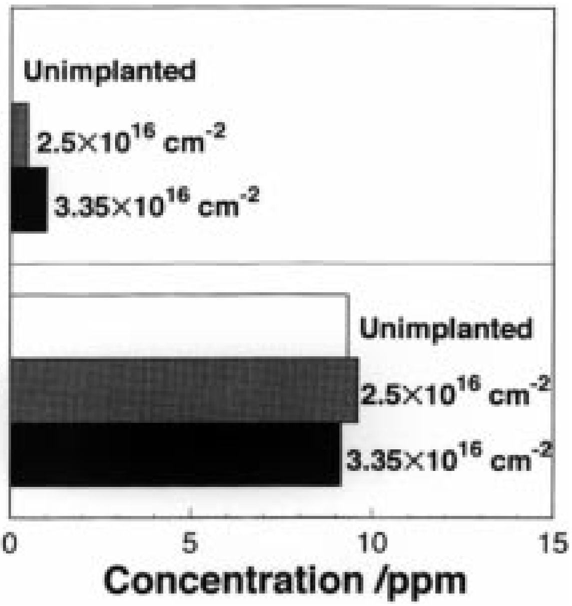

Figure 6 Concentrations of P and Si released from silica glass microspheres implanted with P^+ ions at 50 keV with nominal doses of 2.5×10^{16} and $3.35 \times 10^{16}\,cm^{-2}$ and then soaked in water at 95 °C for seven days.

In the survey XPS spectrum shown in Fig. 4, no peak ascribed to phosphorus was observed. This means that the implanted phosphorus is mainly localized in deep regions of the glass microsphere with little distributing to the surface of the glass microsphere. Since the glass microspheres are colored brown by the ion implantation, the implanted phosphorus is present as colloids [23] in the glass microsphere, as in previous P^+ ion-implanted silica glass plates [14–18].

As shown in Fig. 5, the peak at $1050\,cm^{-1}$ of the silica glass microspheres shifted to a lower wave number by P^+ ion implantation. This shift is attributed to structural damage caused by ion implantation, and is represented as a decrease in the Si–O–Si bond between SiO_4 tetrahedra [21, 24] at the surface of the glass microsphere, as in the case of the silica glass plate.

The silica glass microspheres, implanted with P^+ ions at 50 keV with nominal doses of 2.5×10^{16} and $3.35 \times 10^{16}\,cm^{-2}$, hardly released both the phosphorus and silicon (see Fig. 6). The small amount of phosphorus released from these samples is attributed to the absence of phosphorus at the surface of the glass microsphere as discussed above. The release of silicon from these samples is as little as that from the unimplanted silica glass microspheres (see Fig. 6). This means that structural damage, which was formed at the surface of silica glass microspheres by ion implantation (see Fig. 5), has no effect on the chemical durability of the silica glass microspheres, as in the case of the silica glass plate.

The amount of the phosphorus ion released from the silica glass microspheres implanted with P^+ ions at 50 keV with a nominal dose of $3.35 \times 10^{16}\,cm^{-2}$ into hot water is $2.75 \times 10^{-9}\,mol\,cm^{-2}$. This value is much less than the amount of yttrium, $3.04 \times 10^{-8}\,mol\,cm^{-2}$, released from $17Y_2O_3-19Al_2O_3-64SiO_2$ (mol %) glass into the same hot water, which was measured by the present authors.

The number of phosphorus ions present in one silica glass microsphere 25 μm in size implanted with a dose of $1.5 \times 10^{17}\,cm^{-2}$, is 4.9×10^{-12} mol. This amount is a little lower than that (9.5×10^{-11} mol) for yttrium present in a microsphere of the same size with a glass composition of $17Y_2O_3-19Al_2O_3-64SiO_2$ (mol %), which is already clinically used for radiotherapy. In order to obtain a silica microsphere containing phosphorus ions equivalent to that of the yttrium ions in the latter glass in number, the required dose is estimated to be $2.9 \times 10^{18}\,cm^{-2}$. On the basis of previous results of P^+ ion implantation into silica glass plates [14–18], silica glass microspheres, which contain such a large amount of phosphorus and still show little release of phosphorus and silicon, can be obtained when the P^+ ion is implanted at a higher energy than 50 keV. Thus prepared, a silica glass microsphere could give a much larger irradiation dose of β-rays to tumors compared with $17Y_2O_3-19Al_2O_3-64SiO_2$ (mol %) glass microspheres, since the half-life of ^{32}P (14.3 days) is about five times as long as that of ^{90}Y (64.1 h).

5. Conclusions

Silica glass microspheres were successfully implanted with P^+ ions at 50 keV with different doses by the present method. Glass microspheres even implanted with a dose of $1.5 \times 10^{17}\,\mathrm{cm}^{-2}$ released both phosphorus and silicon into hot water at 95 °C for seven days. Highly chemically durable silica glass microspheres containing larger amounts of phosphorus could be obtained if the P^+ ion could be implanted at higher energy than 50 keV to be localized in a deeper region, even if the surface structure of the glass microsphere is damaged by the ion implantation. Such glass microspheres are believed to be useful for *in situ* irradiation of cancer, since they can be activated to β-emitters with a half-life of 14.3 days.

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