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Y₂O₃ microsphere

Porous TiO₂ microsphere

SiO₂-cored Fe₃O₄ microsphere

Alternating magnetic field

β-ray / Heat / Anticancer drug

Artery

Catheter

Tumor

Alternating magnetic field
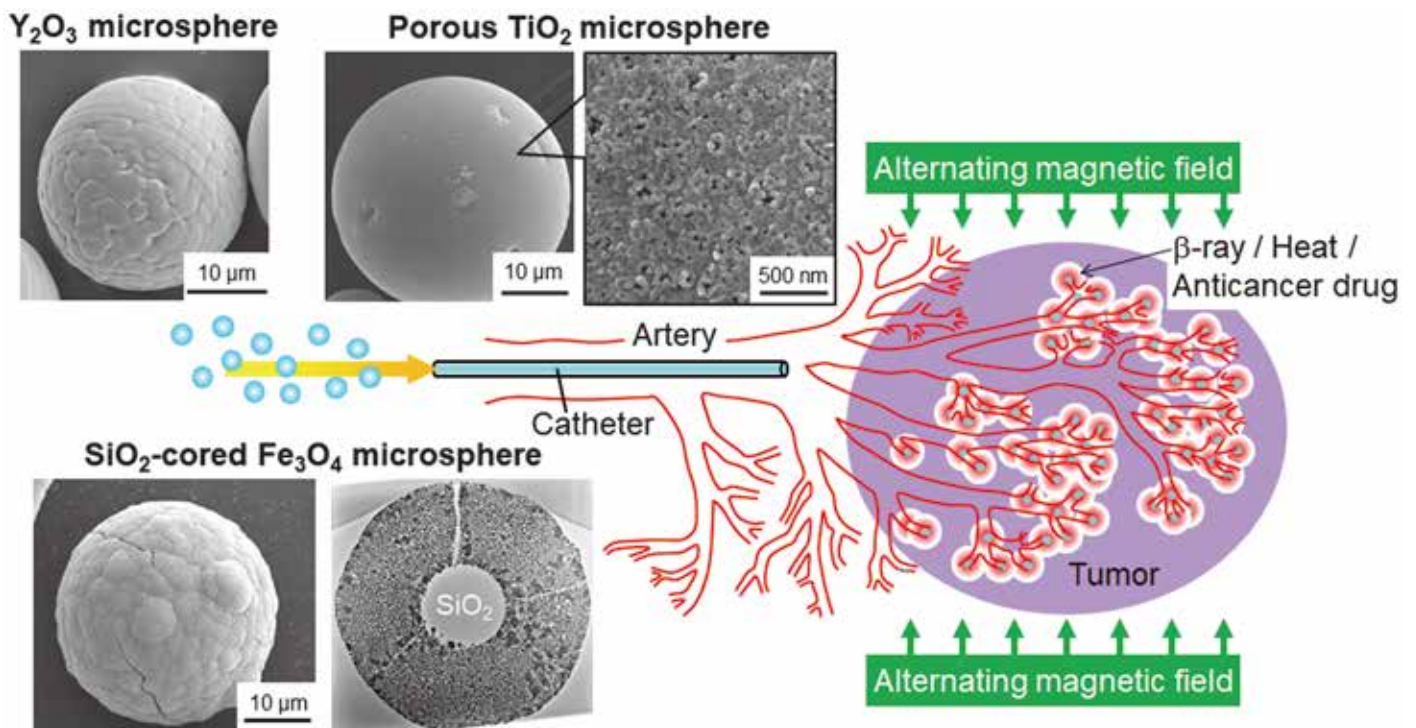
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Development and evaluation of the properties of functional ceramic microspheres for biomedical applications

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Radioactive or magnetic ceramic microspheres 20–30 μm in diameter are useful for intra-arterial radiotherapy or hyperthermia. Antibacterial ceramic microspheres can provide antibacterial activity for biomedical polymers such as dental resin. Bioactive ceramic microspheres with drug load/release properties are useful, moreover, as inorganic fillers for bone cement and can also be used in chemoembolization therapy. The author introduces some successes and challenges associated with the development of functional ceramic microspheres for biomedical applications.

1. Introduction

Organs diseased with cancer are generally surgically resected, but the functions of the resected organ are often not recovered. It is therefore obviously desirable to develop treatments for cancer that can destroy only the cancerous cells, enabling healthy tissues to regenerate after treatment. Radiotherapy is one treatment that shows such potential, but the source of radiation is most often located outside the body. Insufficient doses of radiation are often received by the cancer as a result, especially in the case of deep-seated cancers, and the irradiation can also cause severe damage to healthy tissues. Radioactive microspheres 20–30 μm in diameter that contain β-emitters such as yttrium-90 (^{90}Y) and/or phosphorus-32 (^{32}P) are useful for intra-arterial radiotherapy of cancers, especially for tumors located deep inside the body. These spheres are entrapped in the capillary bed of the tumors when they are implanted through blood vessels, and can thus irradiate cancers locally.

Cancer cells generally perish at approximately 43°C because their oxygen supply via the blood vessels is insufficient, whereas normal cells are not damaged by even higher temperatures. In addition, tumors are more easily heated than the surrounding normal tissues, since the blood vessels and nervous systems are poorly developed in the tumor.[1)–3)] Hyperthermia is therefore expected to be a very useful treatment for cancer, with few side effects. Various techniques for heating tumors, such as treatment with hot water, infrared rays, ultrasound, and microwaves have been attempted. However, deep-seated tumors cannot be heated effectively and locally using these techniques. In this respect, magnetic microspheres 20–30 μm in diameter might be useful as thermoseeds for intra-arterial hyperthermia in deep-seated cancers. These microspheres are entrapped in the capillary bed of the tumors when implanted through blood vessels, much like the radioactive microspheres described above, and can heat cancers locally using their loss of hysteresis and/or loss of relaxation when placed in an alternating magnetic field. Intra-arterial radiotherapy or hyperthermia using radioactive or magnetic microspheres are illustrated in **Fig. 1**.

Antibacterial biomaterials have received much attention in recent years. The advantages of silver (Ag)-doped materials are their antibacterial characteristics and nontoxicity. Various types of antibacterial Ag-doped materials have been developed, and some are currently being used com-
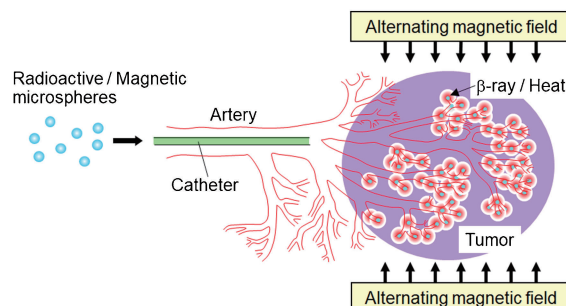
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Fig. 1. Schematic representation of intra-arterial radiotherapy or hyperthermia using radioactive or magnetic microspheres.

mercially. Most previous antibacterial agents have been based on organic materials, but these cannot be used under conditions requiring durability. Ag-doped inorganic materials are more useful than those based on organic materials from the viewpoint of chemical durability. Successful antibacterial materials must be colorless, highly chemically durable, and able to release Ag^+ ions slowly over a long period, especially when they are mixed with organic polymers and, in particular, with fine-spun polymer fibers. It is highly desirable for antibacterial materials to take the form of monodispersed microspheres measuring less than 1 μm in diameter, as the exposed surface area of the antibacterial particles is maximized, and fine fibers or thin polymer films containing a homogeneous distribution of the antibacterial particles can be easily prepared. For example, Ag-containing fine fibers are expected to be useful for the manufacture of antibacterial curtains for use in hospitals.

As discussed above, ceramic microspheres can play important roles in biomedical applications such as intra-arterial cancer therapy and antibacterial treatment. This paper describes several attempts to develop functional ceramic microspheres for biomedical applications.

2. Ceramic microspheres for intra-arterial radiotherapy

2.1 Y_2O_3 microspheres

Radioactive microspheres for intra-arterial radiotherapy were first reported in 1987 by Day et al.[4),5)] The microspheres were composed of $17Y_2O_3$–$19Al_2O_3$–$64SiO_2$ (mol %) (YAS) glass. The ^{89}Y in this glass is a nonradioactive isotope that occurs naturally with an 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 these radioactive glass microspheres 20–30 μm in diameter are injected into a target organ (usually a liver tumor), they become trapped inside small blood vessels in the tumor, and block its nutritional supply, in addition to providing a large, localized dose of short-range, highly ionizing β-rays. Since the β-rays do not affect any other chemical elements and have a short penetration range of only about 2.5 mm in living tissue, they present little radiation danger to neighboring healthy tissues. These microspheres have high chemical durability,[6)] and the radioactive ^{90}Y thus remains essentially within the microspheres when inside a patient and does not affect neighboring healthy tissues. The radioactivity of ^{90}Y decays to a negligible level within 21 d after activation by neutron bombardment; therefore, the microspheres become inactive soon after the cancer treatment. They (TheraSphere®) are already used clinically for intra-arterial radiotherapy of unresectable hepatocellular carcinoma in the U.S.A., Canada, South Africa, China (Hong Kong) and some European counties.[7),8)]

YAS glass microspheres are epoch-making ceramics for intra-arterial radiotherapy, but the Y_2O_3 content in the microspheres is currently limited to just 17 mol %, in so far as they are prepared in the glassy state using the con-
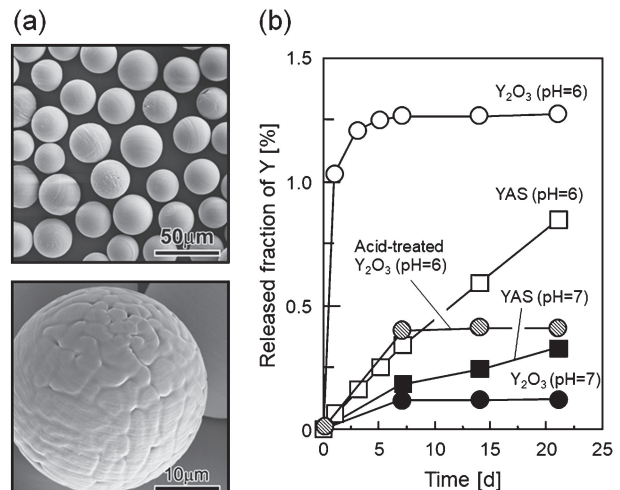

Fig. 2. Scanning electron micrographs of (a) Y_2O_3 microspheres and (b) fractions of Y released from acid-treated Y_2O_3 microspheres, as-prepared Y_2O_3 microspheres, and YAS glass into saline solutions of pH 6 and 7 at 36.5°C, as a function of soaking time.[9)]

ventional melt-quench method. The radioactivity of the microspheres decays significantly even before cancer treatment due to the short half-life. The development of chemically durable microspheres containing a higher Y_2O_3 content is therefore desirable. In 2003, we found that pure, highly spherical Y_2O_3 microspheres, 20–30 μm in diameter and with smooth surfaces, can be obtained by a high-frequency induction thermal plasma melting method.[9),10)] When high-purity Y_2O_3 powder is entered into a plasma flame, it melts and takes the form of microspheres because of surface tension in the plasma flame. These are quenched and solidified in the chamber and then sieved using a nylon mesh to obtain microspheres 20–30 μm in diameter.

These microspheres are highly spherical, have smooth surfaces, and are formed of cubic Y_2O_3 crystal grains with a grain size of about 2 μm, as shown in **Fig. 2**(a). The pH of normal body fluids is maintained at approximately pH 7, but this value is liable to fall to approximately pH 6 in the vicinity of a cancer due to lactic acid production. The chemical durability of the microspheres was therefore examined by soaking them in pH 6 and 7 saline solutions at 36.5°C for 21 d. The Y_2O_3 microspheres released less Y than the YAS glass in saline solution at pH 7, but they released more Y in saline solution at pH 6, especially during the early stage of soaking, as shown in Fig. 2(b). This can be explained by acid-soluble impurities being concentrated at the grain boundaries of the as-prepared microspheres. Y_2O_3 microspheres subjected to pre-treatment in pH 6 saline solution resulted in the release of a much lower fraction of Y compared with the YAS glass, however, even in pH 6 saline solution, as shown in Fig. 2(b).

Animal experiments have been conducted using Y_2O_3 microspheres.[10)] VX2 tumors were transplanted into the liver of a Japanese white rabbit. Two weeks after transplantation, radioactive Y_2O_3 microspheres 20–30 μm in
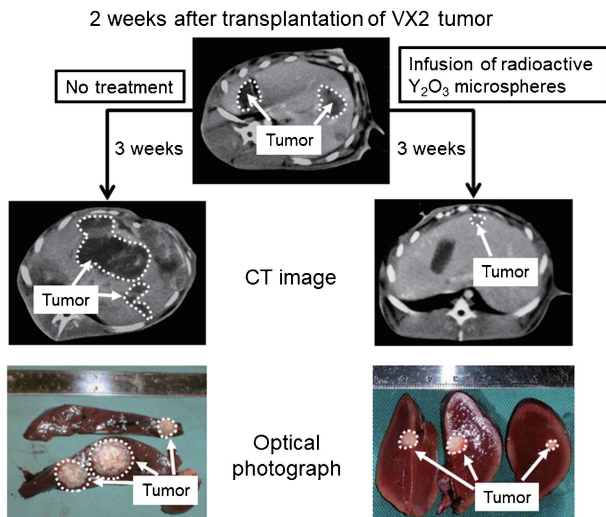
2 weeks after transplantation of VX2 tumor

Fig. 3. Representative CT and optical photographs of rabbit liver with and without infusion of radioactive Y_2O_3 microspheres.[10]
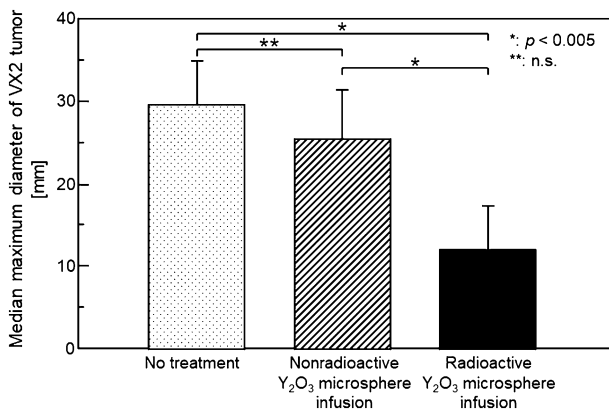

Fig. 4. Median maximum diameter of VX2 tumor in rabbit liver with no treatment, nonradioactive Y_2O_3 microsphere infusion, and radioactive Y_2O_3 microsphere infusion.[10]

diameter with 131–173 MBq were infused into the liver of the rabbit through the hepatic artery using a micro-catheter. As shown in **Fig. 3**, the VX2 tumor grew significantly in the rabbit liver without injection, whereas it showed no growth in the rabbit liver infused with radioactive Y_2O_3 microspheres. **Figure 4** shows the median maximum diameter of VX2 tumors in rabbit liver without treatment and with the infusion of nonradioactive and radioactive Y_2O_3 microspheres, respectively. The median maximum diameter of the VX2 tumors in the nonradioactive Y_2O_3 microsphere infusion group is slightly smaller than that in the no-treatment group, since arterial embolization caused by the infused nonradioactive Y_2O_3 microspheres slightly suppresses tumor growth. The median maximum diameter of the VX2 tumors in the radioactive Y_2O_3 microsphere infusion group was significantly smaller than that in the control group, indicating that the infusion of radioactive Y_2O_3 microspheres is significantly effective in suppressing growth of VX2 tumors.

Although Y_2O_3 microspheres can show excellent radio-

therapeutic efficacy, as described above, their high density remains a drawback. It is feared that Y_2O_3 microspheres implanted into a tumor may accumulate in the dorsal blood vessels of patients due to this high density. Thus, hollow Y_2O_3 microspheres synthesized by enzymatic reaction[11] or sol–gel reaction in a water-in-oil (W/O) emulsion[12] have been developed in an attempt to address the problem. The density of these hollow Y_2O_3 microspheres is believed to be appropriate for clinical application. Further, their hollow structure could serve as a drug container, which suggests that the hollow microspheres have the potential to be used as drug carriers in the future.

2.2 YPO₄ microspheres

^{90}Y may decay substantially, even before cancer treatment, owing to its short half-life of 64.1 h. An alternative possibility would be to activate phosphorus-31 (^{31}P), which occurs in 100% natural abundance, by neutron bombardment to form the β-emitter ^{32}P, which has a half-life of 14.3 d. Microspheres with high phosphorus content are therefore expected to be more effective for cancer treatment than those presently in use. Phosphorus-rich glasses prepared by conventional melt-quenching methods are usually less chemically durable, however. In 1999, we found P^+ ion implantation into silica (SiO_2) glass to be useful for obtaining a chemically durable phosphorus-containing glass.[13] When P^+ ions are implanted into SiO_2 glass at high energy, such as 200 keV, SiO_2 glass with a large amount of phosphorus and high chemical durability is obtained. It is difficult to implant a large amount of P^+ ions into SiO_2 glass microspheres 20–30 μm in diameter, however, because the surface area for ion implantation becomes extremely large.

YPO_4 microspheres could also be obtained by a high-frequency induction thermal plasma melting method,[9] but these microspheres lose a certain amount of phosphorus to form Y_2O_3, and their shapes are irregular and their surfaces rather rough owing to the loss of phosphorus from volatilization at higher synthesis temperatures (>10,000°C), as shown in **Fig. 5**(a). The roughness of the surfaces of the microspheres is considered to be such that it would damage blood vessels. In 2010, we successfully obtained YPO_4 microspheres with smooth surfaces and diameters of approximately 25 μm by cooling gelatin droplets containing yttrium and phosphate ions, followed by solidification in a W/O emulsion and heat treatment at 1100°C as shown in Fig. 5(b).[14] The YPO_4 microspheres scarcely released yttrium and phosphorus into a simulated body fluid at pH = 6 and 7. We believe that the present YPO_4 microspheres are useful for intra-arterial radiotherapy of cancer. Alternatively, hollow YPO_4 microspheres can also be obtained by the spray dry method[15] or a wet process in a W/O emulsion.[16] The hollow YPO_4 microspheres have a clinical advantage over dense YPO_4 microspheres, because their modest density may avoid undesirable accumulation in the dorsal blood vessels of patients, much like the hollow Y_2O_3 microspheres described in the previous section.
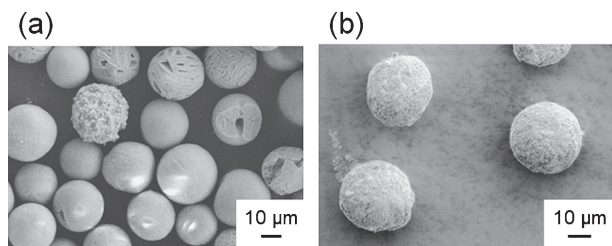
Fig. 5. Scanning electron micrographs of YPO$_4$ microspheres (a) prepared by a high-frequency induction thermal plasma melting method and (b) prepared from gelatin droplets containing yttrium and phosphate ions.
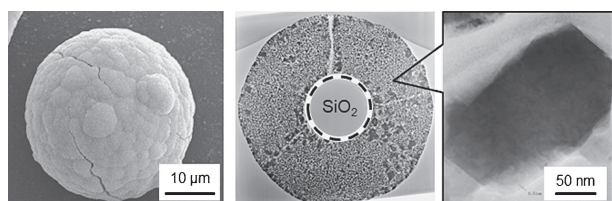

Fig. 6. Scanning electron micrograph of SiO$_2$-cored Fe$_3$O$_4$ microspheres[19] and transmission electron micrographs of cross-sections of the microspheres.[20]

3. Ceramic microspheres for intra-arterial hyperthermia

3.1 SiO$_2$-cored Fe$_3$O$_4$ microspheres

Thus far, various kinds of glass-ceramics containing ferrimagnetic crystals have been proposed as thermoseeds in hyperthermia,[10],[17],[18] but the fabrication of ferrimagnetic microspheres with diameters in the range of 20–30 μm is challenging. We successfully prepared SiO$_2$-cored Fe$_3$O$_4$ microspheres with diameters in this range that are composed of small crystals of Fe$_3$O$_4$ or γ-Fe$_2$O$_3$ by precipitation from an aqueous solution and subsequent heat treatment, as shown in **Fig. 6**.[19],[20] The microspheres are mainly composed of small crystals of Fe$_3$O$_4$ or γ-Fe$_2$O$_3$ and show ferrimagnetism, with a saturation magnetization of 53 or 68 emu·g^{-1} and coercive force of 156 or 198 Oe. They produced a magnetization curve with a large area, and heat generation of 41 or 42 W·g^{-1} under 300 Oe and 100 kHz. Actually, they showed in vitro heat generation when they were dispersed in an agar phantom and placed under an alternating magnetic field.[20] The heat they generated under a magnetic field lower than 300 Oe, however, was insufficient for clinical application. Also, precise control of the crystalline size of ferrimagnetic crystals with a remarkable effect on heat-generating ability is extremely difficult. Like the hollow Y$_2$O$_3$ microspheres described in section 2.1, Fe$_3$O$_4$ microspheres with a hollow structure can be formed by employing an enzymatic reaction.[21]

3.2 Magnetic nanoparticle (MNP)-containing SiO$_2$ or TiO$_2$ microspheres

As described above, controlling the crystalline size of ferrimagnetic crystals such as Fe$_3$O$_4$ or γ-Fe$_2$O$_3$ is crucial for obtaining magnetic microspheres with high heat-
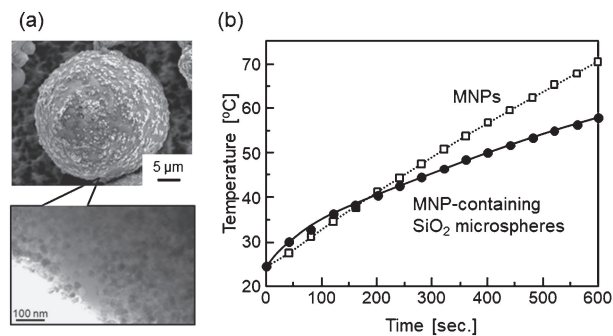

Fig. 7. Scanning electron micrograph and transmission electron micrograph of cross-section of (a) MNP-containing SiO$_2$ microspheres and (b) time-dependent temperature curves of the agar phantom, in which samples were dispersed in agar under an applied AC magnetic field of 100 kHz and 300 Oe.[24]

generating ability under given alternating magnetic fields. In 2010, we revealed that magnetic nanoparticles (MNPs) approximately 25 nm in size can generate heat with relatively high efficacy under alternating magnetic fields of 100–300 Oe and 100 kHz.[22],[23] Thus, we prepared MNP-containing SiO$_2$ microspheres 20–30 μm in diameter by directly introducing MNPs of approximately 25 nm in size into microparticles of a SiO$_2$ gel matrix derived through hydrolysis of tetramethyl orthosilicate (TMOS) in a W/O emulsion, as shown in **Fig. 7**(a).[24] The microspheres contained up to 60 mass % of MNPs consisting mainly of Fe$_3$O$_4$, and showed an excellent heat-generating ability under an alternating current magnetic field of 300 Oe and 100 kHz, which is comparable to the starting MNPs, as shown in Fig. 7(b). Interestingly, the specific absorption ratio (SAR) of the microspheres (43.7 W·g^{-1}) was higher than that of the starting MNPs (25.2 W·g^{-1}). This can be attributed to the smaller MNPs in the microspheres resulting from a silica coating reaction and/or reduction reaction of the starting MNPs in the synthesis procedure.

MNP-containing TiO$_2$ microspheres can also be synthesized by a sol–gel process using W/O emulsions when titanium tetraisopropoxide is used instead of TMOS.[25]–[27] Typically, the microspheres measuring around 30 μm in diameter contained up to 60.5 wt % MNPs 30–40 nm in size, and their saturation magnetization and coercive force were 44.3 emu·g^{-1} and 100 Oe, respectively.[27] Furthermore, they had an SAR of 20.0 W·g^{-1} under an alternating magnetic field of 300 Oe and 100 kHz and showed in vitro biocompatibility similar to that of MNP-free TiO$_2$ microspheres.[27] Iron (α-Fe)-containing TiO$_2$ microspheres were also proposed, although the content of α-Fe was still low (10.4 wt %) and the heat-generating ability required further improvement.[28]

4. Antibacterial ceramic microspheres

SiO$_2$ glass containing silver is expected to be a candidate antibacterial material for medical applications, since it is assumed to show high chemical durability. Ag$_2$O–SiO$_2$ glasses prepared by the sol–gel method are often yellow or brown in color, however, owing to the presence
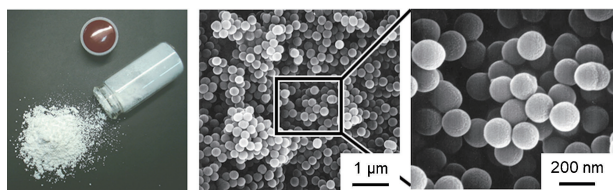
Fig. 8. Optical photograph and scanning electron micrographs of Ag-containing SiO_2 glass microspheres.[30],[31]
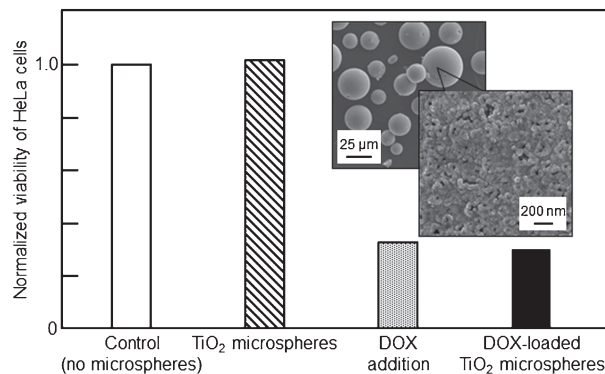

Fig. 9. Normalized viabilities of HeLa cells against samples and field-emission scanning electron micrographs of porous TiO_2 microspheres (insets).

of Ag colloid particles. The yellow or brown color of the glasses is undesirable for medical applications, such as composite resin for dental restoration. In 2000, we reported that, when SiO_2 glasses doped with Ag^+ ions together with aluminum (Al^{3+}) ions are prepared using the sol–gel method, the resultant products are colorless, highly chemically durable, and slow to release silver ions into water over a long period.[29] Further, a composite of the obtained powders with an Al/Ag atomic ratio of 1 with bis-GMA/TEGDMA showed excellent antibacterial properties.[29] These doped SiO_2 glasses had to be mechanically crushed, however, to obtain a fine powder form. The resultant grains were irregular in shape, and pulverizing them into fine powders with diameters less than 1 µm was not easy.

We found that monodispersed silver-containing SiO_2 glass microspheres less than 1 µm in diameter could be obtained by modifying the Stöber method, as shown in **Fig. 8**.[30],[31] The microspheres were colorless, showed high chemical durability, and released Ag^+ ions into water slowly at 37°C via ion exchange with the H_3O^+ ions in the water. The microspheres with a Si/Al/Ag = 1/0.01/0.01 composition showed excellent antibacterial activity against *Escherichia coli*. (*E. coli*), and the minimum inhibitory concentration (MIC) of the microspheres was 200 or 400, which is less than the MIC value (800) of commercial antibacterial materials. It was also confirmed that polypropylene plates and films mixed with the microspheres showed excellent antibacterial properties against *E. coli*. and *Staphylococcus aureus*.[31]

5. Bioactive and drug-eluting ceramic microspheres

Porous microspheres possess unique characteristics such as low density. They are also highly hydrophilic, making them ideally suited to use as drug carriers when developing drug delivery systems. At the same time, anatase-type TiO_2 nano- or micro-particles have been considered for use as bioactive ceramic fillers in bone cements.[32],[33] Porous anatase-type TiO_2 microspheres can therefore be used as drug-releasing bioactive cement fillers for chemotherapeutic treatment of metastatic bone tumors.

Porous anatase-type TiO_2 microspheres of approximately 5 or 15 µm in diameter were obtained through a sol–gel process involving a W/O emulsion and subsequent NaOH solution treatment.[34],[35] This approach entails first incorporating colloidal SiO_2 nanoparticles (SiO_2 NPs) into TiO_2 microspheres, after which the particles are leached out with a NaOH aqueous solution to leave behind a porous

structure. Within 8 days, apatite with a network-like surface structure forms on the surface of the microspheres in simulated body fluid,[34],[35] suggesting that the microspheres are bioactive. The good apatite-forming ability of the microspheres is attributed to their porous structure and the negative zeta potential of TiO_2. The release of rhodamine B, a model hydrophilic drug, was rapid for the first 6 h of soaking but diffusion-controlled thereafter.[35] The burst release during the first 6 h is problematic for clinical applications; nevertheless, the present results highlight the potential of porous TiO_2 microspheres as drug-releasing cement fillers able to form apatite.

Transcatheter arterial chemoembolization (TACE) is a specific type of chemoembolization that blocks the hepatic artery to treat liver cancer. Drug-eluting beads (DEBs) such as DC Bead®, HepaSphere™ and Embozene TANDEM™ have been approved as embolic materials for TACE. It is often difficult to confirm the site of embolization by interventional-radiology computed-tomography (IVR-CT) in clinical practice, however, because these DEBs are highly radiolucent polymeric materials. Radiopaque TiO_2 microspheres can provide a sharper IVR-CT image in TACE.

Recently, we found that the addition of 1-butanol as a co-surfactant to the oil phase in the sol–gel process involving a W/O emulsion and subsequent treatment by NaOH solution increases the size of porous TiO_2 microspheres to 20 µm and above, a size suitable for TACE,[36] as shown in **Fig. 9** (inset). The resultant porous TiO_2 microspheres had different loading capabilities for doxorubicin hydrochloride (DOX), an anticancer drug, depending on the size and contents of SiO_2 NPs in the starting solution. They showed Rat-1 cell compatibility under controlled administration and antitumor activity against a HeLa cell, moreover, as shown in Fig. 9. The present porous TiO_2 bead is a candidate DEB for TACE.

6. Summary

Several attempts to obtain ceramic microspheres for biomedical applications are described in this paper. Various kinds of these microspheres have been developed for biomedical applications to date. Radioactive or magnetic

microspheres 20–30 μm in diameter have the potential to realize intra-arterial radiotherapy or hyperthermia of cancer without surgery. Such intra-arterial therapy can improve the Quality of Life of patients to a remarkable extent. Thus, it is desirable that a novel cancer treatment using ceramic microspheres is developed as soon as possible. Monodispersed silver-containing silica glass microspheres less than 1 μm in diameter are expected to find new applications, moreover, such as in antibacterial polymer fibers, films, or plates. Porous TiO_2 microspheres are also expected to be useful as drug-eluting bioactive filler in bone cement or drug-eluting microspheres in TACE.

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