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Preliminary results on a new method for producing yttrium phosphorous microspheres

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HIGHLIGHTS

- A new way to production of phosphorus yttrium aluminum silicate microspheres is reported.
- In the new way the requiring high temperature is eliminated.
- The glass plate crushing stage is eliminated.
- In this paper we could eliminate P^+ ion implantation stage by embedding of phosphorus particles in the matrix of glass microspheres.

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ABSTRACT

This paper reports on a new method to embed phosphorus particles into the matrix of yttrium aluminum silicate microspheres. Yttrium phosphorus glass microspheres about 20 μm in size were obtained when an aqueous solution of YCl_3 and $AlCl_3$ were added to tetraethyl orthosilicate (TEOS) (phosphoric acid was used to catalyze the hydrolysis and condensation of TEOS) and was pumped into silicone oil under constant stirring. The shapes of the particles produced by this method are regular and nearly spheric in shape. Paper chromatography was used to determine the radiochemical impurity of radioactive microspheres. Radionuclide purity was determined using a gamma spectrometry system and an ultra-low level liquid scintillation spectrometer. The P^+ ions implantation stage was eliminated by embedding phosphorus particles in the matrix of the glass microspheres. This paper shows that a high temperature is not required to produce yttrium phosphorus aluminum silicate microspheres. The result shows that the silicone oil spheroidization method is a very suitable way to produce yttrium phosphorus glass microspheres. The topographical analysis of microspheres shows that the Y, P, Si, and Al elements are distributed in the microspheres and the distribution of elements in the samples is homogenous.

1. Introduction

The internal radionuclide therapy with radioactive microspheres Is one of the most effective treatments of cancers. There are currently two commercially available microsphere devices in which ^{90}Y are incorporated: one has microspheres made of glass (Therasphere; MDS Nordion, Ottawa, Canada) and the other has microspheres made of resin (SIR-Spheres; Sirtex Medical, Sydney, Australia). Unfortunately, resin microspheres May contain trace amounts of free ^{90}Y on their surfaces (leaching), equaling as much as 0.4% of the ^{90}Y administered activity, which can be excreted in the urine during the first 24 h. Trace amounts (25–50 kBq/l/GBq) of urinary excretion have been found in the first 24 h after implantation (Gulec and Siegel, 2007).

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 (Christie and Tilocca, 2010; Heness and Nissan, 2004; Kawashita et al., 2006, 2010; Simon et al., 2005). The melting method used to synthesize yttrium aluminum silicate microspheres from yttrium, aluminum and silicone oxides requires high temperatures (>1600 °C) (Cho, et al., 2003; Day and Ehrhardt, 1991; Kawashita et al., 2003; Seza et al., 2007). Spherical particles reduce or prevent the formation of particle clusters within peripheral vessels and allow for deeper penetration in the neoplasm vasculature, providing permanent and effective staining. The yttrium-89 in the glass can be activated using neutron bombardment to the beta emitter ^{90}Y ($\sigma=1.31b$), which has a half-life of 64.1 h. The β rays emitted by its decay have an average value of 0.9367 MeV while their maximum energy reaches 2.284 MeV. Its average range in tissue is about 2.5 mm and its maximum about 11 mm while the distance within which the β partical transfers 95% of its energy to the target tissue is about $R_{95}=5.94$ mm. Other elements in the glass are not

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activated by neutron bombardment. The radioactivity of these microspheres decays significantly even before cancer treatment is started because of the short half-life. Therefore, the development of chemically durable microspheres having higher yttrium content is desirable (Robbins, 1984).

The isotope ^{31}P is similar to ^{89}Y and can be transmuted to ^{32}P ($\sigma = 172$ mb), which is a beta emitter with a half-life of 14.3 d and can be more effective for cancer treatment than ^{90}Y (Sene et al., 2008). It emits a β particle with a maximum energy of 1.71 MeV and an average mean energy of 0.70 MeV. The mean and the maximum particle range in soft tissue are 3 mm and 8 mm, respectively. However, ^{90}Y may undergo substantial decay even before the cancer treatment because of its short half-life of 64.1 h. Phosphorus-31 is 100% naturally abundant and can be activated via neutron bombardment to become the beta emitter ^{32}P with a longer half-life. Moreover, the biological effectiveness of ^{32}P is more than ^{90}Y (Kalogianni et al., 2007; Kawashita et al., 2003; Tandon et al., 2006). Chemically durable microspheres containing high phosphorus content are expected to be more effective for cancer treatment. Pure, smooth, highly spherical polycrystalline Y_2O_3 and YPO_4 microspheres have been prepared using a high-frequency induction thermal plasma melting technique. Both the Y_2O_3 and YPO_4 microspheres show high chemical durability in saline solutions buffered at pH = 6 and 7. These microspheres are expected to be more effective than the conventional glass microspheres for the in situ radiotherapy of cancer (Kawashita et al., 2011; Rajput and Agrawal, 2010).

Phosphorus can be a problem for some types of glass because it usually plays an important role in the nucleation of crystalline phases, as observed for some silicate glass (Sene et al., 2008). The ion implantation method used to produce yttrium phosphosilicate microspheres. P^+ ions implanted in Y_2O_3–Al_2O_3–SiO_2 glass show promising results (Kawashita et al., 1994, 1997a, 1997b, 1999a, 1999b, 1999c).

This study developed a new method for embedding the phosphorus element into the matrix of the glass microspheres using the sol gel method (Ghahramani et al., 2014). The aim of this is the spheroidaization of phosphorus yttrium silicate microparticles without requiring high temperatures and embedding of the phosphorsus element in to the matrix of the microspheres without using ion implantation. The phosphorus yttrium microspheres obtained using this method has been named Az spheres.

2. Materials and methods

2.1. Microspheres preparation

Yttrium chloride (YCl_3) was produced by the reaction of yttrium oxide (Purity as 99.99%, Aldrich, Cat. No. 205168) with hydrochloride acid (37%, Merck, Cat. No. 109763). SiO_2 colloids were produced by adding tetraethyl orthosilicate (TEOS purity as 99%, Aldrich, Cat. No. 86578) to water under constant stirring at room temperature. The molar composition of TEOS: H_2O:H_3PO_4 (85%, Merck, Cat. No. 100573) was 1:1:0.1, which is described as the optimum composition to obtain yttrium aluminum silicate sol. The Y and Al ions were incorporated into the SiO_2 by replacing the water with an aqueous solution of YCl_3 and $AlCl_3$, respectively.

Prepared sol was loaded into a syringe and pumped through a 0.4 mm diameter nozzle into silicone oil (Shenzhen Hong Ye Jie Technology Co., Ltd.) heated to 50 °C under constant magnetic stirring (500 rpm). Sol droplets in the silicon oil were converted into spherical shapes by surface tension forces. These microsols converted to solid state after 30 min in the silicon.

Microspheres were separated from the silicone oil by precipitation and washed with 30 ml of petroleum ether. This process was repeated at least three times. They were then washed with 10 ml of diethyl ether to remove any trace of silicone oil from the surface of the particles. The microspheres were finally washed with 100 ml of water.

To remove remaining acids and other additives, the microspheres were heated up to 500 °C for 3 h in a furnace. The temperature was increased by 5 °C/min until it reached 500 °C; after 3 h, the temperature was decreased by 10 °C/min.

To determine the crystallization of samples, they were analyzed using X-ray diffraction analysis (XRD) (Siemens D5000, Cu-Kα radiation).

To determine the chemical bonds, the microspheres are analyzed using Fourier transform infrared spectroscopy (FTIR) (TENSOR27, Bruker). For the FTIR spectra, a 2 mg sample was added to 300 mg of spectral grade potassium bromide (KBr). The mixtures were ground and pressed to form a transparent disk. The transmittance technique was used to scan the samples.

Approximately 1 mg of dry powder was placed onto a 1 cm^2 glass slide and two droplets of petroleum ether were added to evenly distribute the powders on the surface of the glass slide. After drying, the samples were sputter-coated with Au-Pd to reduce electrostatic interactions for scanning electron microscopy (SEM) (model: VEGA\\TESCAN-XMU)) analysis.

2.2. Preparation of mounted microspheres for SEM/EDS map and line scan

Microsphere samples were mounted for ease of manipulation during preparation on a polycarbonate disc 30 mm in diameter and 5 mm in length. Compression molding techniques are used to produce hard mounts in a minimum amount of time. Temperature and pressure were held constant in the mounting press.

The mount was inserted into the polishing tool, firmly held in place by hand and moved 20 times back and forth across abrasive paper in a straight line across the abrading surface toward or away from the operator. This process was performed sequentially with water and 1000-, 1500-, 2000-, 2500- and 3000-grit paper. SEM/EDS mapping analysis was performed by SEM (VEGA\\TESCAN-LMU).

SEM/EDS line scan techniques were employed to determine elemental redistribution across the cross-section of the microspheres.

2.3. Neutron activation

For this procedure, 200 mg of microsphere powder was poured into a quartz ampoule (6 cm height, 0.7 cm diameter) and the ampoule was sealed using an oxygen flame. The sample was irradiated inside a sealed aluminum container (7 cm height, 3 cm diameter) for 10 h in the (5 MWth pool-type light water) research reactor. The medium neutron flux was about 3.0×10^{13} n/(s cm^2).

After cooling for 3 d, the sealed aluminum container was cut and the quartz ampoule was crushed. The activity of the sample was measured in another vial using a curimeter calibrator (Atomlab™ 400 dose) to be about 0.817 mCi for ^{32}P and 5.45 mCi for ^{90}Y. These microspheres were subsequently added to a 10 ml vial to form an elution with 5 ml of saline. These radioactive microspheres were then analyzed to determine the following parameters:

- radiochemical purity: percentage of free ^{90}Y and ^{32}P on the eluate using ascending paper chromatography
- radionuclide purity: presence of gamma emitter radionuclides in the microsphere eluate using gamma spectrometry and an ultra-low level liquid scintillation spectrometer

2.3.1. Paper chromatography

Paper chromatography was used to determine radiochemical impurities in the radioactive microspheres (Robbins, 1984).