Mass Production of Source Core for Iodine-125 Seed

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Nowadays, brachytherapy using a sealed source called a 'seed' has drawn attention for the treatment of various cancers. Generally, Iodine-125 (^{125}I) has been used for the seed in the radiation therapy of eye disease and prostate cancer.[1-3] ^{125}I has a half-life of 59.4 days, and emits 27 keV and 31 keV X-rays, and a 35 keV γ-ray through an internal conversion process. An ^{125}I seed of 4.5 mm (*l*) × 0.8 mm (Ø)[4] has a structure composed of an inner source core and an outer shell capsule. ^{125}I is adsorbed on the source core's surface and a titanium capsule surrounds it. The seed is directly inserted into the human body to treat cancer cells, and the seed may be permanently left in tissues owing to the low activity and the excellent biocompatibility of Ti capsule[5] (Fig. 1).

The diverse materials and preparation of the source core have been reported for many years, for example, a palladium (Pd) coated silver wire,[6,7] a silver (Ag) rod[5,8,9] and a porous ceramic tube[10] *etc.* The Korea Atomic Energy Research Institute (KAERI) previously used a bare ceramic rod[11] and an Ag+Al$_2$O$_3$ rod[12] as the core. With regard to the preparation of an ^{125}I seed, the electro deposition technique was used for adsorption of iodine on the silver surface.[13,14] In addition, a chemical adsorption on the Pd coated silver wire, the impregnation into ceramics and iodine substitution after forming an intermediate having chloride (Cl$^-$)[5,8] or bromide (Br$^-$)[9] were reported.

In our previous investigation, the effect of the various intermediates (N$_3^-$, CO$_3^{2-}$, C$_2$O$_4^{2-}$, AsO$_4^{3-}$, Cl$^-$ and PO$_4^{3-}$) using each set of 10 Ag rods were reported.[15] Among them, Ag rods modified using phosphate (PO$_4^{3-}$) showed the highest adsorption ability with the good substitution effect of iodine. On the basis of this technique, the studies on mass production using 100 Ag rods and leachability test of a finished source core prior to encapsulation were performed in this work.
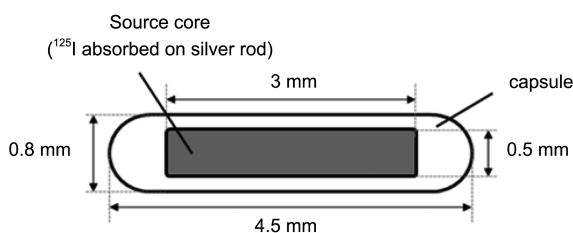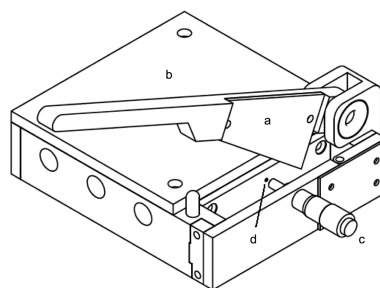
Figure 2. Cutting device (a: steel blade, b: heating part, c: micrometer, d: end of the syringe needle).

The uniformity of iodide adsorption on every silver rod in the same batch is important for mass production to reduce the number of abandoned rods. For this reason, we developed a cutting device (Fig. 2) precisely manufacturing the silver rods in 3 mm (*l*) and compared the iodide adsorption with the handmade rods. A silver wire of 0.5 mm (Ø) passes through a syringe needle (d) of 0.584 mm (Ø), and the wire is softened through the heating part (b). The length of this wire is adjusted with the help of micrometer (c) and can quickly cut to a uniform shape by using a steel blade (a). In the case of handmade rods, the wire was cut by using scissors, and both ends were manually polished with sandpaper.

Experimental Section

Surface Modification of Ag Rod. For mass production, 100 Ag rods were used as a batch in all experiments. The cut rods were etched by 3 M HNO$_3$ at 70 °C until the surface changes white color. Then, all rods were immersed in 15 mL of the solution contained 0.610 M sodium phosphate (Na$_3$PO$_4$) and 0.084 M hydrogen peroxide (H$_2$O$_2$) as an oxidant for 24 hours at room temperature to modify the surface with PO$_4^{3-}$. For comparison, another set of rods was treated with chloride (Cl$^-$), as reported in the literature.[8]

Iodine-Adsorption on Ag Rod. Each set of 100 rods was immersed in 5 mL of 0.01 M sodium hydroxide (NaOH) solution containing non-radioactive iodide (^{127}I) and ^{131}I (half-life 8.02 days) as the tracer instead of ^{125}I in a 5 mL vial. The radioactivity of the non-radioactive iodide and tracer was equivalent to 14800 MBq (400 mCi, calculated by previous report[15]) and 14800 kBq (400 μCi) of ^{125}I,

Figure 1. Schematic diagram of ^{125}I seed.
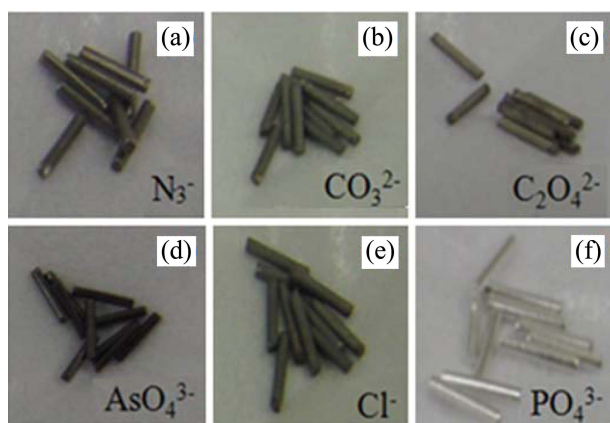
Figure 3. Profiles of the Ag rods treated with various anions.

respectively. The vials were rotated with a roll mixer at a speed of 200 rpm for 24 h at room temperature. The solution was then removed, and the rods were washed with a saline solution and deionized water. The activities of the rods were measured individually by the HPGe detector (ORTEC Inc. GEM 20P4-70).

Leachability Test. For the leachability test, 5 rods adsorbed with ^{131}I were selected randomly and placed individually in 1 mL of deionized water or serum albumin for 48 h at room temperature. Then, the activities of the 0.5 mL of the solution were measured by using the HPGe detector.

Results and Discussion

For an effective iodide-adsorption on Ag rods, a novel method was developed using a phosphate intermediate.[15] To prepare phosphorylated Ag rods, Ag rods were reacted with a sodium phosphate solution under a strong oxidant not containing chlorine, *e.g.*, H_2O_2. When H_2O_2 is added to the solution, at first, the silver surface is oxidized to form an ionized atmosphere, Ag rod-Ag^+, and the phosphate ions then react with its surface at the same time. To increase the surface area, a surface etching was performed using 3 M HNO_3 for about 2 min before the phosphorylation. Iodination was carried out by simply mixing the phosphorylated Ag rods and iodide solution. In previous reports for chlorinated intermediate, the exchange reaction can be explained by using K_{sp} value.[5,8] In general, a lower K_{sp}, *e.g.*, AgI, 8.52×10^{-17}, shows robust precipitation to the silver surface after forming an exchange reaction with a higher K_{sp} substance, *e.g.*, AgCl, 1.77×10^{-10}. However, the substitution reaction of phosphate with iodine cannot be explained by K_{sp}. This mechanism, we hypothesized, is based on the distortion effect that phosphate, PO_4^{3-}, would bind to the surface without its own angles. The angle strain easily induces the substitution reaction with iodine ions. To find the optimum condition of iodide adsorption on a Ag surface, 10 Ag rods were used in our previous study. The profiles of the rods treated with various anions (N_3^-, CO_3^{2-}, $C_2O_4^{2-}$, AsO_4^{3-}, Cl^- and PO_4^{3-}) are as shown in Figure 3. Only the PO_4^{3-}-based rods retained glossy silver color, whereas those of N_3^-,

Table 1. Average activity of adsorbed iodide on Ag rods treated with PO_4^{3-} and Cl^-

| Surface modification	number of rods	Iodide concentration[a]	q[b] (MBq/rod)	E[c] (q/148 MBq)
(a) PO_4^{3-}			102.60 (2.773 mCi)	0.69
(b) Cl^-	100 rods	2960 MBq/mL (80 mCi/mL) at volume 5 mL	54.21 (1.465 mCi)	0.36

[a]maximum adsorbable activity of iodide is 148 MBq/rod (4 mCi/rod) in all tests. [b]average adsorbed activity of rod. [c]E = average adsorbed activity/maximum adsorbable activity

CO_3^{2-}, $C_2O_4^{2-}$ and Cl^- had dark grey colors and AsO_4^{3-} was dark brown without luster. It was observed that PO_4^{3-}-based Ag rods adsorbed 137.90 MBq (3.7269 mCi), which was the highest efficiency, > 74%, and 4.5 times greater than that of Cl^--based Ag rods at a 0.5 mL volume of 100 mCi/mL solution.[15]

In this study on the mass production of the source cores, all subsequent tests were carried out using the phosphorylation method, and 100 rods were used in each test. First, the iodide-adsorption efficiency was confirmed in comparison with the chlorinated rods as a reference[8] under the same experimental condition, and the result is presented in Table 1. The PO_4^{3-}-based rods could take up to ~70% (102.60 MBq (2.773 mCi)) of the iodine activity from the contact solution, which was 1.9 times higher than the activity of Cl^--based rods, 54.21 MBq (1.465 mCi). There is a difference between the two cases of using 10 rods and 100 rods. This may be because the friction among many rods rotating fast in the vial occurs frequently, and also found that the reproducibility of the chlorination method is very low.

As a quality assurance of the sources, a leachability test before encapsulation for checking leached iodine from rods, and a leak test after encapsulation for checking the sealing condition, should be carried out. In this report, a leachability test was performed by randomly choosing 5 rods of (a) and (b) in Table 1. When H_2O was used, the obtained results show that the iodine from the surface of the rods leached 0.06%, and 0.23%, respectively. From these results, it could be found that PO_4^{3-}-based Ag rods firmly adsorb iodide and show a safer and more stable state in the aqueous solution. On the other hand, an additional test was carried out with serum albumin, plasma protein in humans, and the results revealed that more than 30% of the activities of both rods were leached in the test solutions. Therefore, in the case of radioisotope-leakage of therapeutic seeds, a leak test is a very essential part along with the leachability test. It should be performed after sealing the rods and before implanting the seeds into the human body.

Figure 4 shows the adsorption activity distribution charts of the rods cut by using a cutting device and by handmade. When using the cutting device, the number of rods having an average of ± 5% activities was 55, which is higher than that of handmade cutting. The reason may be that the rods having a fixed length of 3 mm (*l*) can be uniformly fabricated by the
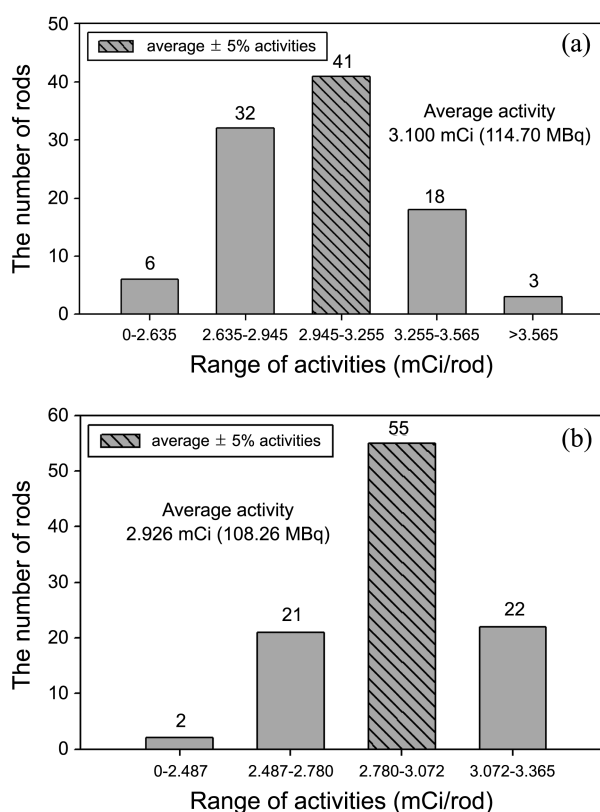
Figure 4. Distribution charts for the adsorbed activities of the rods ((a) production by hand, (b) by cutting device).

cutting device. In addition, this enables producing the uniform rods more easily and quickly. These advantages can render the distribution of activities relatively focused in same batches, and the total production time of ^{125}I seed can be shortened during mass production.

The effect of iodide concentration in the solutions was investigated with 100 rods manufactured by the cutting device, and the results are depicted in Figure 5. Various iodine solutions in 5 mL volume of 0.01 M NaOH were used. It was found that the iodide adsorption ratio was increased according to the iodine concentration. The highest loaded activity was 199.73 MBq/rod (5.398 mCi/rod), and the efficiency was > 77% in the 140 mCi/mL (700 mCi/5 mL) solution, but not reached the saturation point. It is possible
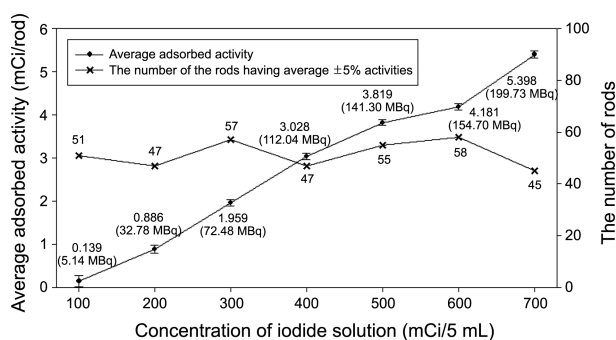
Figure 5. The average adsorbed activity and the number of the rods having average ± 5% activities at various concentrations of iodide (All rods were cut by cutting device).

that the source cores of higher activity are produced at a higher concentration. The numbers of rods having an average of ± 5% activities were 51, 47, 57, 47, 55, 58 and 45, beginning at the left in Figure 5, and the proportion obtained was approximately 50% of all 100 rods. To obtain a dense distribution of the rod activity and the higher obtainment, various reaction tools has been being studied.

Conclusion

In conclusion, the mass production of the source core inside the ^{125}I seed was performed using phosphate-based Ag rods. The ^{125}I source core fabricated by using this method is more advantageous than other methods in terms of quantitative iodide-adsorption yield, iodine-leachability, and stability of iodine activity in H_2O due to the formation of robust adsorption between Ag rods and iodide. Furthermore, the specially designed cutting device is very useful for mass production of rods owing to its easy, fast, and high reproducibility. The combination of these two techniques based on the phosphate modification of Ag rod and the special cutting device can effectively abbreviate the radioactive wastes and total time consumption during mass production of source core. This report suggests a novel direction for the preparation of ^{125}I seeds used for prostate or eye cancer treatments. Recently, a sealing technology by laser welding and a leak test of seeds are under investigation at our institute.

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