Improvement and Optimization of Clinically Potent Positron Emitter ^{76}Br Isolation Using the Dry Distillation Approach for its Future Automation

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Dry distillation has been mainly used for the isolation of bromine-76 (^{76}Br), a clinically potent radionuclide for positron emission tomography (PET). However, dry distillation systems are not considered suitable for an automated isolation module, which is necessary for routine clinical production. Therefore, a new dry distillation system including a water trap for the recovery of ^{76}Br was investigated. Prior to isolation studies, isotopically enriched $\text{Cu}_2^{76}\text{Se}$, the target material for ^{76}Br production, was prepared by heating a mixture of Cu and ^{76}Se under high vacuum; formation of $\text{Cu}_2^{76}\text{Se}$ was confirmed by X-ray diffractometer (XRD). Isolation studies using ^{77}Br demonstrated reasonable recovery efficiency ($66.5 \pm 5.3\%$) from the new system. Large-scale isolation studies using ^{76}Br led to recovery of highly pure ^{76}Br with radioactivity on the order of GBq under optimized conditions. This improved dry distillation method shows promise as a future automated isolation process.

Key words: Radioisotope production, Ion beam, Target material, Positron Emission Tomography, Bromine-76

1. INTRODUCTION

Positron emission tomography (PET) is an imaging technique that non-invasively provides functional information to identify diseases and abnormalities. Most of the practical positron emitting radionuclides for clinical PET imaging have short half-lives. The longest-lived radionuclide available, ^{18}F , has a half-life of only 110 min. Therefore, small molecules that are rapidly distributed to target tissues can be used as carrier molecules for the radionuclides. Furthermore, positron emitters are produced by irradiating a target material with ion beams from a cyclotron. However, due to the short half-lives, most of the positron emitters have to be produced on-site by a cyclotron installed in a hospital. This has impeded expansion of clinical PET imaging [1-4].

Bromine-76 (^{76}Br , half-life: 16.1 h) has been of interest for application to clinical PET imaging. Its long half-life allows not only rapidly excreted small molecules but also slowly excreted proteins and peptides to be used as carrier molecule for ^{76}Br . In addition, unlike conventional positron emitters, the long half-life enables commercial delivery to hospitals that do not have an in-house cyclotron for radionuclide production [1-4]. Procedures for radionuclide productions are usually involved the following three steps: 1) target preparation, 2) ion beam irradiation of the target material, and 3) isolation using a chemical method. In case of ^{76}Br , proton (H^+) beams irradiated an isotopically enriched selenium-76 (^{76}Se) target to employ the $^{76}\text{Se}(\text{p},\text{n})^{76}\text{Br}$ nuclear reaction [5-7]. Since the target is heated (to approximately 400 °C) during the irradiation, the high melting point of the Se alloy is used

to prevent melting of elemental Se (m.p.: 220 °C). However, the most frequently used isolation method, a wet chemistry technique, is difficult to use for the semi-metallic selenium due to its complicated chemical properties. Therefore, dry distillation is the most suitable for the isolation of ^{76}Br from the Cu_2Se target.

An automated isolation module is required for routine radionuclide production for clinical purposes, because it enables large-scale isolation with high reproducibility, reliable quality, and faster production, while avoiding unnecessary radiation exposure to operators [8-11]. Previous studies have demonstrated that vaporized ^{76}Br and selenium was isolated by “thermal chromatography” during dry distillation [5,6] (Fig.1).

Fig.1 Conventional dry distillation setup. Electric furnace 1 and 2 were heated at 1050 °C and 200 °C, respectively

However, the low reproducibility of the radionuclide distribution in polytetrafluoroethylene (PTFE) tubing of this method is poor and requires time-consuming steps for ^{76}Br recovery. Therefore, improvements are needed

to incorporate the distillation system into an automated module. The objective of the present study was to improve the dry distillation system and optimize recovery efficiencies for future automation of the ^{76}Br isolation process.

In this new system, ^{76}Br was recovered selectively in a trap placed at the end of the dry distillation system, instead of using thermal chromatography (Fig. 2). To optimize the isolation of ^{76}Br , distributions of radiobromine were examined using ^{77}Br (half-life: 57.0 h), which is readily detectable and cost-effectively producible radionuclide. Large-scale isolation of no-carrier added ^{76}Br (more than 500 MBq) was also examined under the condition studied. Efforts to prepare an enriched $\text{Cu}_2^{76}\text{Se}$ target are also described.

Fig. 2. Partially enlarged illustrations of recovery setup

2. MATERIAL AND METHODS

2.1. Target preparation

A Cu_2Se pellet was prepared using procedures described previously [10]. Isotopically enriched selenium-76 (^{76}Se) or naturally abundant selenium (^{nat}Se) (2.16 g each) and naturally abundant copper powder (3.44 g) were mixed and pulverized in an agate mortar. The mixture was heated in a metallic chamber *in vacuo* at 417 °C for 4 days, 553 °C for 21 h, 418 °C for 6 days, and then 125 °C for 4 days. After cooling to room temperature, the mixture was characterized by X-ray diffractometer (XRD) (SmartLab; Rigaku Corporation). The mixture was triturated again and pressed to form a pellet (10 mm diameter $\times$ 6 mm thickness).

2.2 Irradiation

Irradiation was conducted using an AVF cyclotron installed at the Takasaki Ion Accelerators for Advanced Radiation Application (TIARA) of the National Institutes for Quantum and Radiological Science and Technology (QST). Proton beams of 18.6 MeV irradiated the target at 0.1–5 μA of beam current. Irradiation time was up to 6.5 hours. Radionuclides produced in the target were characterized and quantified by γ -ray spectroscopy using a high-purity germanium (HPGe) detector (Ge crystal 58 mm diameter $\times$ 63.7 mm height) coupled with a multichannel analyzer (MCA 7700; Seico EG&G).

2.3. Isolation using the dry distillation system

An illustration of the new distillation system is shown in Figure 3. The tubular electric furnace contained two heating areas; a main and an auxiliary heating area (280 mm length $\times$ 30 mm diameter each). A tapered quartz tube was placed inside the furnace and PTFE tube (1/8-inch o.d.) leading to a H_2O trap (15 mL) was inserted

into the quartz tube. The irradiated target was placed on a quartz boat (16 mm $\times$ 77 mm $\times$ 10 mm) or tungsten (W)-backing (20 mm $\times$ 20 mm $\times$ 1.5 mm thickness) at the middle of the main heating area, and then was heated at 1050 or 1120 °C under continuous flow of argon gas (flow rate: 30 mL/min.).

Fig. 3. Improved distillation setup and target backings used in this study.

The radiation level of the trap was monitored by a cadmium-zinc-telluride (CZT) detector (GR-1; Kromek group, crystal size: 10 mm $\times$ 10 mm). The distribution of radioactivity in the target, PTFE tubes, and the trap was also determined using the HPGe detector.

2.4 Chemical analysis

The chemical forms of isolated radiobromines in the trap were analyzed by thin-layer chromatography (TLC) with acetone: H_2O = 7:1 as a mobile phase. The radioactivity distribution on the plate was visualized and quantified using a bioimaging analyzer system (Typhoon FLA 7000; GE Healthcare Japan). Non-radioactive bromine, copper, and selenium contained in the trap were characterized by inductively coupled plasma-mass spectroscopy (ICP-MS, Agilent 7700x; Agilent Technologies).

3. RESULTS AND DISCUSSIONS

3.1. Target preparation

Isotopically enriched $\text{Cu}_2^{76}\text{Se}$ was used as a target in this study because its sufficiently high melting point (1113 °C)^[7] prevents melting during the irradiation. The X-ray diffractometry pattern of the mixture heated under 75 Pa (Fig. 4C) was quite different from those of the commercial source (Fig. 4A) and the pattern obtained from powder diffraction file-4 (PDF-4) of Cu_2Se (Fig. 4B). In contrast, highly pure $\text{Cu}_2^{76}\text{Se}$ was prepared successfully when the mixture was heated under higher vacuum condition (Fig. 4D). These results indicate that high-vacuum conditions were necessary to synthesize highly pure Cu_2Se target.

3.3. Optimization of radiobromine recovery

Prior to optimization studies, radionuclides produced in the $\text{Cu}_2^{76}\text{Se}$ target were characterized and quantified using the HPGe detector.

Fig. 4. X-ray diffractometry patterns of prepared Cu_2Se . (A) $\text{Cu}_2^{\text{nat}}\text{Se}$ from a commercial source, (B) peaks obtained from powder diffraction file-4 (PDF-4), (C) synthesized Cu_2Se heated in the metallic chamber under 75 Pa and (D) 30 Pa. Arrows in panel D indicated the peaks identical to those of panels A and B

The results show that radiobromines, ^{76}Br , ^{75}Br (half-life: 1.61 h) and the by-products, ^{75}Se (119.8 days), ^{62}Zn (9.2 h), ^{63}Zn (38 min), and ^{65}Zn (244.3 days) were detected in the target (data not shown). Radioactive rhenium (^{186}Re) was also detected when the W-backing was used. These results prompted to determine distribution of radiobromine, ^{75}Se , ^{65}Zn , and ^{186}Re during optimization studies.

The distribution of produced radionuclides in the new distillation system was investigated under four isolation conditions. Long-lived ^{77}Br was used because it emits readily detectable gamma-rays and it can be produced cost-effectively by irradiating inexpensive $\text{Cu}_2^{\text{nat}}\text{Se}$. The distribution of ^{77}Br in each component (target, PTFE tube, and the trap) was summarized in Table I.

Table I, Distribution of ^{77}Br inside the conventional and improved distillation setup

Cond.	Temperature (°C)		Target Backing	%Distribution of ^{77}Br			n
	Main	Auxiliary		Target	PTFE tubing	Trap	
1	1050	200	Quartz boat	29.1 ± 2.9	16.1 ± 5.4	31.4 ± 4.4	4
2	1050	*	Quartz boat	32.5 ± 5.2	5.7 ± 4.0	41.5 ± 13.4	4
3	1050	*	W-backing	63.6 ± 4.2	3.0 ± 0.8	21.9 ± 6.0	4
4	1120	*	W-backing	6.3 ± 4.6	5.2 ± 1.9	66.5 ± 5.3	4

*Auxiliary heating area was not heated.

Approximately 31% of the ^{77}Br was distributed in the H_2O trap, but significant amounts were remained in the target (29%) and PTFE tubing (16%) under condition 1. In contrast, the radioactivity of ^{77}Br in the H_2O trap (41.5%) increased under condition 2, perhaps due in part to a more favorable temperature distribution and the position of PTFE tube inside the auxiliary heating area. To reuse the expensive $\text{Cu}_2^{76}\text{Se}$ target, the W-backing was used instead of the quartz boat under condition 3. However, the radioactivity in the trap was decreased dramatically, while about 67% of the radiobromine remained in the target due to the lower set temperature

(1050 °C) of the main heating area. Accordingly, the distribution of ^{77}Br was investigated at higher temperature (1120 °C) (condition 4). The result showed that the ^{77}Br distribution in the trap improved to $66.5 \pm 5.3\%$ comparable to the efficiency obtained by thermal chromatography (65-70%) [5,6]. The gamma-ray spectra obtained with the HPGe detector showed that negligible amounts of radioactive impurities, such as ^{75}Se and ^{65}Zn , existed in the trap. These results suggested that condition 4 certainly would successfully isolate ^{76}Br in good recovery efficiencies. The radioactivity in the trap was also monitored by a CZT detector as shown Fig. 5. The radiation level of the trap was nearly saturated at 150 minutes of heating; therefore 150 minutes were chosen as the isolation time.

Fig.5. Radioactivity of ^{77}Br in the trap with time. (a temperature of 1120 °C in the main area was achieved at 70 minutes.)

3.4. Large-scale isolation of ^{76}Br with the new distillation system

Large-scale isolations were performed using ^{76}Br with radioactivity on the order of GBq to validate the new distillation system. The recovered activity (decay corrected) under condition 4 ($n = 10$) is summarized in Table II. The recovered radioactivity (630-1200 MBq) was four- to six-fold greater than that obtained under condition 1 (147-287 MBq). A previous study demonstrated that about 50 MBq of ^{76}Br administrated to a patient was adequate to perform clinical brain PET imaging [12]; therefore, these results demonstrate that the amount ^{76}Br even after syntheses of its labeled compounds probably deliver radioactivity to several patients.

Table II, Recovered radioactivity of ^{76}Br under optimized conditions

Run	Irradiation Time (h)	Recovered activity* (MBq)
1	6.0	1200.0
2	6.0	879.0
3	6.3	1070.0
4	6.0	788.0
5	6.0	920.0
6	4.0	760.0
7	3.7	630.0
8	4.6	820.0
9	6.0	896.0
10	3.2	1126.0

*Radioactivity was decay corrected.

Gamma-ray spectroscopy indicated negligible radioactivity from expected radioactive impurities (^{75}Se , ^{65}Zn , ^{186}Re) in the H_2O trap. The TLC analysis showed a single spot at R_f of 0.36, which was identical to that of bromide [6]. Selenium is an important trace element for humans, but high intake (400 μg or more) can cause acute or chronic symptoms [13]. Hence, the amount of non-radioactive selenium in the trap was also evaluated using ICP-MS spectroscopy. The contained amount of Se in the trap was about 750 ng, but the amount decreased to 138–503 ng when the target was used repeatedly. To reduce the amount of Se in the ^{76}Br solution, the target material should be heated repeatedly prior to use for irradiations.

Fig. 6. (A) TLC analysis of ^{76}Br visualized by BAS, (B) amount of non-radioactive selenium in the trap.

Clinical potent ^{76}Br -labeled compounds, ^{76}Br -MBBG, a PET tracer for norepinephrine-transporter expressing tumors [14] and ^{76}Br -labeled amino acid tracers for various kinds of cancer imaging [15,16] were successfully synthesized using ^{76}Br isolated by the new system. These results indicate that enough amounts of highly pure ^{76}Br for clinical applications is isolated by the improved system under optimized condition and can be useful for the synthesis of clinically potent PET tracers.

Since the development of an automated isolation module is required for routine production of radionuclides in clinical applications, many attempts to develop such an automation system have been reported [8–11]. For example, Aneheim *et al.* reported an automated module for isolations of ^{211}At , an alpha-emitting radiohalogen, using the dry distillation approach [11]. They demonstrated that ^{211}At was recovered successfully in a cryotrap at the end of the distillation system. In addition, the recovered ^{211}At was then provided to the automated module for the synthesis of ^{211}At labeled compounds. Thus, the results reported here indicate the new system can function as an automated module for ^{76}Br isolation and can be connected to automated radiolabeling module for ^{76}Br labeled compounds.

4. CONCLUSION

A dry distillation system for ^{76}Br isolation was improved and optimized for future automation. The new system showed good recovery efficiencies ($66.5 \pm 5.3\%$) and resulted in the isolation of highly pure ^{76}Br with radioactivity on the order of GBq (630–1200 MBq) under the optimized condition. In addition, the ^{76}Br isolated can be applied to the synthesis of clinically

potent ^{76}Br -labeled tracers for PET imaging. This system has the potential to be incorporated into an automated dry distillation system for clinical PET applications and to be contributed for the automation.

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