



## Efficient preparation of high-quality $^{64}\text{Cu}$ for routine use



Tomoyuki Ohya, Kotaro Nagatsu\*, Hisashi Suzuki, Masami Fukada, Katsuyuki Minegishi, Masayuki Hanyu, Toshimitsu Fukumura, Ming-Rong Zhang

National Institutes for Quantum and Radiological Science and Technology, 4-9-1 Anagawa, Inage-ku, Chiba 263-8555, Japan

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### ABSTRACT

**Introduction:** Copper-64 is an attractive radionuclide for positron emission tomography and is emerging as a radiotherapeutic agent. The demand of  $^{64}\text{Cu}$  with low metallic impurities has increased because of its wide applications when incorporated with antibodies, peptides, and proteins. In this study, we propose a new separation method to produce high-quality  $^{64}\text{Cu}$  using a cation exchange column, as well as an automated separation system suitable for large-scale production.

**Methods:**  $^{64}\text{Cu}$  was produced from an electrodeposited  $^{64}\text{Ni}$  target via the  $^{64}\text{Ni}(p,n)$ -reaction with a 24 MeV HH+ beam at 10  $\mu\text{A}$  (electrical microampere) conducted for 1–3 h. The irradiated target was transported to a hot cell and disassembled remotely.  $^{64}\text{Cu}$  was separated by a solvent mixture of HCl and acetone on a cation-exchange resin, AG50W-X8. The chemical purity of  $^{64}\text{Cu}$  final product was evaluated using ion-chromatography coupled with a UV detector and inductively coupled plasma mass spectroscopy for quality as well as metallic impurities.

**Results:** We obtained  $^{64}\text{Cu}$  in dried form at a yield of 5.2–13 GBq at the end of separation, or  $521 \pm 12 \text{ MBq}/\mu\text{A h}$  as the final product within 2.5 h of processing time. The metallic impurities were a satisfactory low level in the order of ppb. Major contaminants of Co and Ni were lower than those samples obtained by a widely accepted separation using an anion-exchange resin.

**Conclusion:** Using a cation-exchange resin and a systematic operation, we successfully reduced the contamination level of the  $^{64}\text{Cu}$  product. As a straightforward separation method, which shortened the entire processing time, we obtained a satisfactory amount of high-quality  $^{64}\text{Cu}$  available for routine use.

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### 1. Introduction

Copper-64 is an attractive radionuclide in nuclear medicine for both positron emission tomography and radiotherapy [1], because of its intermediate half-life and a characteristic decay process ( $T_{1/2} = 12.7 \text{ h}$ ;  $\beta^+$  17.6%,  $\beta^-$  38.5%, and EC 43.9%). Many production routes and processes have been reported to obtain no-carrier-added  $^{64}\text{Cu}$  from targets of Ni and Zn [2]. Among them, the  $^{64}\text{Ni}(p,n)^{64}\text{Cu}$  reaction is a promising route [3,4], because this reaction can be performed by low energy protons from a compact cyclotron at a high production yield [5–7].

In several pre-clinical and chemical studies,  $^{64}\text{Cu}$  has utilized by incorporating with a chelating agent like Cu-ATSM (Cu-diacetyl-bis( $\text{N}^4$ -methylthiosemicarbazone)) [8–10]. However, owing to the potential and favorable accessibility of  $^{64}\text{Cu}$ , large molecule agents, i.e., antibodies, peptides, and proteins, have emerged as new candidates for  $^{64}\text{Cu}$  labeling. Therefore, high-quality  $^{64}\text{Cu}$  is in high demand, and its quality control (QC), especially radionuclidic purity and chemical purity

(cold metallic impurities in the product), has become important to assure labeling efficiency besides the proficiency of the person doing the labeling. The low specific activity of  $^{64}\text{Cu}$  or a certain amount of metallic contaminants causes a negative impact on labeling [7,11]. In addition, although it has been less effective in 'radiopharmaceutical' society, a guideline called ICH-Q3D regulates the permission limit of elemental impurities in conventional drugs [12]. Hence, we should consider and prepare to reflect such regulation into daily radio-pharmaceutical productions in the near future.

With respect to the above and to obtain high-quality  $^{64}\text{Cu}$ , an anion-exchange resin, e.g., AG1-X8, has been conventionally used as a separation material in  $^{64}\text{Cu}$  production from a  $^{64}\text{Ni}$  target [3,7,13,14]. However, this method has a critical issue because the elution order of elements is  $\text{Ni} \rightarrow \text{Co} \rightarrow \text{Cu}$ . The fraction of Cu is at a risk of contamination by the  $^{64}\text{Ni}$  target material and  $^{55,61}\text{Co}$  that has half-lives of 17.5 h and 1.65 h generated via the  $^{58}\text{Ni}(p,\alpha)$ - and  $^{64}\text{Ni}(p,\alpha)$ -channels, respectively. Alliot et al. [14] showed a successful result for the separation of  $^{64}\text{Cu}$ , suggesting that the contamination risk is not inevitable; however, elution profiles in some reports exhibit that both peaks of Co and Cu were slightly overlapped [7,15], and the radio-Co was slightly detected in a  $^{64}\text{Cu}$  product [16]. Moreover, a high level of contamination by Ni was reported [7]. Because of the highest amount of 'cold' origin in this system, Ni is a certainly risky element that can readily compete to the trace amount

\* Corresponding author at: Targetry and Target Chemistry Division, Radiopharmaceutical Development Department, National Institutes for Quantum and Radiological Sciences and Technology, 4-9-1 Anagawa, Inage-ku, Chiba 263-8555, Japan. Tel.: +81 43 206 4039; fax: +81 43 206 3261.

E-mail address: [nagatsu.kotaro@qst.go.jp](mailto:nagatsu.kotaro@qst.go.jp) (K. Nagatsu).

of  $^{64}\text{Cu}$  and interfere with the labeling of target molecules [11]. Beside this, radio-Co shows similar attributes to produce inappropriate labeled conjugates. Thus, both metallic contaminants should be removed by chemical purification. However, a tailing profile is frequently present in any chromatography elution including ion exchange applied in these studies, and it is sensitively affected by many factors, for example, column structure, volume of resin, flow rate of mobile phase, pH, temperature, and amount of loaded sample; thus achieving an ideal separation conditions is a challenge. Although the separation efficiency can be improved by employing a long column with a large amount of resin and a slow flow rate of eluent [17], a considerable time is needed for separation that causes a loss of activity because of physical decay of radionuclide.

The separation method using a cation-exchange resin is less frequently used compared with an anion-exchange resin. The cation exchange method is unsuitable for the separation of  $^{64}\text{Cu}$ , because the distribution coefficients ( $K_d$ ) on a cationic exchanger are very similar among metal ions with identical charges [18]. However, the difference among respective  $K_d$  can be enhanced using an eluent mix of acetone and acid at appropriate ratios [19]. We previously obtained no-carrier-added radio-copper,  $^{61}$ ,  $^{62}\text{Cu}$ , using various ion-exchange resins [20,21], and we reported the fine separation of  $^{61}\text{Cu}$ , produced via the  $^{nat}\text{Co}(\alpha,2n)$ -channel, on a cation-exchange resin, AG50W-X8 [22]. Thus, in this study, we employed the same strategy with a slight modification, in which  $^{64}\text{Cu}$  was separated from a bulk amount of  $^{64}\text{Ni}$ .

The advantage of this method is that, with the appropriate composition of the eluent, we are able to elute Cu as the primary fraction, i.e., the elution order of  $\text{Cu} \rightarrow \text{Co} \rightarrow \text{Ni}$ , and reduce the risk of contamination by Co and Ni because their tailing profiles would not affect the Cu fraction.

In this paper, we report an efficient method to produce high-quality  $^{64}\text{Cu}$  using a cation exchange column, and we developed an automated apparatus, including solid target handling system suitable for large scale remote production.

## 2. Materials and methods

### 2.1. Materials

Ultrapure grade reagents of hydrochloric acid, nitric acid, and aqueous ammonia were purchased from Kanto Kagaku (Ultrapur, Tokyo, Japan). Ultrapure water (UPW) for ultratrace analysis and acetone (semiconductor grade) were obtained as the finest grade available from Wako Pure Chemical Industries (Tokyo, Japan). The eluent with respective concentration was prepared using these reagents.

For ion chromatography analysis, 4-(2-pyridylazo)resorcinol (PAR), MetPac PDCA eluent (7.0 mM pyridine-2,6-dicarboxylate, 66 mM KOH, 5.6 mM  $\text{K}_2\text{SO}_4$ , 74 mM HCOOH), and MetPac PAR Post-column diluent (1.0 M 2-dimethylaminoethanol, 0.5 M  $\text{NH}_4\text{OH}$ , 0.3 M  $\text{NaHCO}_3$ ) were purchased from Thermo Fisher Scientific (Sunnyvale, CA, USA). The TraceCERT® inductively coupled plasma mass spectrometry (ICP-MS) standard (10 mM mixture of Fe, Cu, Ni, Co, and Mn in 0.1 M  $\text{HNO}_3$ ) was obtained from Sigma-Aldrich (St. Louis, MO, USA).

The target material, isotopically enriched  $^{64}\text{Ni}$ , was purchased from Isoflex (San Francisco, CA, USA), whose certification of analysis was as follows:  $^{64}\text{Ni}$  (99.07 atom%),  $^{58}\text{Ni}$  (0.52 atom%),  $^{60}\text{Ni}$  (0.25 atom%),  $^{61}\text{Ni}$  (0.01 atom%), and  $^{62}\text{Ni}$  (0.15 atom%); and chemical impurities of Cu (<10 ppm), Zn (40 ppm), Fe (100 ppm), and Co (<10 ppm).

### 2.2. Preparation of the cation exchange column

A portion of cation-exchange resin (AG50W-X8, 100–200 mesh,  $\text{H}^+$  form; Bio-Rad, Tokyo, Japan) was soaked in a beaker filled with 1 M HCl overnight. The HCl medium was decanted, and the resin was washed repeatedly with Milli-Q water (18 M $\Omega$ cm; Millipore, Billerica, MA, USA) by decantation until the pH of the medium became almost neutral. The conditioned resin (7 mL, wet volume) was then filled into a glass

tube ( $\phi 10 \times 105$  mm) to prepare the separation column and washed with 100 mL of UPW.

### 2.3. Preparation of $^{64}\text{Ni}$ target

A fresh target material as purchased, as well as recovered  $^{64}\text{Ni}$  post production, was refined prior to electroplating by the following process. For fresh target preparation, 500 mg of enriched  $^{64}\text{Ni}$  was dissolved in about 10 mL of 6 M  $\text{HNO}_3$  at 120 °C on a hot plate and diluted with a 6-fold volume of UPW. For recycling  $^{64}\text{Ni}$ , the recovered solution of  $^{64}\text{Ni}$  in HCl was reduced in its volume below a few mL at 150 °C on a hot plate and diluted with a 12-fold volume of UPW to obtain  $^{64}\text{Ni}$  solution in <1 M HCl.

Both  $^{64}\text{Ni}$  solutions from above were applied onto a column filled with AG50W-X8 resin (resin volume, 30 mL; this column was the same as that described in 2.2). A series of eluates at different compositions, 50 mL of UPW, 200 mL of 2 M HCl/acetone (1:9), 300 mL of 5 M HCl/acetone (1:9), and 200 mL of UPW, was loaded into the column sequentially at a flow rate of 0.5 mL/min to remove potential metallic impurities. Finally, 200 mL of 2 M HCl was loaded to recover the  $^{64}\text{Ni}$  fraction as the refined  $^{64}\text{Ni}$  solution.

For electroplating  $^{64}\text{Ni}$ , we employed a method reported by Obata et al. [13] with a slight modification. Briefly, the refined  $^{64}\text{Ni}$  solution described above was evaporated on a hot plate, and the precipitant ( $^{64}\text{NiCl}_2$ ) collected in a quartz crucible was heated in a muffle furnace to oxidize and obtain NiO (thermal program was +5 °C/min, at 300 °C for 5 h, +3 °C/min, at 900 °C for 24 h, and left to cool to room temperature). Weighed NiO, which was used for the preparation of  $^{64}\text{Ni}$  plating solution, was dissolved into excess 6 M  $\text{HNO}_3$  on a hot plate and evaporated ( $\text{NiO} \rightarrow \text{Ni}(\text{NO}_3)_2$ ). The precipitant was reconstituted in 15 mL of UPW and conc.  $\text{H}_2\text{SO}_4$  (600  $\mu\text{L}$  per 200 mg of  $^{64}\text{Ni}$ ). This solution was further quasi-azeotropically evaporated to remove nitric acid by addition of UPW to produce  $\text{NiSO}_4$ . Finally,  $(\text{NH}_4)_2\text{SO}_4$  (600 mg for 200 mg of  $^{64}\text{Ni}$ ) and UPW were added, and the pH of the solution was adjusted to pH 9 by adding aqueous ammonia. An apparatus for electrodeposition was made from that described in a previous report [3]. A graphite bar ( $\phi 4 \times 120$  mm, 99.9%; Toyo Tanso, Tokyo, Japan) and an Au disk ( $\phi 10 \times 1.5$  mm, 99.99%; Fuchikawa Rare Metal, Tokyo, Japan) were used for the anode and cathode, respectively. The graphite bar and the Au disk were cleaned prior to use, soaked in 6 M  $\text{HNO}_3$  overnight, washed with Milli-Q, and dried in oven at 60 °C.

The electrodeposition of  $^{64}\text{Ni}$  was performed using the above two electrodes and the refined  $^{64}\text{Ni}$  solution (90 mg in 4 mL) filled in a glass tube ( $\phi 15 \times 98$  mm height) for 12–16 h at a constant current of 10–11 mA at 3–4 V. The area for the electrodeposition was adjusted using a masking plate made of Teflon inserted between the glass tube and the Au disk. During the electrodeposition, the graphite anode was rotated (120–140 rpm) to remove the evolving  $\text{H}_2$  gas. Therefore, a  $^{64}\text{Ni}$  layer of 8 mm diameter was electroplated with a density of  $182 \pm 13$  mg/cm $^2$ , or about 190  $\mu\text{m}$  in thickness, which was slightly larger than the diameter of the proton beam (aperture of the collimator was 6 mm in our target system).

### 2.4. Target holder

Fig. 1 shows the design of our target holder made of aluminum. In this study, we employed indirect cooling, where the target disk does not contact the cooling water to avoid contamination from circulating coolant. The aim of the target holder design was to show good operability, e.g., a secure grip by the robot arm, stability on transfer, ready handling by manipulator, and a disassembling feature by a special device placed in the hot cell (Figs. 2 and 3). The target holder, which enclosed the  $^{64}\text{Ni}$  target disk inside, was set to the irradiation port.

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