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A simple Cu-64 production and its application of Cu-64 ATSM

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ABSTRACT

One of the positron emission radionuclides, ^{64}Cu, has been reported to be a particularly effective radioisotope in PET imaging study. This utility of ^{64}Cu depends on the chemical stability in water with proper energy and half-life as γ-emitters.

Hence, we tried to develop a simple method for producing this isotope using an old cyclotron model in our site (50 MeV, Scantronics co.). In particular, we designed the equipments of enrich ^{64}Ni plating system and radioactive ^{64}Cu separation using plastic cartridge column; ^{64}Ni plating system on gold foil which located in the 13° angle target toward beam irradiation. For the nuclear reaction of ^{64}Cu, it was applied to ^{64}Ni(p, n) ^{64}Cu at low energy under the degrader composed of Al and Ta foils. After beam irradiation, ^{64}Cu was identified by multichannel analyzer installed for a HPGe detector and its utility was certified by the microPET images of ^{64}Cu-ATSM (CT-26 tumor bearing mouse as reported previously). The image quality of ^{64}Cu was also very similar to that of ^{18}F radioisotope in microPET scanner. In conclusion, a method of ^{64}Cu production and its application was successfully established in old cyclotron having high energy.

1. Introduction

The radioactive ^{64}Cu for molecular imaging has been recently studied in nuclear medicine because of physical properties ($T_{1/2}$ = 12.7 h, β$^-$ 37.1%, β$^+$ 17.9%). It has reported to be particularly effective in hypoxia tumor diagnosis after labeling with diacetyl-bis(N^4-methylthiosemicarbazone (ATSM)) ligand (McCarthy et al., 1999; Lewis et al., 2002). In aspect of chemical reaction ^{64}Cu also has the potential to prepare many radiotracers, due to oxidation state of +2 ($CuCl_2$) and good solubility in water (Novak-Hofer and Schubiger, 2002). By these possibilities of positron emission tomography (PET) agents, ^{64}Cu radioisotope has been produced continuously in parts of molecular imaging research, which can be obtained from neutron reaction in nuclear reactor such as ^{63}Cu(n, γ)^{64}Cu, ^{64}Zn(n, p)^{64}Cu and proton irradiation in medical cyclotron such as ^{64}Ni(p, n)^{64}Cu, ^{64}Ni(d, 2n)^{64} (Hou et al., 2002). Among these reactions, ^{64}Ni(p, n)^{64}Cu method has known as high specific activity and purity (McCarthy et al., 1999).

In this study we used a simple ^{64}Ni(p, n)^{64}Cu reaction which was applied to 13° angle target toward proton beam and old cyclotron model (50 MeV, Scantronics Co., 1985). Furthermore, we designed the advanced system of (a) easy plating using recrystallization of enrich nickel sulfate, (b) fixing a gold foil on the surface of 13° angle target, and (c) quickly separation of ^{64}Cu and ^{64}Ni using disposable resin column (plastic cartridge type to design by ourselves). After ^{64}Cu production, we were compared ^{64}Cu-ATSM with [^{18}F]FDG at the experiments of phantom and mouse in microPET scanner to inspect the quality of radioisotope imaging. Its chemical efficiency and biological effect carried out in vivo test after labeling with ATSM ligand.

In summary, we developed a simple process of ^{64}Cu production using old cyclotron model, which could have application to any cyclotron site. This system can be applied the ^{64}Cu of high quality for researcher and widen the use of ^{64}Cu in molecular imaging based on PET technology.

2. Materials and methods

All chemicals used in this study were obtained from Aldrich Chemical Company without further purification. Ion exchange resin (AG1-X8) was purchased from BioRad company. The radioTLC system used AR-2000 (Bioscan Co.) in thin layer chromatography. Multichannel analyzer including HPGe detector (gamma detect type, Ortec Co.). ^{64}Cu production was performed using enrich ^{64}Ni (Isoflex Co.) and 50 MeV cyclotron (Scantronics co., 1985).

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2.1. Preparation of ^{64}Ni sulfate

Enrich ^{64}Ni metal (0.5 mg, 0.008 mmol) was dissolved in nitric acid (6.0 M) and then was dried with heating. The green-colored residue was added to concentrated sulfuric acid and then was dried with heating (Fig. 1). The crude product was cooled down to room temperature and then diluted with distilled water. After recrystallization of ^{64}Ni sulfate in acetone, it was filtered and evaporated in vacuum for 24 h. The dried ^{64}Ni sulfate became a green–yellow colored powder (1.2 mg, >95%). FT–IR (cm^{-1}, KBr pellet): 1100, 1380, 1480, 1650 (S=O).

2.2. Plating and target of enrich ^{64}Ni

^{64}Ni sulfate solution (150 mg, pH = 4–5) in distilled water (10 mL) was transferred to the cell and used for electroplating. The cell in plating equipment was supplied with 0.73 mA current for over 12 h. The gold foil (0.001 mm of thickness × 10 mm of diameter) was used as cathode and Pt wire was used as anode in the electroplating experiment (Fig. 2). After electroplating, a gold foil having 10–20 μm (in thickness) and 35 mg (in amount) was obtained (Fig. 3). For ^{64}Cu production, enriched ^{64}Ni was irradiated at about 18 MeV (used the degrader composed of 0.8 mm duralumin and 0.025 mm Ta on 13° angle target in 50 MeV cyclotron) with 23–25 μA current for an hour (Fig. 4).

2.3. Separation of enrich ^{64}Ni and ^{64}Cu

After target irradiation, the gold foil was dissolved in hydrochloric acid (6.0 M, 10 mL) at 80 °C (Fig. 5). Then this solution was eluted through a column cartridge (PEEK material case of 1 × 4 cm, ion exchange resin; AG1 × 8 100–200 mesh). After switching to distilled water (10 mL), the purified ^{64}Cu was obtained. ^{64}Cu production yield was about 20 mCi/h in distilled water (10 mL).

2.4. Preparation of ^{64}Cu-ATSM

In a typical experiment (McCarthy et al., 1997) ^{64}Cu solution (1 mCi/mL) was added to glycine buffer (0.6 M, 2 mL). This solution (pH = 5–6) was added to 0.2 mg H_2ATSM in 0.1 mL of DMSO. After 30 min, the mixture was purified into C18 Sep-Pak column and eluted in 1.0 mL of ethanol. The product was diluted with distilled water and passed into 0.22 μm of sterile filter.

2.5. PET imaging study of ^{64}Cu-ATSM

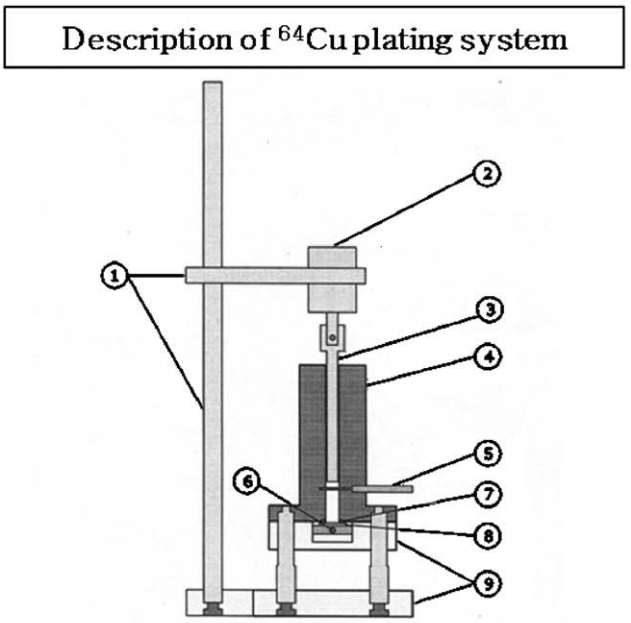
The characteristic of ^{64}Cu-ATSM was also evaluated by means of PET imaging of ^{64}Cu and ^{18}F, using a resolution phantom with cold-insert structure and small animal with tumor. All PET studies were performed using a small animal dedicated PET scanner (microPET-R4, CTI Concorde Microsystems, Knoxville, TN). After transforming dimensional format of sinogram using Fourier Rebinning (FORE), PET images were reconstructed and generated by two-dimensional ordered subset expectation maximization (OSEM) reconstruction method. In phantom experiment, the resolution phantom (Micro Deluxe Phantom, Data Spectrum Co., Hillsborough, NC) was filled up water that was mixed with ^{64}Cu or ^{18}F of 0.2 mCi, and both PET images of ^{64}Cu and ^{18}F were obtained

$$^{64}Ni + 2HNO_3 \rightarrow {}^{64}Ni(NO_3)_2 + H_2(g)$$

$$^{64}Ni(NO_3)_2 + H_2SO_4 \rightarrow {}^{64}Ni(SO_4) + 2HNO_3$$

Fig. 1. Preparation of enrich ^{64}Ni sulfate.

a



No.	Symbol	Parts Name	No.	Symbol	Parts Name
1	Al	Aluminum	6	Cu	Copper Electrode
2	MT	Motor	7	OR	O-ring
3	P	Polypropylene	8	Au	Gold Plate
4	A	Acrylic	9	PTFE	Polytetrafluoroethylene
5	Pt	Platinum Electrode			

b

Fig. 2. (A) Simple drawing of plating equipment. (B) Photo of electric plating unit for gold foil target.

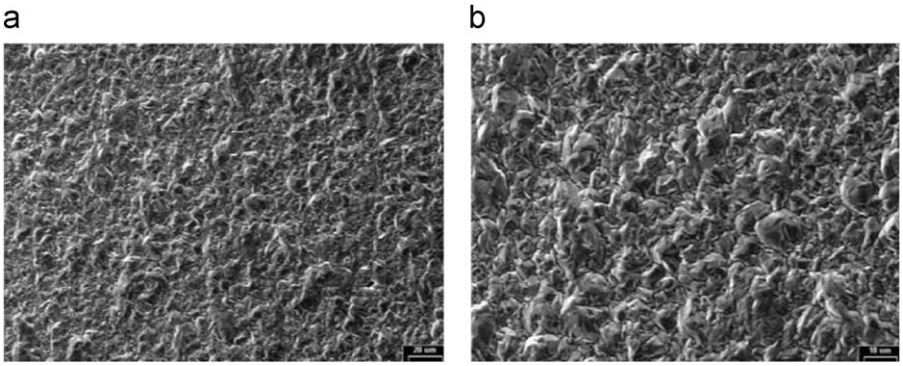


Fig. 3. (A) ^{64}Ni surface on gold foil in × 500 SEM. (B) ^{64}Ni surface on gold foil in × 1000 SEM.

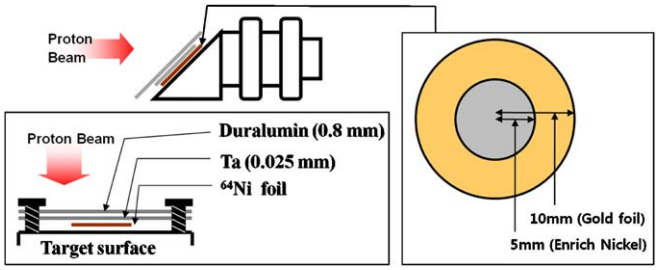


Fig. 4. Modification drawing of target body and foil plated enrich nickel for beam irradiation in 50 MeV cyclotron type.

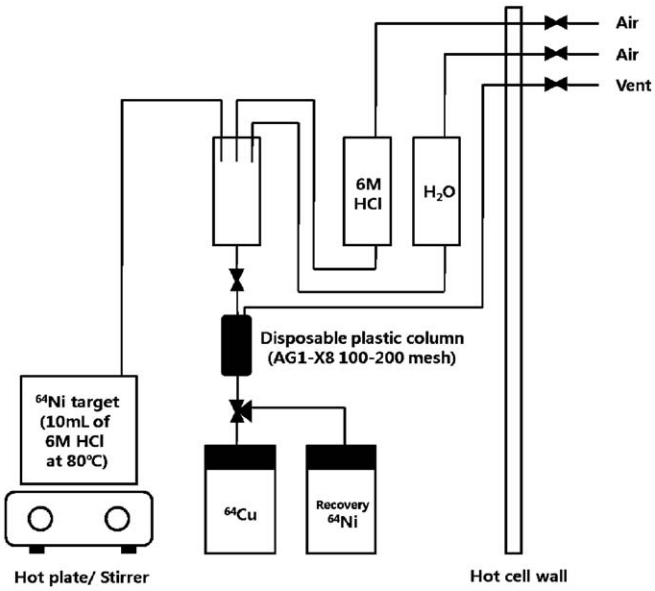


Fig. 5. Separation and purification of ^{64}Cu used plastic (PEEK) column cartridge which was filled with cotton filter and resin (AG1- × 8 100–200 mesh), and recycle of ^{64}Ni.

for an hour, respectively, as described above. Image quality and characteristics of ^{64}Cu and ^{18}F were evaluated qualitatively, in the both PET images. For tumor imaging of ^{64}Cu-ATSM, [^{18}F]FDG (0.193 mCi) was injected in CT-26 bearing mouse, and then [^{18}F]FDG imaging was obtained from it after 1 h. When the mouse was over the decay of [^{18}F]FDG, ^{64}Cu-ATSM (0.2 mCi) was injected in it again. The tumor imaging of ^{64}Cu-ATSM was obtained.

Table 1
Preparation of solution and electric conditions for ^{64}Ni plating.

Plating solution			Plating condition					
$^{64}Ni(SO)_4$	solvent	pH	Anode	Cathode	Wave	Current	Time	Thickness
150 mg	D.W.	4–5	Pt	Au	sin	0.73 mA	20 h	10–20 μm

3. Results and discussion

3.1. Preparation and plating of ^{64}Ni sulfate

In previous method, ^{64}Ni was easily converted into ^{64}Ni sulfate by nitric acid and sulfuric acid (McCarthy et al., 1999), but ^{64}Ni sulfate powder was contained a little amount of acid as solvent, due to high boiling point of acid (pH = 1–2). In order to neutralize it, ^{64}Ni solution for electronic plating needed to add some materials. This plating method caused many impurity particles around an electrode into plating equipment.

To overcome these drawbacks, we had used the plating source of high purified enrich ^{64}Ni. After ^{64}Ni sulfate recrystallized in acetone and water (3:1), a yellow–green powder (recovery ratio, >95%) and dissolved in distilled water (pH = 4–5). It could plate on gold foil in about 12 h without additive and neutralizer (Table 1). There were also no impurities around an electrode and in solution. In particular, we used the simple equipment of enrich ^{64}Ni plating on gold foil (Fig. 2) and it was manufactured by ourselves. The thickness of ^{64}Ni plating for beam irradiation was analyzed by SEM (scanning electron microscope). Here we obtained an interesting result; the yield of ^{64}Cu can be changed according to thickness and amount of enrich nickel on gold foil (Fig. 3). For the most suitable condition for nuclear reaction at 50 MeV cyclotron, the thickness of ^{64}Ni was 10–20 μm and plating amount was 35 mg for 12 h (plating ratio, 42 ± 5%).

3.2. Targetry of ^{64}Ni

^{64}Cu nuclear reaction was performed using 95% enriched ^{64}Ni (10 mm plating diameter) with 30–50 μA at 18 MeV for an hour. This proton beam must be reduced by the degrader composed of Al and Ta foils in 50 MeV cyclotron (it is very difficult to control energy for producing a specific radioisotope because of old model, so we always do maintain the cyclotron voltage of 28 MeV). As its necessary consequence, the yield of radioisotope (about 20 mCi/h for ^{64}Cu purified) cannot be low against a ratio of irradiation time to production in cyclotron.

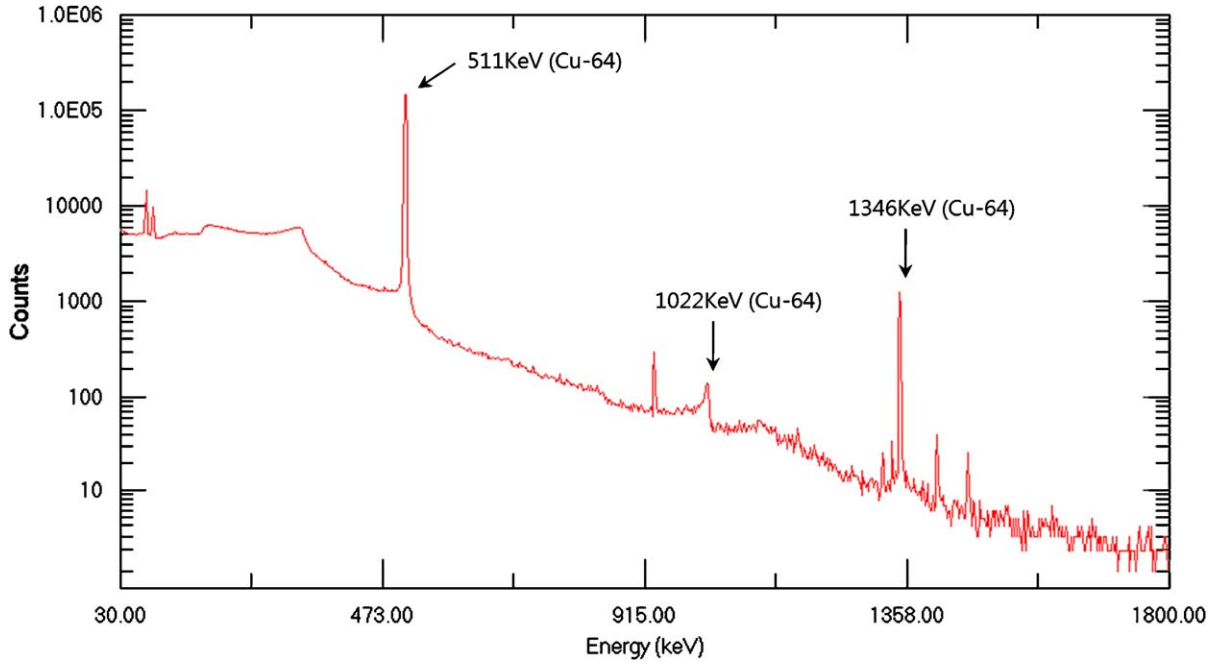


Fig. 6. Gamma spectra data of ^{64}Cu fraction purified.

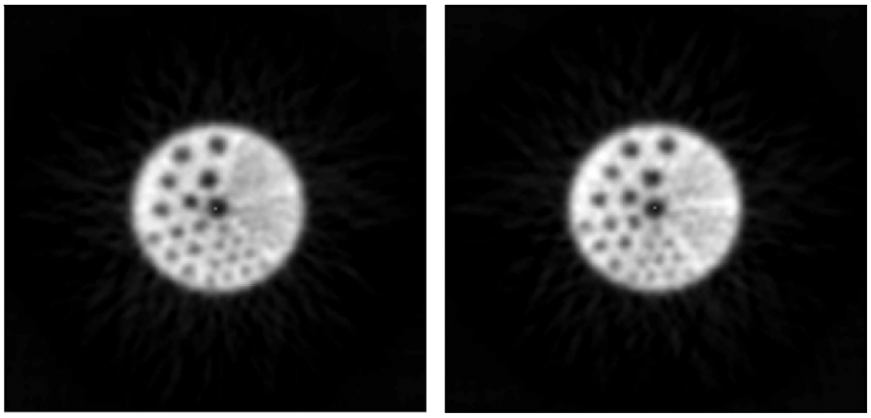


Fig. 7. Transverse images of resolution phantom filled with ^{64}Cu (left) and ^{18}F (right) solution.

3.3. Separation and purification of ^{64}Cu

^{64}Cu radioisotope was easily and quickly purified by ion exchange resin in plastic case (PEEK, dimension as 1 (diameter) × 4 cm (height)) (Fig. 5). In our specific method using disposable cartridge, ^{64}Cu production was not only stable, but also less contaminated. In order to obtain the high quality of ^{64}Cu, separation and purification process must be done within average 25 min. By the use of multichannel analyzer installed HPGe detector, ^{64}Cu was identified with the energy of its gamma ray at 511, 1022 and 1346 KeV as reported previously (Hou et al., 2002). Its radiochemical purity was over 99% in Fig. 6.

3.4. PET imaging and preparation of ^{64}Cu-ATSM

^{64}Cu-ATSM was prepared as described above and purified by short column like ^{99m}Tc compounds (McCarthy et al., 1999). Labeling efficiency after purification using C18 cartridge was $98 \pm 0.8\%$ ($n = 3$). The image quality and resolution of phantom for ^{64}Cu were very similar with those of ^{18}F, which is consistent with our expectation that was based on the physical characteristics (e.g. positron energy and range) of ^{64}Cu. PET imaging of ^{64}Cu-ATSM was very similar to that of [^{18}F]FDG at same phantom study (Fig. 7). ^{64}Cu-ATSM could be imaged CT-26 tumor bearing mice by microPET scanner. In tumor model of same mouse, ^{64}Cu-ATSM and [^{18}F]FDG showed the different uptake images in microPET after 1 h injection as reported (Fujibayashi et al., 1999).

4. Conclusion

We suggested that ^{64}Cu production was performed novel method and old cyclotron model; The method contained new equipments of separation, plating and target parts. In this study, the improvement of ^{64}Cu production may be extended to the synthesis of new radiotracer for molecular imaging and clinical study.

Acknowledgments

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