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ORIGINAL PAPER

Routine simultaneous production of no-carrier-added high purity ^{64}Cu and ^{67}Ga

Abdul H. Al Rayyes, Yasser Ailouti

Abstract. A routine production method of no-carrier-added ^{64}Cu was performed. A copper target support is electroplated by gold then an optimized thickness of enriched ^{68}Zn layer is deposited. The ^{68}Zn target was bombarded with a 23.5 MeV and 250 μA proton beam, generating the main nuclear reactions ^{68}Zn(p,2n)^{67}Ga and ^{68}Zn(p,αn)^{64}Cu. A semi-automated separation method using a chromatographic column system was developed for ^{64}CuCl$_2$ production. A 600 mCi batch of ^{64}Cu is produced at the end of separation and purification chemistry. The radionuclidic purity of ^{64}Cu was > 98% as required by the United States and European Pharmacopoeias. Radiochemical purity and activity concentration is suitable for labeling different ligands to produce diagnostic and therapeutic radiopharmaceuticals.

Key words: ^{64}Cu • targetry • radioisotope production • ion exchange chromatography

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Introduction

The radionuclide ^{64}Cu ($T_{1/2}$ = 12.7 h) emits β$^-$ 39% and β$^+$ 17.4% ($E_{\beta^+_{max}}$ = 656 KeV; $E_{\beta^-_{max}}$ = 573 KeV). These characteristics make it useful for both high resolution positron emission tomography (PET) imaging and targeted endoradiotherapy. In addition, its electron capture decay associated with Auger emission gives more efficient cell killing when this radioisotope is deposited in the cell [3].

Another advantage of this important radionuclide is the stability of its complexes with bifunctional chelators consisting of the metal complexing ligand and the functional group for attachment to the targeting molecule [12].

Until now ^{64}Cu-ATSM is the most investigated radiolabeled compound and it seems to be a promising agent for endoradiotherapy [7, 8, 10].

Many methods for the production of ^{64}Cu have been investigated based on low energy cyclotron via the nuclear reaction ^{64}Ni(p,n)^{64}Cu [2, 4, 9].

In this study, our production method is based on two nuclear reactions on the same target material ^{68}Zn.

The production of ^{67}Ga is carried out via the reaction ^{68}Zn(p,2n)^{67}Ga. The energy threshold of this reaction is about 12 MeV and its maximum cross-section is about 700 mb at 21 MeV. Whereas ^{64}Cu is produced via the reaction ^{68}Zn(p,αn)^{64}Cu. Its energy threshold is about 8 MeV with a maximum cross-section of about 23 mb at 28 MeV. The proton beam energy used for this production is 23.5 MeV. This particular energy has been choosen to minimize the activities of ^{67}Cu ($T_{1/2}$ = 58.6 h) and ^{66}Ga

($T_{1/2}$ = 9.4 h) by-products produced during proton bombardment by the reactions $^{68}Zn(p,2p)^{67}Cu$ and $^{68}Zn(p,3n)^{66}Ga$, respectively [6, 11].

Materials and methods

Materials

Enriched ^{68}Zn (enrichment > 97%) was purchased from ISOFLEX (Russia). Tetrachloroauric (III) acid trihydrate 99.5% GR for analysis was obtained from Merck. Chemicals for zinc and gold electroplating, (HCl, hydrazine hydrate, NaOH, KCN and Na_2HPO_4 of analytical grade) were purchased from Merck. Ion exchange resin (Dowex 1 × 8) was obtained from Sigma-Aldrich.

Methods

The surface of the copper target support, (2 × 10 cm), was cleaned by fine abrasive wool and acetone. This surface is electroplated by gold using alkaline a gold cyanide bath. The voltage and current density used for gold electroplating were 100 mV, 1 mA/cm^2, respectively. The usefulness of the electroplated gold layer is to prevent the dissolution of copper target support in order to produce non-carrier-added ^{64}Cu. Taking into account that copper target support is used for one time, the thickness of electroplated gold layer is 3–5 μm for economical reasons.

On the gold layer, the enriched zinc-68 has been electroplated on a smaller surface (1 × 10 cm) using electrolytic slightly acidic (pH ≈ 2.5) solution containing hydrazine hydrate as anodic depolarizer. The current density was 20 mA/cm^2 and the electroplated quantity was about 0.8 g.

The electroplated target was irradiated by a 23.5 MeV proton beam and a 250 μA beam using Cyclone-30 cyclotron (IBA, Belgium) for 6 h. The back side of the target was cooled with a very high speed stream of deionized water using the ion beam applications (IBA) irradiation station.

Developed anodic stripping voltammetry system purchased from Metrohm (VA processor 693 with VA stand 694) was used for trace metals analysis in produced ^{64}Cu bulk. This system uses a working electrode, a hanging mercury dropped electrode (HMDE), a reference electrode Ag/AgCl/KCl (3 mol) and an auxiliary electrode from platinum.

Radioisotopes were identified by gamma spectrometry using a high purity germanium (HPGe) detector with 25% efficiency, where the amplifier output of the detector was processed by a 4096 channels multi-channel analyzer (MCA) system. The fitting program (INTER WINER) was used for spectral data processing.

Results and discussion

The production process of ^{64}Cu was performed in three steps. Figure 1 shows the production scheme of ^{64}Cu.

The first step of the ^{67}Ga production process involved dissolution of the irradiated ^{68}Zn target layer

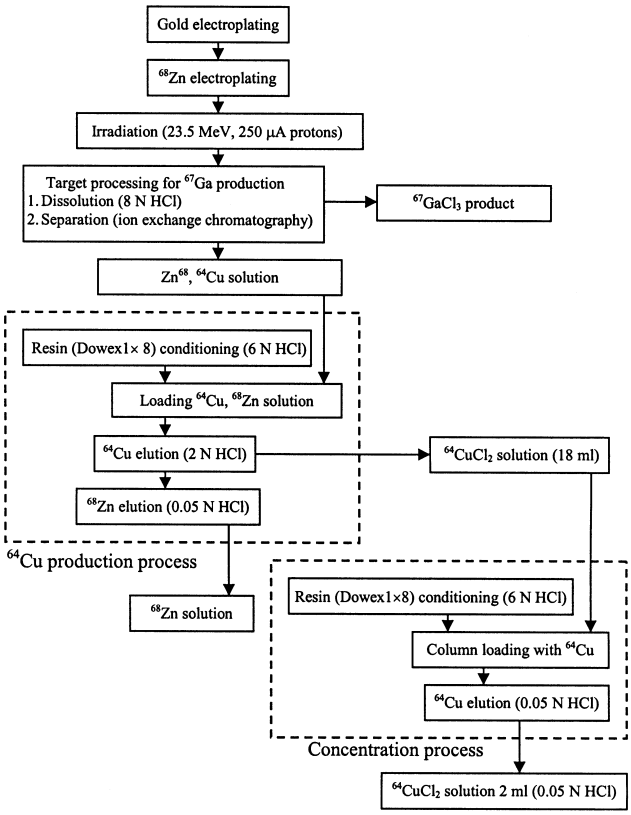

Fig. 1. Production of ^{64}Cu process.

gradually by 10 N HCl using a peristaltic pump. A Plexiglas chromatographic column (1.2 cm inner diameter and 6.0 cm long) packed with ion exchange resin (Dowex 50 × 4, 200 mesh) was used to separate enriched ^{68}Zn and ^{64}Cu from ^{67}Ga using 9 N HCl with a flow rate of 1 ml/min.

In the second step of the ^{64}Cu production process, the eluted fraction from the first step containing ^{68}Zn and ^{64}Cu was loaded on a second chromatographic column (2.0 × 12 cm) packed with ion exchange resin (Dowex 1 × 8). Before loading, the column was preconditioned by HCl 6 N. After loading, the elution of ^{64}Cu from the column was performed using HCl 2 N, then ^{68}Zn was eluted from the column by HCl 0.05 N. The elution flow rate was 3 ml/min. Figure 2 shows the elution profile of the ^{64}Cu separation. The volume

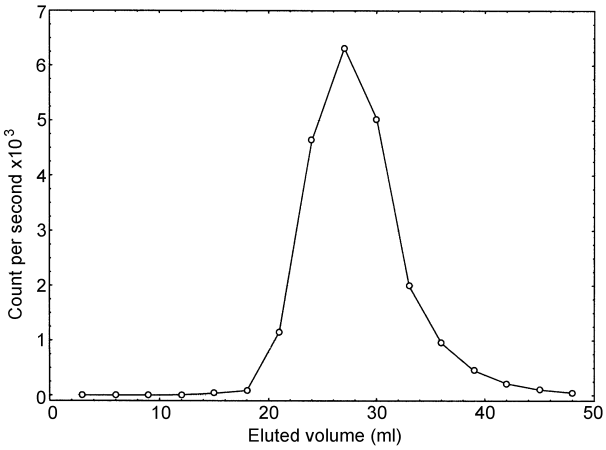

Fig. 2. Elution profile of the ^{64}Cu using ion exchange resin (Dowex 1 × 8). Eluent: HCl 2 N. Flow rate: 3 ml/min.

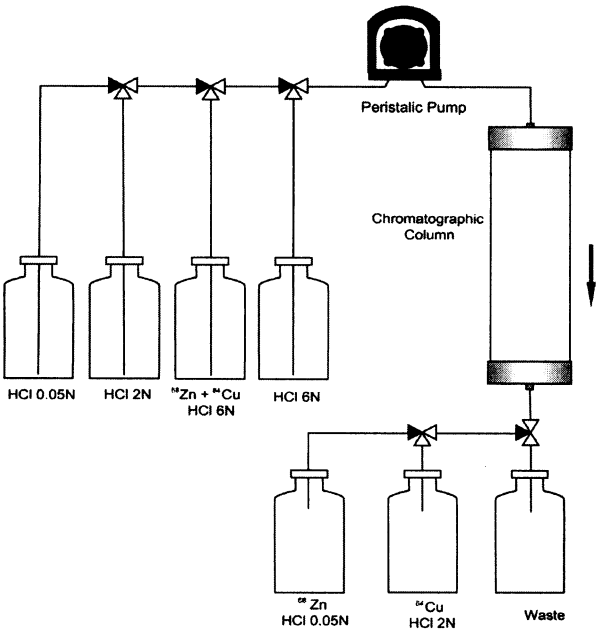

Fig. 3. Scheme of the original apparatus of ^{64}Cu production process.

of the obtained solution containing ^{64}Cu was 18 ml, whereas the solution containing ^{68}Zn, to be reused in electroplating of enriched zinc on a new target support, was 150 ml. Figure 3 shows the production unit of ^{64}Cu.

The ^{64}Cu solution volume is too large to be used in labeling process. For this reason, ^{64}Cu solution is concentrated in the third step using a semi-manual unit to concentrate ^{64}Cu to a smaller volume. All the ^{64}Cu activity was obtained through this unit in 2 ml of 0.05 N HCl. A small column, 3 × 10 mm, filled with ion exchange resin (Dowex 1 × 8) was used for this purpose. Figure 4 shows the concentration unit of the produced ^{64}Cu.

At the end of the separation and purification chemistry, the production yields of ^{67}Ga and ^{64}Cu were 5500 ± 300 mCi and 600 ± 40 mCi, respectively using the irradiation condition of 23.5 MeV and 250 μA of proton beam for 6 h.

By this method, the simultaneous production of ^{67}Ga and ^{64}Cu, normally going to the waste during the production process of ^{67}Ga, we offer a good opportunity to a different ^{67}Ga production centers to recover and purify ^{64}Cu in order to be used in PET imaging and targeted endoradiotherapy.

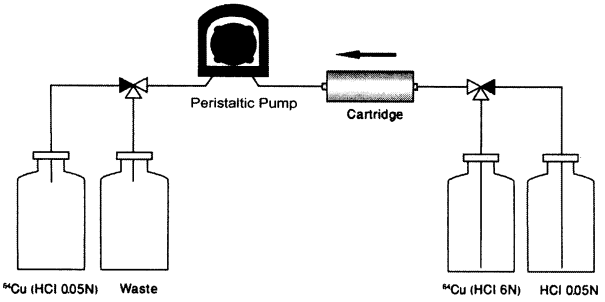

Fig. 4. ^{64}Cu concentration unit.

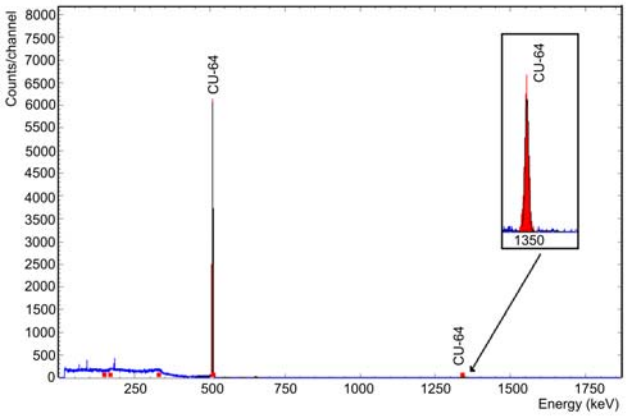

Fig. 5. γ-Spectrum of the produced $^{64}CuCl_2$ solution.

Quality control of the produced ^{64}Cu

Radioisotope purity

Due to the efficient separation of ^{67}Ga and ^{66}Ga in the ^{67}Ga production process, no Ga isotopes were detected in the final solution of $^{64}CuCl_2$. Figure 5 shows the gamma-ray spectrum obtained of the final product.

The target is electroplated with a gold layer of 2.3 μm of thickness, then with a ^{68}Zn layer of 115 μm of thickness. The angle between the incident proton beam and the target is 6°. It means that the effective thickness of ^{68}Zn layer is 1100 μm. The power degradation for this thickness will be from 23.5 to 10 MeV [13]. This energy can be considered as the optimum energy to maximize the ^{67}Ga and ^{64}Cu yield and minimize the quantities of ^{67}Cu and ^{66}Ga produced [5].

The proton beam energy used (23.5 MeV) gives the quantity of ^{67}Cu < 0.2% required (US, European Pharmacopoeia) and this value was calculated by Adam-Rebeles *et al*. [1].

Chemical purity

The chemical purity of $^{64}CuCl_2$ produced by our method of production was determined by anodic stripping voltammetry. The concentration of zinc and copper were 0.1 and 0.05 μg/ml, respectively.

Conclusion

A routine production method of no-carrier-added ^{64}Cu was performed. This method of production was developed by the optimization of target electroplating for high current proton beam bombardment (250 μA) and efficient radiochemical separation of the irradiated target material. The described method offers the possibility to a different cyclotron centers, carrying out routine production of ^{67}Ga via the ^{68}Zn(p,2n)^{67}Ga reaction on highly enriched ^{68}Zn targets, to recover and purify ^{64}Cu in order to be used in PET imaging and targeted endoradiotherapy.

The radionuclidic purity of ^{64}Cu measured by γ-spectrometry was > 98%. Radiochemical purity and activity concentration are suitable to label different ligands in order to produce diagnostic and therapeutic radiopharmaceuticals.

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