RESEARCH ARTICLE | DECEMBER 19 2012

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AIP Conf. Proc. 1509, 91–95 (2012)
https://doi.org/10.1063/1.4773947

Cyclotron Production of ^{61}Cu using Natural Zn & Enriched ^{64}Zn Targets

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Abstract. Copper-61 (^{61}Cu) shares with ^{64}Cu certain advantages for PET diagnostic imaging, but has a shorter half-life (3.4hr vs. 12.7hr) and a greater probability of positron production per disintegration (61% vs. 17.9%). One important application is for *in vivo* imaging of hypoxic tissue. In this study ^{61}Cu was produced using the ^{64}Zn(p,α)^{61}Cu reaction on natural Zn or enriched ^{64}Zn targets. The enriched ^{64}Zn (99.82%) was electroplated onto high purity gold or silver foils or onto thin Al discs. A typical target bombardment used 30μA; at 11.7, 14.5 or 17.6MeV over 30-60min. The ^{61}Cu (radiochemical purity of >95%) was separated using a combination of cation and anion exchange columns. The ^{64}Zn target material was recovered after each run, for re-use. In a direct comparison with enriched ^{64}Zn-target results, ^{61}Cu production using the cheaper ^{nat}Zn target proved to be an effective alternative.

Keywords: ^{61}Cu – Production – ^{64}Zn electroplating – Separation
PACS: 25.30.Hm Positron-induced reactions

INTRODUCTION

The radiometal copper-61 (^{61}Cu; β^{+}_{mean} range = 0.242-0.527MeV) can be used to label bioactive molecules for positron emission tomography (PET) imaging [6]. Several studies have employed ^{61}Cu for studying hypoxia (e.g. using radiolabeled diacetyl-bis(N^4-methylthiosemicarbazone) [^{61}Cu-ATSM]) or blood flow [1,3,4,9]. For such applications the shorter half-life (3.4hr vs. 12.7hr) and larger positron abundance (61% vs. 17.9%) of ^{61}Cu makes it a competitive PET imaging reporter to ^{64}Cu. Large activities of ^{61}Cu can be produced via the ^{61}Ni(p,n)^{61}Cu reaction using a highly enriched nickel target [4]. The major advantage for this production route is the ability to achieve high specific activities ^{61}Cu and the use of the convenient production energy range (E_p= 10.5-10.3MeV) of a standard biomedical cyclotron [6]. A disadvantage of this pathway is the high cost of the enriched ^{61}Ni. An alternative approach is to utilise the ^{64}Zn(p,α)^{61}Cu reaction, which can utilise (cheap) natural zinc (^{nat}Zn) foil which contains 48.6% of ^{64}Zn, or enriched ^{64}Zn (~10% of the price of ^{61}Ni). Enriched ^{64}Zn can be easily electroplated onto a substrate [5,7]. This study explored production of ^{61}Cu from ^{nat}Zn and enriched ^{64}Zn targets using an energy-degraded proton beam of approximately 10mm diameter from an 18MeV cyclotron. A challenge is the development of a rapid and efficient separation process to isolate the desired ^{61}Cu, including removing gallium radioisotopes co-produced during bombardment, as well as (in the case of the enriched target) recovering ^{64}Zn for re-use.

14th International Workshop on Targetry and Target Chemistry
AIP Conf. Proc. 1509, 91-95 (2012); doi: 10.1063/1.4773947

MATERIALS & METHODS

All reagents used at this study were of analytical grade. The enriched ^{64}Zn powder (isotopic purity >99.82%) was obtained from Isoflex (San Francisco, CA). ^{nat}Zn, Ag and Au foils (all 99.99% purity), 50μm, 125μm & 125μm thick, respectively, as well as Al rod (99.99% purity, for fabricating Al substrates for electroplating) were obtained from Goodfellow (Cambridge, UK). Hydrochloric and sulphuric acids were purchased from Sigma-Aldrich. Anion exchange resin AG1-x8 (200-400 mesh), cation exchange resin AG 50W-x8 (200-400 mesh) and the column cylinders (1.5x10cm and 1x10 cm) were supplied by BioRad (Australia).

Target Preparation & Cyclotron Bombardment

Target preparation was achieved using either ^{nat}Zn foils (50μm thick), or the electroplating of enriched ^{64}Zn on to substrate foils (Ag or Au; 125μm thick & 15mm in diameter) or discs (Al; 500μm thick & 25mm in diameter, machined from rod). Electroplating of a 10mm diameter 'footprint' was carried out using an in-house apparatus, constructed originally for the electroplating of ^{64}Ni onto a gold-foil substrate for ^{64}Cu production [10].

The ^{64}Zn (200mg) was dissolved in 1 ml of concentration of H_2SO_4, then 1ml of water was added to the mixture and it was left overnight. The following day the solution was heated at 150°C and then evaporated to dryness. The process was repeated on the resultant residue. To the $ZnSO_4$ residue was added 40mL of water, and a 10mL aliquot of this solution was transferred to the electroplating cell, which is capable of plating single or multiple substrates. The anode was a platinum rod (99.99% purity) and the cathode was either a high purity Al disc or an Au or Ag foil. Achieved target thicknesses ranged from 26.7 to 32μm.

Production of ^{61}Cu was performed on an 18/9MeV cyclotron (IBA, Belgium). The metal target (^{nat}Zn foil or ^{64}Zn electroplated onto a substrate) was placed in a cradling aluminium backing plate, part of an in-house designed and built external beam line, so that the beam was normal to the target surface. The target was cooled from behind with chilled distilled water at a flowrate of 50L/min and He gas was used to cool in the space between the leading surface of the target and a 25μm Havar® vacuum window [11]. Typical run duration was 30-60min at 30μA, with energies 11.7, 14.5 or 17.6 MeV.

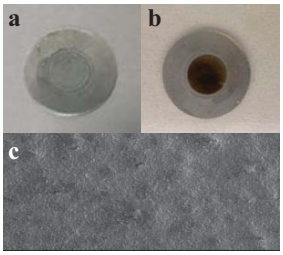

FIGURE 1. ^{64}Zn electroplated onto its substrate (here, 500μm thick Al is the example): **(a)** before bombardment; **(b)** following bombardment with 11.7 MeV protons and proton charge of 30μA.hr; **(c)** scanning electron micrograph of electroplated surface before bombardment (100 x magnification).

Radiochemical Separation of ^{61}Cu & Recovery of Zn Target

At EOB the ^{64}Zn target was transferred to a shielded fumehood, and the electroplated material dissolved off the substrate using 500µL of 10M HCl solution at room temperature. In the case of ^{nat}Zn, the target was wholly dissolved. The digest was quantitatively transferred to a cation exchange column (10x1.5 cm) with (200-400) mesh H^+. Cu and Zn isotopes were eluted using 25mL of 10M HCl (from 4x5mL fractions), while the Ga radioisotopes remained on the column. Separation efficiency was monitored using the characteristic γ-ray signatures of the Ga isotopes. Eluted fractions were combined and then loaded on to an anion exchange column (10 x1.0 cm). Copper was eluted using 20mL of 2M HCl, while Zn remained on the column. Combined Cu fractions were evaporated to dryness and then the residue dissolved in 0.05M HCl.

The target Zn material was later eluted from the column with 30mL 0.05M HCl. In the case of ^{64}Zn, fractions containing Zn were combined and then evaporated to dryness at 150°C. The residue was then digested with 6M H_2SO_4. The process was repeated and the resultant product was dissolved in 10mL of water. Following vigorous stirring the solution could then be transferred to the electroplating cell for re-use. The schematic for post-bombardment processing is shown in Figure 2. Total processing time was approximately 120 min. Radionuclidic purity of the ^{61}Cu was assessed by gamma spectroscopy and then corrected to end of bombardment (EOB). The specific activity of the ^{61}Cu was retrospectively determined using ICP-MS analysis, once samples were decayed.

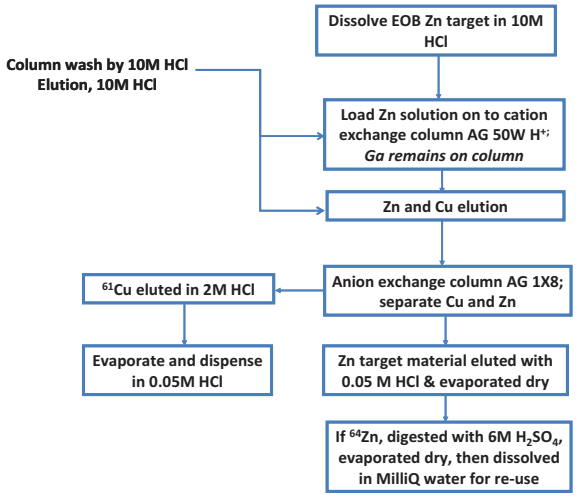

FIGURE 2. Schematic of post-bombardment processing of bombarded zinc targets.

RESULTS & DISCUSSION

Copper-61 was produced by proton bombardment of natural Zn and ^{64}Zn targets using protons of varying energy (11.7 to 17.6MeV). When using a natural Zn target, significant quantities of unwanted Ga isotopes ^{66,67,68}Ga ($T_{1/2}$= 9.4hr, 78.3hr & 68.1min, respectively) are produced. These Ga isotopes can be significantly reduced when using enriched (99.82%) ^{64}Zn at the target. Tables 1 and 2 summarize the results of three runs for each target material. Radionuclide purity of the final product was characterised using gamma spectroscopy at end of

synthesis (EOS) and found to contain high purity ^{61}Cu (>95%). The ^{61}Cu samples were decayed and analysed by ICP-MS for Zn, Ga, Al, Ag, Au and Cu, the latter used to determine the specific activity of the final product. The Zn and Cu content were <8.6ppm and <2.9ppm, respectively. No other ions were detectable. The recovery of ^{64}Zn after processing was approximately 90%.

Tables 1 and 2 show that ^{61}Cu was produced from all runs. Since the targets were thin (26.7-50μm) the energy samples only a narrow energy-band of the reaction cross section [3,8]. *Ceteris paribus*, the highest yield would thus be expected at 14.5MeV, where this function peaks. The results are too variable for ^{nat}Zn (Table 1) to draw a conclusion. The 11.7MeV run may be anomalous, as evidenced by the ICP-MS Cu/Zn ratio. However, results for ^{64}Zn enriched targets (Table 2) correlate broadly with the cross sections reported. Variability of the yield (normalised to target mass) may be due partly to variation in the area of the 'footprint' of the beam on the target, which is not monitored.

TABLE 1. Production of ^{61}Cu using ^{nat}Zn foil targets

Zn (mg of ^{64}Zn)	Energy (MeV	Activity (MBq)	Yield (MBq/μA.hr/mg)	ICP-MS SA (GBq/μmol)	ICP-MS Cu/Zn Ratio
[a]13.6	11.7	162.21	0.80	12.96	0.88
[a]13.1	14.5	95.29	0.24	20.02	0.03
[a]12.6	17.6	62.80	0.33	15.49	0.04

[a]Target mass corrected to actual area of foil exposed to beam, plus ^{64}Zn natural abundance in ^{nat}Zn (48.6%). Bombarded at 30μA for 30min.

TABLE 2. Production of ^{61}Cu using enriched ^{64}Zn target

Zn (mg)	Energy (MeV	Activity (MBq)	Yield (MBq/μA.hr/mg)	ICP-MS SA (GBq/μmol)	ICP-MS Cu/Zn Ratio
[a]15	11.7	75.77	0.34	3.57	2.25
[b]15	14.5	195.16	0.43	4.31	0.92
[c]18	17.6	91.80	0.34	12.4	0.53

[a]Target bombarded at 30μA for 30min, electroplating on Au foil substrate. [b]Bombarded at 30μA for 60min, Ag foil substrate. [c]Bombarded at 30μA for 30min, Al thin-disc substrate.

Current data show that five of the six runs are in reasonable agreement, given the confounding variation in the cross section over the sampled proton energy range. Also the general agreement of the mass-normalised yields for the ^{64}Zn-target runs suggests that different electroplating substrates (Au, Ag & Al) are not major confounders.

Though insufficient production runs have been accumulated to perform a valid error analysis, this study has shown that the two-column chemical separation technique is equally valid for ^{nat}Zn and enriched ^{64}Zn targets in its ability to produce ^{61}Cu of acceptable radionuclidic and chemical purities; as well as (in the case of ^{64}Zn), to efficiently recover Zn for re-use in target fabrication.

CONCLUSIONS

Production of preclinical research-level activities of ^{61}Cu of acceptable radionuclidic purity (>95%, including removal of Ga isotopes) and chemical purity (including reduction of elemental Zn and Cu contamination to <8.6 and <2.9ppm,

respectively), has been demonstrated. The primary or stepwise degraded proton beam from a standard 18MeV medical cyclotron was used to elicit the reaction $^{64}Zn(p,\alpha)^{61}Cu$ in either ^{nat}Zn foils or electroplated enriched ^{64}Zn targets on a range of foil substrates. Future work will optimise the choice of substrate, reduce the variability in the target-mass-normalised yield and boost the EOB activity.

The use of a ^{nat}Zn target is a cost-effective ($2.70/mg; $15/50μm foil) option for production of (at least) research activities of ^{61}Cu and a viable alternative to ^{61}Ni targetry (natural abundance 1.14%, $30+ /mg) utilising the reaction $^{61}Ni(p,n)^{61}Cu$. It is likely that one if the major preclinical or clinical applications will be in PET imaging of hypoxic tumorous tissue, utilising ^{61}Cu-labeled ATSM.

ACKNOWLEDGMENTS

The Australian Nuclear Science and Technology Organisation provided funding for equipment to support solid target research at Sir Charles Gairdner Hospital (SCGH), Perth. AHA acknowledges funding support from SCGH and the Australia Research Council through the Centre for Excellence in Antimatter-Matter Studies at the Australian National University, Canberra. The Rapid Labs Clinical Team is acknowledged for technical & logistical support. SVS gratefully acknowledges support from Brookhaven National Laboratories.

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