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ARTICLE

Fast and cost-effective cyclotron production of ^{61}Cu using a ^{nat}Zn liquid target: an opportunity for radiopharmaceutical production and R&D

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Following our previous work on the production of radiometals, such as ^{64}Cu and ^{68}Ga, though the irradiation of liquid targets using a medical cyclotron, we describe in this paper a technique to produce ^{61}Cu through the irradiation of natural zinc using a liquid target. The proposed method is very cost-effective as it avoids the use of expensive enriched material and fast as a purified solution of $^{61}CuCl_2$ is obtained in less than 30 min after End Of Beam. Considering its moderate half-life of 3.33 h and favourable decay properties as a positron emitter, ^{61}Cu is a very attractive nuclide for the labelling of PET tracers for pre-clinical and clinical use with PET as well as to support the intense R&D programs being carried worldwide taking advantage of the rich and versatile chemistry of copper.

Introduction

The multiple radioisotopes of copper (^{60}Cu, ^{61}Cu, ^{62}Cu, ^{64}Cu, ^{66}Cu and ^{67}Cu) present a vast and unique diversity of characteristics, particularly in terms of half-life (ranging from a few minutes to several hours) and decay properties; making them attractive for a wide range of molecular imaging and/or targeted radionuclide therapy applications.[1] These useful qualities have fostered the expansion of copper radiochemistry in the past aiming at the discovery and development of radiopharmaceutical applications for multiple diagnostic and therapeutic applications.[2-4] The variety of half-lives allow us to select the most suitable radioisotope for each application[5]. Studies presenting the use of isotopes with short half-lives, such as ^{60}Cu or ^{62}Cu (23.7 and 9.74 min, respectively), are equally established as works based on the use of the radioisotopes of copper with longer half-lives, namely ^{64}Cu and ^{67}Cu (12.7 h and 2.58 days, respectively).[6,7] Several reviews inclusively compare the use of the different copper radioisotopes in terms of their physicochemical characteristics and therapeutic and/or diagnostic properties.[8-11]

Such a wide range of half-lives also presents production challenges and limitations because, on the one hand, radiopharmaceuticals based of radioisotopes with short half-lives can only be used by imaging centres with in-house cyclotrons and, on the other hand, isotopes with long half-lives require long irradiations with problematic but inevitable use of large beam currents in order to produce quantitatively relevant activities. Moreover, independently of their half-life, the production of copper radiopharmaceuticals is usually based on a $^{6\gamma}$Ni(p,n)$^{6\gamma}$Cu type nuclear reactions; inevitably requiring the use of expensive enriched nickel isotopes in order to produce quantitatively relevant activities and/or achieve nominal purity.

^{61}Cu represents an exception to the latter statement as it can also be efficiently produced without the need of expensive enriched nickel; through the irradiation of natural zinc as the ^{64}Zn(p,α)^{61}Cu nuclear reaction is extensively prevalent and with almost no competitive copper radioisotopes involved in the process to deteriorate the purity.[12] ^{61}Cu is also a positron emitter with an advantageous intermediate half-life of 3.33 h, a good compromise between imaging protocol requirements and production/distribution feasibility. The nuclide also presents better decay characteristics when compared with the more established ^{64}Cu (61.5 % positron decay branch vs. 17.5 %), has no β^- emission and exhibits a moderate average positron energy of 1160 keV.[13]

Despite some reports in the literature of experiments conducted with ^{61}Cu-labelled radiopharmaceuticals,[14,15] the use of this nuclide has remained remarkably low. The main reason for that, might be the convenience of the long half-life of ^{64}Cu for some particular applications with slow *in vivo* kinetics such as the use of radiolabelled antibodies with long circulation times. Nevertheless, the possibility of a very economical production of ^{61}Cu makes it a particularly attractive radionuclide of copper for the development and optimization stages of any new copper-labelled radiopharmaceutical independently of which copper isotope is

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intended to for the final labelling, thus reducing the use of enriched material and significantly cutting costs of the radiopharmaceutical development process.

Considering the potential of fast and inexpensive production of ^{61}Cu in medical cyclotrons, we present here a fully automated process for the production of purified ^{61}Cu through cyclotron irradiation of natural zinc dissolved in a liquid target solution; in a process similar to that successfully used to produce ^{64}Cu-based radiopharmaceutical suitable for human use[16] The technique is capable of delivering consecutives batches of purified ^{61}Cu within only 30 min after End-Of-Beam (EOB) while avoiding the pre- and post- irradiation technical difficulties arising from the use of conventional solid targets.[16,17]

Method

The target solution was prepared by dissolving natural zinc (99.1 % purity, from Sigma Aldrich) in a nitrate solution which was then diluted in 10 mM nitric acid[17]. Since natural zinc is very affordable, the amount of dissolved zinc was maximized and concentrations up to 250 mg/ml were used, in order to maximize the production of ^{61}Cu. A Cyclone 18/9® cyclotron (IBA, Belgium) delivering protons with a fixed energy of 18 MeV, was used to bombard the zinc-based target solutions. An IBA Nirta® liquid target system (IBA, Belgium) with niobium insert and a PEEK valve was used to automatically load, irradiate and transfer the target solution. The target window is the arrangement of a 35 µm thick Havar foil followed by a 35 µm thick niobium, resulting in impinging protons with 16.9 MeV, so that the target solution only contacts with the chemically inert niobium, as reported in ref. 17.

Calculations were conducted to determine the production yields for several possible nuclear reactions on the natural zinc contained in the liquid target. Experimental cross-sections data from several authors were used, as indicated in Table 1, to fit the excitation functions to polynomial functions in the energy

Table 1 - Proton-induced nuclear reactions occurring in natural zinc and theoretical productions yields for a typical irradiation with 16,9 MeV protons impinging on a target solution containing a 250 mg/ml concentration of natural zinc

Zinc nuclide (%)	Nuclear reaction	Decay					Theoretical yield	Cross-sections references	Activity @ EOB (MBq)
		Half-life	β⁻ (MeV)	β⁺ (MeV)	EC (%)	γ-rays (keV)	(MBq/µA $_{sat}$)		for a 3 h long irradiation with 50 µA
^{64}Zn 48,6%	^{64}Zn(p,α)^{61}Cu	3,33 h		1215 (61,5 %)	38,5%	283 (12,0%) 511 (123%) 656 (10,4%)	109,3	18,19	2538,0
	^{64}Zn(p,pn)63Zn	38,5 min				669,6 (8 %)	64,97	18	3121,8
	^{64}Zn(p,γ)65Ga	15,2 min				115,09 (54 %) 751,8 (8,1 %)	0,886	20,21	44,27
	^{64}Zn(p,n)64Ga	2,63 min				807,8 (14,54 %) 991,6 (46 %)			
^{66}Zn 27,9%	^{66}Zn(p,n)^{66}Ga	9,49 h		4,153 (56 %)	44%	511 (114%) 833 (5,9%) 1039 (37%) 2190 (5,3%) 2751 (22,7%)	530,1	18,22,23	5215,8
	^{66}Zn(p,2n)65Ga	15,2 min				115,09 (54 %) 751,8 (8,1 %)	1,288	18	64,4
	^{66}Zn(p,pn)65Zn	244,0 days		0,33 (1,42 %)	98,6%	1115 (50,23%)	98,02	18,22,24	1,740
^{67}Zn 4,1%	^{67}Zn(p,n)67Ga	3,26 days			100%	93,3 (70,6%) 184,6 (21,3%) 300,2 (16,67%)	75,97	22,25	99,6
	^{67}Zn(p,α)64Cu	12,7 h	0,579 (38,5 %)	0,653 (17,52 %)	43,5%	511 (35,04%) 1346 (0,475%)	4,259	18,26	32,16
	^{67}Zn(p,2n)66Ga	9,49 h		4,153 (56 %)	44%	511 (114%) 833 (5,9%) 1039 (37%) 2190 (5,3%) 2751 (22,7%)	7,831	18,22,23	77,0
^{68}Zn 18,8%	^{68}Zn(p,n)68Ga	67,8 min		1,899 (88,9 %)	11%	511 (178%) 1077 (3,24%) 1883 (0,142%)	516,67	18,22,23	21731,7
	^{68}Zn(p,2n)67Ga	3,26 days			100%	93,3 (70,6%) 184,6 (21,3%) 300,2 (16,67%)	119,0	22,25	156,0
	^{68}Zn(p,nα)64Cu	12,7 h	0,579 (38,5 %)	0,653 (17,52 %)	43,5%	511 (35,04%) 1346 (0,475%)	3,12	27	23,6
^{70}Zn 0,6%	^{70}Zn(p,α)^{67}Cu	2,58 days	0,577 (100 %)			184.6 (48,7 %)	0,181	18,28	0,299
	^{70}Zn(p,n)^{70}Ga	21,1 min	1,66 (99,6 %)		0,41%	176 (0,29%) 1039 (0,65%)		29	
	^{70}Zn(p,pn)69Zn	56,4 min	0,906 (100 %)			319 (0,0012%)	0,215	18	9,56

range of interest. ^{13}N from the $^{16}O(p,\alpha)^{13}N$ reaction from the water of the target solution was not considered because the purification process guarantees the exclusion of ^{13}N from the final product. Table 1 presents the predicted production yields and activities from a typical irradiation. On the other hand, Table 1 also shows that other copper radionuclides are also produced, namely ^{64}Cu and ^{67}Cu. These radioisotopic impurities are particularly relevant because their larger half-life means that the purity of the ^{61}Cu produced will deteriorate with time. Figure 1 shows the production yields of both ^{61}Cu and ^{64}Cu as a function of the proton beam energy. As there is no clear energy window to choose in order to improve the final product purity by maximizing the $^{61}Cu/^{64}Cu$ activities ratio, we use 16.9 MeV protons in order to maximize the production of ^{61}Cu.

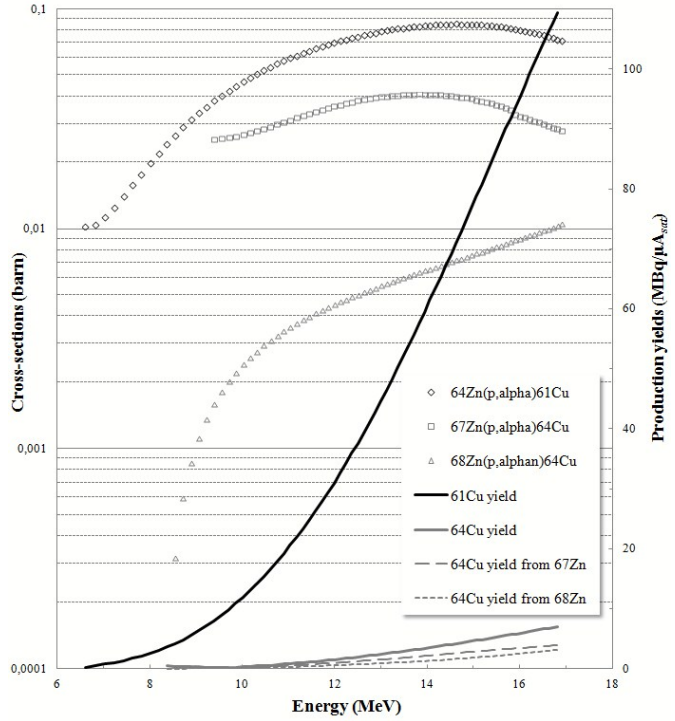

Figure 1 Thick targets yields at saturation (curves) for the production of ^{61}Cu and ^{64}Cu from a typical proton-irradiation of a liquid target containing of a 250 mg/ml concentration of natural zinc and excitations functions fits (open symbols) of the nuclear reactions of interest.

For our particular case, a typical production of ^{61}Cu consisted in a 45 min long irradiations with around 25-30 μA, resulting systematically in around 300 MBq of ^{61}Cu, as indicated in Table2, which corresponds to around 70 % of the theoretical predictions and a deduced experimental production yield of 83 MBq/uA at saturation. Table 2shows that the measured activities for the others radionuclides produced are also in agreement with the theoretical predictions. Moreover, it is possible to produce about 5 GBq of ^{61}Cu by simply scaling up the irradiation time and the beam current by using a larger target. If necessary, the use of enriched ^{64}Zn can also increase the production of ^{61}Cu to about 10 GBq; in addition of the advantage of increasing the purity of the ^{61}Cu produced. The activities were determined through γ-spectroscopy with a High Purity Germanium detector (HPGe), model GEM30P4-76 from ORTEC (ORTEC, Tennessee, US), placed in a low-background shielding and calibrated with a ^{152}Eu radioactive source. The software package GammaVision (ORTEC Inc.) was used to determine photopeak areas of the γ-spectra acquired using point-source like samples and keeping a dead-time inferior to 4 %.

Table 2 – Activities produced after a typical 45 min long irradiation of natural Zn

Nuclide	Activity Produced @ EOB (MBq)	(percentage from calculated predictions) (%)
^{61}Cu	271.9	68.8
^{66}Ga	344.8	48.1
^{67}Ga	22.4	69.6
^{68}Ga	2209.5	46.4
^{65}Zn	0.225	103.3
^{64}Cu	n.a	n.a

As indicated in Table 2, it was not possible to determine the activity of ^{64}Cu produced, even several hours after EOB, because of the inevitable large amount of radioimpurities with both half-life and characteristic γ-rays close to the singular characteristic of 1345.7 keV line from ^{64}Cu (only 0.47 % of decays, with half-life of 12.7 hours); in particular the 1333.3 keV characteristic line from ^{66}Ga (1.17 % decays, with half-life of 9.49 hours). The activity of ^{64}Cu was however determined in the final product since only the copper radioisotopes ^{61}Cu and ^{64}Cu were present. Such measurements enabled the determination of the purity of the ^{61}Cu produced, which remains superior to 95 % even several hour after EOB as illustrated in Figure 2. The other non-copper radionuclides produced were not considered since the purification process guarantees the exclusion of other radioimpurities[16]. As pointed out earlier, the purity of ^{61}Cu can be improved if necessary by using enriched ^{64}Zn, which the additional advantage of increase by a factor 2 the production yield of ^{61}Cu.

The irradiated solution was then purified using the procedure described in Ref. 16 for ^{64}Cu, with identical typical 80 % yield; resulting in a purified solution containing $^{61}CuCl_2$ only 30 min after EOB, that can be used subsequently for radiolabelling radiopharmaceuticals.

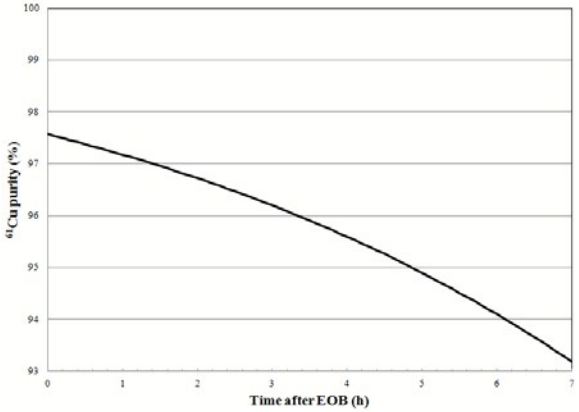

Figure 2 - Experimentally deduced purity of the ^{61}Cu produced, as a function of time after EOB.

Since several irradiations with distinct conditions were performed for the present work, particularly with distinct zinc concentrations, this study allowed to evaluate a concern raised by several authors regarding the transfer efficiency of radio-metals produced by the irradiation of liquid targets; namely the need of rinsing the target to recuperate significant activity. For instance, Hoehr *at al.* and Tim Grado *et al.*[30] reported that a "rinse" solution loaded into the target enables to recover about 30 % of the activity firstly transferred. In order to study such phenomenon, reported as quantitatively identical for other radioisotopes produced through the irradiation of liquid targets, the automatic filling system was modified to enable the load of the liquid target with 10 mM nitric acid and its irradiation immediately after the transfer of the irradiated solution. The presence of ^{67}Ga was then determined several days after bombardment for both irradiated and transferred target solution and "rinse" solution. Such procedure was repeated maintaining identical 45 min long irradiations of the target solution for the production of ^{61}Cu but for several concentrations of natural zinc, for distinct duration of the irradiations of the "rinse" solution and for different material of the transfer lines; namely Teflon and Tefzel lines of equal length. Figure 3 presents results obtained for a 33 mg/ml concentration of natural zinc as a function of the duration of the irradiation of the "rinse" solution. The concentration of 33 mg/ml was chosen because it corresponds to a typical concentration of enriched ^{68}Zn for the production of ^{68}Ga through the irradiation of liquid target, as reported in Refs. 16-17.

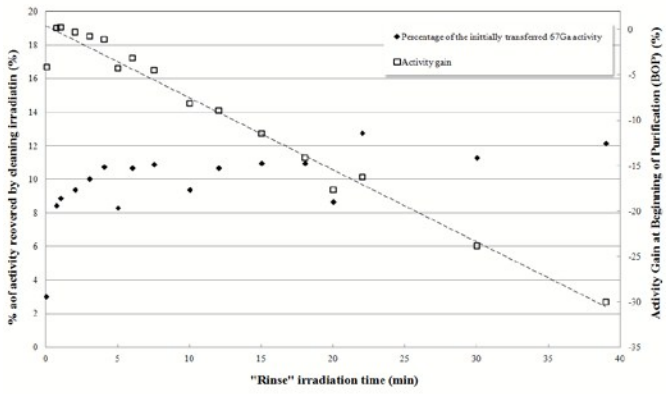

Figure 3 - Percentage of the initially transferred activity of ^{67}Ga recovered in the "rinse" solution (full symbols) and deduced activity gain at beginning of purification, for the case of ^{68}Ga (open symbols), as a function of time.

Figure 3 shows that a maximum of about 12 % of the activity is recovered, although long irradiations of the "rinse" solution are then required. As ^{67}Ga and ^{68}Ga present the same behaviour, Figure 3 also demonstrates that such procedure do not represent any activity gain for the particularly relevant short half-life radioisotope ^{68}Ga, because of the extra time necessary to perform the additional load, irradiation and purge operations before Beginning Of Purification (BOP). Such discrepancy may be explained by the higher concentration of dissolved salts used by *Hoehr et al.*, e.g. about 300 mg/ml for the case of zinc; although our first tests with concentrations of 100 and 250 mg/ml show quantitatively similar results to that presented in Figure 3 for a concentration of 33 mg/ml.

Conclusions

The present work describes a technique for the production of ^{61}Cu through the irradiation of natural zinc using a liquid target. The method is very inexpensive because there is no need to use enriched target material and provides a purified solution of $^{61}CuCl_2$ only 30 min after EOB. About 5 GBq of ^{61}Cu can be produced with a purity remaining superior to 95 % several hours after EOB. The purified ^{61}Cu can then to used to label radiopharmaceuticals for Positron Emission Tomography (PET) imaging and/or to serve as an affordable and practical tool for the development of new radiopharmaceuticals, independently of the copper radionuclide planned to be used later in final product.

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